Progress in Biophysics and Molecular Biology 119 (2015) 111–128

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

# The master switchers in the aging of cardiovascular system, reverse senescence by microRNA signatures; as highly conserved molecules

Fatemeh Pourrajab [a, b, *], Abbas Vakili Zarch [a], Seyedhossein Hekmatimoghaddam [c], Mohamad Reza Zare-Khormizi [a]

[a] School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[b] Department of Clinical Biochemistry and Molecular Biology, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[c] Department of Laboratory Sciences, School of Paramedicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

ARTICLE INFO

*Article history:*
Received 19 November 2014
Received in revised form
17 March 2015
Accepted 27 May 2015
Available online 29 May 2015

*Keywords:*
microRNA
Cardiovascular system
Aging

ABSTRACT

The incidence of CVD increases with aging, because of long-term exposure to risk factors/stressors. Aging is a complex biological process resulting in progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death. The main hallmarks of aging are cellular senescence, stem cell exhaustion, and altered intracellular communication. The major hallmarks of senescence are mitochondrial dysfunction, genomic instability, telomere attrition and epigenetic alterations, all of which contributing to cellular aging. Such events are controls by a family of small, non-coding RNAs (miRNAs) that interact with component of cellular senescence pathway; mitochondrial biogenesis/removal, DNA damage response machinery and IGF-1 signaling pathway.

Here, we review recent in vivo/in vitro reports that miRNAs are key modulators of heart senescence, and act as master switchers to influence reprogramming pathway. We discuss evidence that abrupt deregulation of some mit-miRNAs governing senescence programs underlies age-associated CVD.

In particular, due to the highly conserved nature and well-recognized target sites, miRNAs have been defined as master switchers in controlling heart progenitor cell biology. Modulation of mit-miRNA expression holds the great promise in switching off/on cellular senescence/reprogramming to rejuvenate stem cells to aid regenerative process.



## 1. Introduction

### 1.1. A brief introduction to cardiovascular system (CVS) aging

**A**ging is the established risk factor for cardiovascular disease (CVD), which is controlled by biochemical pathways and genetic processes (Rippe et al., 2012; Dutta et al., 2012; Zhang et al., 2012).

It is now well established that chronological age and physical age do not necessarily coincide. Not necessary, an 80-year-old person becomes as old as he is, but he can appear as young as a 60-year-old individual (Chimenti et al., 2003).

Cardiac aging is characterized by a series of complex events which lead to prevalence of CVD. The events consisting of left ventricular hypertrophy, diastolic dysfunction, and increased risk of atrial fibrillation, valvular degeneration and fibrosis (Zhang et al., 2012; van Rooij et al., 2008; Ikeda et al., 2007).

The main molecular hallmarks of cardiac aging in mammalian cells are indicated as genomic instability, telomere attrition, epigenetic alterations, mitochondrial dysfunction, cellular senescence and stem cell exhaustion (Lopez-Otin et al., 2013; Rodier and Campisi, 2011; Seeger et al., 2013). In particular, DNA damage and genomic instability are enough to favor cellular senescence, the main hallmark of the aging process. Cellular senescence at the basis of ageing, is believed to be the major player in the cardiovascular ageing process (Chimenti et al., 2003; Lopez-Otin et al., 2013; Konstantinidis et al., 2012; Tsirpanlis, 2008; Schroen and Heymans, 2012). During aging there is a gradual accumulation of senescent cells in cardiovascular tissues, which its outcomes are several age-related diseases (Rippe et al., 2012; Tsirpanlis, 2008).

In premature cardiac aging, the pool of old cardiomyocytes and

* Corresponding author. School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
*E-mail address:* mina_poorrajab@yahoo.com (F. Pourrajab).

http://dx.doi.org/10.1016/j.pbiomolbio.2015.05.004
0079-6107/

senescent cardiac progenitor cells (CpCs) progressively increases, and ventricular function is impaired. Accumulation of aging CPCs which generate progenies that rapidly acquire the premature senescence, contribute to the premature senescence of the organ and impaired ventricular function (Chimenti et al., 2003; Torella et al., 2004).

Cardiac senescence is the effect of age per se and in addition, intrinsic senescence mechanisms involved accrual of macromolecular oxidative damage, cause the development of structural and functional alterations during aging and render the heart more vulnerable to various stressors, which ultimately favors the development of CVD (Rippe et al., 2012; Dutta et al., 2012; Zhang et al., 2012; Tsirpanlis, 2008). The intrinsic senescence mechanisms involve mitochondrial/DNA damage responses which may lead to death signaling (Konstantinidis et al., 2012; Rippo et al., 2014).

Increasing age is also an independent risk factor for prevalence of atherosclerosis and is associated with decreased compliance of blood vessels, endothelial dysfunctions, arterial remodeling and impaired angiogenesis (Schraml and Grillari, 2012; Magenta et al., 2013).

In endothelium dysfunction, antithrombotic and vasodilatatory properties are reduced, and inflammatory activity increases (Rippe et al., 2012; Magenta et al., 2013).

## 2. The mechanisms contributing to intrinsic aging in the CVS

Accumulating evidence has defined cardiac senescence as the pathogenesis conditions which ultimately lead to heart diseases (e.g. of specifically left ventricular hypertrophy, ischemic heart disease, heart failure, and diabetic cardiomyopathy) (Konstantinidis et al., 2012; Rippo et al., 2014; Li et al., 2012).

Also, myocardial aging in humans is defined as attenuation of cell growth with accumulation of premature senescent cells (Chimenti et al., 2003; Torella et al., 2004).

In general, three mechanisms link senescence with aging: 1) cellular senescence depletes tissues organ of stem/progenitor cells compromising tissue repair, regeneration, and normal turnover, leading to functional decrements; 2) senescent cells induce several potent inflammatory cytokines and oxidative specious; 3) senescent cells secret factors inhibiting cell growth and migration, and remodeling tissue and blood vessel architectures, all of which cause tissue dysfunction and promote age-related diseases (Chimenti et al., 2003; Rodier and Campisi, 2011; Torella et al., 2004).

Senescent cells undergo irreversible cell cycle arrest due to either critically short telomeres (replicative senescence) or external stress induced by factors such as oxidative stress or DNA damage (stress-induced premature senescence, SIPS) (Li et al., 2009; Maes et al., 2009; Bonifacio and Jarstfer, 2010).

Four major pathways make decision of cell fate and the establishment of senescence. They include p16, p21, p53 and IGF-1 signaling pathways (Fig. 1) (Rippo et al., 2014; Motohashi et al., 2013; Gorospe and Abdelmohsen, 2011; Li et al., 2012; Lafferty-Whyte et al., 2009).

The cardiac aging hallmarks, all are encompassed in the phenotype of senescent heart (Lopez-Otin et al., 2013; Rodier and Campisi, 2011; Gorospe and Abdelmohsen, 2011; Sharma et al., 2013; Magenta et al., 2011). Whereby, increased oxidative stress, loss of mitochondrial function and impaired autophagy are the major cause of theses hallmarks (Rippo et al., 2014; Schraml and Grillari, 2012; Magenta et al., 2011; Jazbutyte et al., 2013). Consistent with this paradigm, the forced entry of primitive cells into an irreversible quiescent state is increased in the aged-diseased heart which is defined by expressing p16 and shortening telomeres (Chimenti et al., 2003; Torella et al., 2004). In other word, CVS senescence is due to premature cellular senescence which is attributed to progressive accrual of macromolecule oxidative damage, in particular DNA damages. ROS are invoked as the major factors for DNA damage. ROS are constantly generated within cells by several enzymatic reactions, especially by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOXs), and mitochondria reactions (Magenta et al., 2013; Li et al., 2012; Magenta et al., 2011; Varga et al., 2013; Braunersreuther et al., 2013).

### 2.1. A brief introduction to the role of adult stem cell in CVS aging

Human cardiac myopathy is the result of premature myocardial aging which has been attributed to attenuation of CpC capacity to renovate aging myocardium (Chimenti et al., 2003; Konstantinidis et al., 2012; Tsirpanlis, 2008). Indeed, the myocardial biopsies obtained from old patients with aged-diseased hearts, capacity of cell regeneration is extremely reduced and additionally is disproportionate to the accumulating old dying cells whose outcome is cardiac senescence and de-compensation (Chimenti et al., 2003).

Heart failure is the result of aging myopathy and coronary artery disease which are dictated by accumulation of premature senescent CPCs and depletion of the fresh ones. The failing heart is depleted from both functionally competent CPCs and myocytes (Torella et al., 2004; Gonzalez et al., 2008). In other word, a premature-senescent/aged-diseased heart is the result of aging myopathy characterized by an enforced premature entry of primitive c-kit-positive stem cells (CPCs) into an irreversible quiescent state, coupled with premature-senescent myocytes (Chimenti et al., 2003).

Accordingly, heart senescence accompanies a primary myocardium aging characterized by depletion of CPC pool and excessive telomere shortening in resistant CPCs, which by necessity generate a differentiated progeny that rapidly acquires the premature senescent phenotype and readily conditioning organ aging (Tsirpanlis, 2008; Torella et al., 2004).

The loss of functionally competent CPCs is due to an imbalance between growth and survival pathways against those inducing death pathways including oxidative stress and telomere attrition (Konstantinidis et al., 2012). In turn, due to an imbalance between myocyte growth and death in an aged heart, the contractile performance of the heart would be depressed. Also, gradual remodeling of the heart is happened due to decreased capacity of myocardial regeneration which is responsible to attenuate the ventricular dilation and to decrease the ventricular mass-to-chamber volume ratio, all of which is the consequence of CPC senescence (Topkara and Mann, 2011).

Additionally, endothelial progenitor cells (EPCs) is reduced in atherosclerotic patients. They play an essential role in endothelial integrity due to their ability to reinforce the endothelium with new healthy ECs to replace damaged or apoptotic cells (Zhao et al., 2010; Menghini et al., 2013; Qin et al., 2012). Aging leads to the accumulation of senescent EPCs in CVS where is proposed to contribute to impaired organ function in elderly patients (Zhao et al., 2010; Menghini et al., 2013).

In summary, cellular senescence and stem cell exhaustion is the major cause of cardiac myopathy and further heart failing, since markers of cellular senescence and death are observed (Chimenti et al., 2003; Lopez-Otin et al., 2013; Konstantinidis et al., 2012; Torella et al., 2004; Gonzalez et al., 2008).

Despite excessive accumulating p16-positive cells in a premature senescent/aged-diseased heart, but it still contains CPCs with stem cell properties that upon reactivation would reprogram and migrate to the regions of damage to regenerate a population of young cardiomyocytes and to reversing the aging myopathy

(Magenta et al., 2013; Li et al., 2012; Sharma et al., 2013; Gonzalez et al., 2008).

### 2.2. A brief introduction to the signaling pathways involved in CVS aging

Otherwise, survival pathways prevents cardiac cell aging through the insulin-like growth factor-1 (IGF-1) system to counteract oxidative stress and those pathways attributed to cellular senescence, growth arrest, and apoptosis in human CVS (Lopez-Otin et al., 2013; Li et al., 2012; Gonzalez et al., 2008). The aging-associated signals would result in myocyte and CPC senescence, via accumulation of oxidative damages (Gonzalez et al., 2008; van Rooij et al., 2008).

In CVS, IGF-1/IRS1/PI3K/Akt signaling is well known to stimulate CPC/myoblast survival pathways, besides increasing protein synthesis. The IGF-1/IGF-1R system induces CPC division and hinders replicative senescence by up-regulating telomerase activity and preserving the pool of functionally competent CPCs. Then, expression of IGF-1/IGF-1R system in CPCs, reactivate cell growth and interfere with oxidative damage and telomeric shortening (Lopez-Otin et al., 2013; Motohashi et al., 2013; Li et al., 2012).

The IGF-1/IRS1/PI3K/Akt pathway downstream effector FOXO is the most relevant one attributable to longevity in mammalians and in human (Dutta et al., 2012; Lopez-Otin et al., 2013; Pourrajab et al., 2014a, 2014b). A growing number of evidence link FOXO to longevity and to chromatin-remodeling system PARP1/SIRT1 which also controls trophic and bioenergetic pathways (Rodier and Campisi, 2011; Gorospe and Abdelmohsen, 2011; Zhao et al., 2010).

The Akt pathway positively regulates cell cycle progression and proliferation by reducing the expression levels of critical cell cycle inhibitors p53/p21/p16 (Motohashi et al., 2013; Gorospe and Abdelmohsen, 2011; Pourrajab et al., 2014a, 2014b).

In human cells, erosion of chromosomes stimulates two endogenous cell pathways 1) up-regulating senescence-associated pathway p16INK4a/Rb alone or in combination with pathway p53/21; 2) activating DNA damage repair (DDR) machinery (Lopez-Otin et al., 2013; Rodier and Campisi, 2011; Tsirpanlis, 2008).

Cdk4/6 inhibitor p16 is the major hallmark of senescence, induces growth arrest and maintains cells at G0 stage. Activation of p16 also triggers cell death through a mechanism decreasing mitochondrial membrane potential, favoring the release of cytochrome-c and activating procaspase-9 in the cytoplasm (Konstantinidis et al., 2012; Li et al., 2009; Motohashi et al., 2013; Gorospe and Abdelmohsen, 2011). The senescent cells that are positive for p16 cannot reenter the cell cycle and are arrested at the G0-G1 transition (Rodier and Campisi, 2011; Li et al., 2009).

The cardiac aging hallmarks, all are encompassed in the phenotype of senescent heart (Lopez-Otin et al., 2013; Rodier and Campisi, 2011; Gorospe and Abdelmohsen, 2011; Sharma et al., 2013; Magenta et al., 2011). Whereby, increased oxidative stress, loss of mitochondrial function and impaired autophagy are the major cause of theses hallmarks (Rippo et al., 2014; Schraml and Grillari, 2012; Magenta et al., 2011; Jazbutyte et al., 2013).

In the senescent heart, the bulk of ROS production mainly occurs as a byproduct of mitochondrial oxidative reactions (Dutta et al., 2012). While, in atherosclerotic lesions and in senescent ECs, progressive ROS production occurs mainly by NOX system, contributing to the associated arterial dysfunction (Varga et al., 2013; Braunersreuther et al., 2013).

In aging heart, mitochondrion electron transport chain and its antioxidant enzymes do not properly work which contributes to excessive ROS generation and its further damages (Magenta et al., 2013; Noren Hooten et al., 2010). Damaged mitochondria not only produce insufficient ATP but also generate increased amounts of ROS/RNS that display a greater toxicity to trigger cellular senescence and death (Dutta et al., 2012; Rodier and Campisi, 2011; Tsirpanlis, 2008; Konstantinidis et al., 2012; Gorospe and Abdelmohsen, 2011). Accumulation of damaged mitochondria intervene, ultimately in cardiac senescence and in the pathogenesis of specific heart diseases (e.g. left ventricular hypertrophy, ischemic heart disease, heart failure, and diabetic cardiomyopathy) (Konstantinidis et al., 2012; Rippo et al., 2014; Li et al., 2012).

Thereby, removal of dysfunctional mitochondria is crucial for the maintenance of cell viability (Dutta et al., 2012; Rippo et al., 2014).

The oxidative stress is initial switching to progenitor cell senescence and development of various diseases, through stimulating DDR pathways (Dutta et al., 2012; Tsirpanlis, 2008; Gorospe and Abdelmohsen, 2011; Pacher and Szabo, 2007).

DNA damage/telomere erosion damps mitochondrial function through inhibiting the SIRT1 de-acetylation activity. SIRT1 activates PGC-1$\alpha$ pathway by deacetylating PGC-1$\alpha$. PGC-1 is the master transcriptional regulator of the pathway inducing removal of dysfunctioning mitochondria, and its biogenesis and activity via a mechanism that needs functional telomeres and upstream activation of SIRT1 versus acetylated/phosphorylated p53. This new pathway involves specially a positive interplay between two DNA-closely associated key enzymes, PARP1 and SIRT1 (Dutta et al., 2012; Tessitore et al., 2014; Bai et al., 2011).

Premature aging or age-associated diseases can be the consequence of ROS-mediated DNA damage, in one side (Lopez-Otin et al., 2013), and over-activation of PARP1 accompanied by NAD+/ATP depletion and SIRT1 inhibition, on the other side (Konstantinidis et al., 2012).

Importantly, the major tumor suppressor pathways p53/p21/Rb and p16/Rb, as hallmarks of SIPS, are activated in human, as a result of PARP over-activation and in response to DDR machinery (Rodier and Campisi, 2011; Tsirpanlis, 2008; Gorospe and Abdelmohsen, 2011; Maes et al., 2009). Oxidative-mediated DNA damage/telomere attrition induces senescence, via p53/p21/p16/Rb pathways, as critical signaling initiate, execute and maintain the senescence (Lopez-Otin et al., 2013; Gorospe and Abdelmohsen, 2011).

Conclusively, DDR machinery needs a network of signaling to induce cell cycle arrest, DNA repair or apoptosis. Early signaling events are initiated by PARP activation which alarms and induces the activation of all three major pathways involved in DNA repair; ATM/Chk1, ATR/Chk2 kinases, and DNA-PKc, the phosphorylation of H2AX, and the recruitment of the complexes Mre11-Rad50-Nbs1 or Rad9-Hus1-Rad1 at the level of damaged sites (Rodier and Campisi, 2011; Tsirpanlis, 2008; Leung et al., 2011; Pacher and Szabo, 2007; Yao and Ventura, 2011; Moskwa et al., 2011a; Csiszar et al., 2005; Bai et al., 2011).

In progenitor cells, Chk1/2 kinases activate the Cdc25 phosphatase whose activation is needed for activation of CDK 4/6 and especially for the G1/S transition. Phosphorylated Cdc25a is functionally inactivated and prevents the activity of CDKs which is needed for G1/S transition, S-G2/M progression.

While, ATM/ATR-dependent p53 phosphorylation triggers G1/S/-G2/M checkpoints, with consequent transcriptional activation of genes involved in cell cycle arrest. At this point, if DNA lesions are adequately repaired, cells can proceed to proliferate again and to inactivate DNA damage checkpoints; otherwise due to PARP over-activation in a feed-forward loop manner, they would undergo senescence then apoptosis (Rodier and Campisi, 2011; Tsirpanlis, 2008; Gorospe and Abdelmohsen, 2011; Pacher and Szabo, 2007; Bai et al., 2011; Tessitore et al., 2014). Notable, activation of acetylated/phosphorylated p53 is mediated by all three major DDR pathways (Tsirpanlis, 2008; Gorospe and Abdelmohsen, 2011),

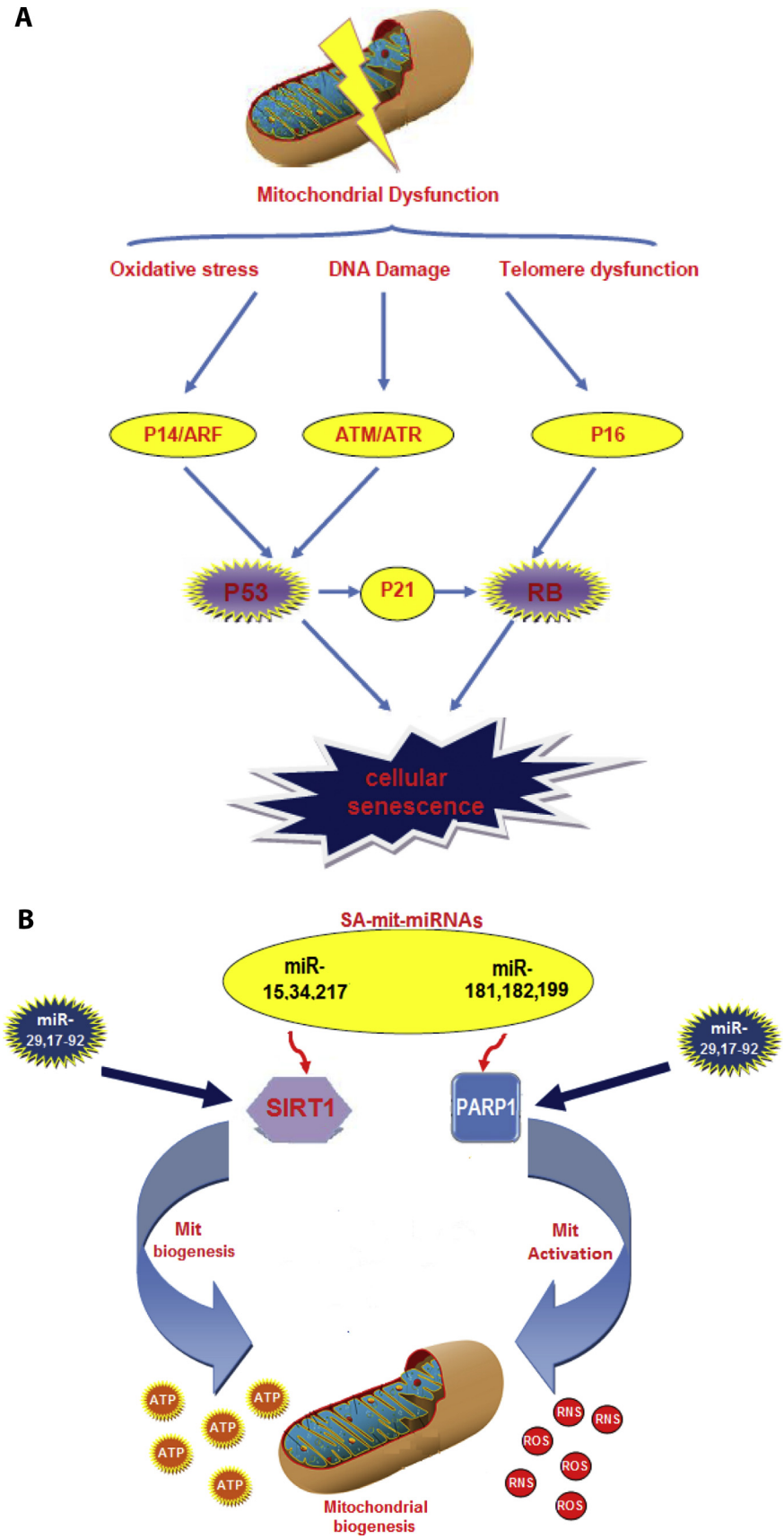


**Fig. 1.** Cellular senescence pathways and SA-miRNAs. (A) Mitochondrial dysfunction leads to excessive ROS production, DNA damage and telomere dysfunction which stimulate a number of signaling pathways that result in the p53/p21/p16/Rb over-activation and the induction of cellular senescence. Rb is activated by either p21 or p16. Phosphorylation and activation of p53 is mediated by ataxia telangiectasia mutated (ATM)/ATM-related (ATR) involved in the DNA damage-response pathway or by alternative reading frame

however, the primary role for switching on DDR machinery is referred to PARP1/SIRT1 system to maintain DNA integrity (Konstantinidis et al., 2012; Pacher and Szabo, 2007).

Noteworthy, p53 activation inhibits IGF-1 signaling, by activating inhibitors of the IGF-1 pathway, including the tumor suppressor PTEN and the IGF-1 factor binding protein 3 (IGFBP3) (Maes et al., 2009).

IGF-1/PI3K signaling is an anti-apoptotic pathway through crosstalk with downstream components of SIER1/PGC-1α and transcription factor (TF) family FOXO-p53 pathway (Lopez-Otin et al., 2013; Motohashi et al., 2013; Li et al., 2012).

Accordingly, miRNAs by targeting multiple components of PI3K/Akt and DDR pathways are able to maintain cells in an irreversible quiescent state or vice versa are able to reprogram senescence (Motohashi et al., 2013; Li et al., 2012; Pacher and Szabo, 2007; Bonifacio and Jarstfer, 2010).

Recent reports specially describe a crosstalk between aging-related inflame, mitochondria and IGF-1 pathways via ROS signaling, to regulate longevity (Rippo et al., 2014; Li et al., 2012). The mentioned relationships are all trough inflam/mit-miRNAs, that specially controls mitochondrial function/dysfunction and heart senescence (Lopez-Otin et al., 2013; Gorospe and Abdelmohsen, 2011; Ito et al., 2010; Ikeda et al., 2007; Vasa-Nicotera et al., 2011).

### 2.3. SIRT/PARP system, as a switcher in DDR and cell fate decision pathways

Data indicate that the major molecular mechanisms responsible for CVD are telomere dysfunction, DNA damage and cellular senescence. We are sure that eroded telomeres generate a persistent DDR, which initiates aging and maintains the senescence-associated growth arrest (Chimenti et al., 2003; Seeger et al., 2013; Tsirpanlis, 2008; Torella et al., 2004).

DDR is the major consequence of mitochondrial dysfunction and abnormal oxidant generation during aging. DDR is the main impact of oxidative stress to be responsible for heart senescence (Dutta et al., 2012; Pacher and Szabo, 2007).

SIRT/PARP system has been accordingly defined as potential switching between aging/anti-aging processes in human, yeast, flies, and worms, whose SIRT/PARP has a remarkable longevity activity (Lopez-Otin et al., 2013; Csiszar et al., 2005).

In CHF associated with advanced aging or hypertension, ROS accumulation causes oxidative/nitrosative stress which invokes PARP1 activation in CVS (Yao and Ventura, 2011). PARP1 is the key modulator of oxidative/nitrosative stress in CVS. It is also the main regulator of SIRT1, which hints the particular role of PARP1 in reverting senescence and longevity (Staszel et al., 2011; Tabuchi et al., 2012; Canto and Auwerx, 2011; Bai et al., 2011). Oxidative/nitrosative stress triggers PARP activation which is able to induce a positive feed-back loop for component over-activation.

Over-activation of PARP, consequently leads to depletion of the cellular stores of its substrate NAD+ and impairing SIRT1/mitochondrial function which eventually makes condition worse and would result in death by necrosis (Gorospe and Abdelmohsen, 2011; Pacher and Szabo, 2007). But, moderate PARP activation facilitates the efficient repair of DNA damage and is intended to rescue organ from the pathological consequence of an uncontrolled mechanism posing cells to dying, a risk for neighboring cells to pro-inflammatory condition (Fig. 3A and B) (Tessitore et al., 2014; Pacher and Szabo, 2007; Csiszar et al., 2005).

Accordingly, PARP1/SIRT1 system is strongly conserved in eukaryotes and shares the particularity of using NAD + as a co-substrate. While PARP1 over-activities confront SIRT1 (Lopez-Otin et al., 2013; Canto and Auwerx, 2011; Kim et al., 2014), activation of SIRT is protective in aging-related disorders (Sharma et al., 2013; Zhang and Kraus, 2010). In particular, SIRT forms a complex with DDR machinery to deacetylate H3K9Ac and H3K56Ac. In humans, suppressing SIRT emerges DNA damage hypersensitivity and also develops a severe premature aging (Sharma et al., 2013; Zhang and Kraus, 2010).

Telomeres are also be protected by PARP which is localized on telomeres and are involved in telomere maintenance. Then, functional defect of PARP is characterized by genomic instability, and causes the premature aging diseases (Csiszar et al., 2005). Modulating PARP-1 activation protects against hypertrophy response, heart failure, and cardiovascular dysfunction (Yao and Ventura, 2011). PARP1 is linked directly to cellular redox status and oxidative stress by regulating FOXO, the stress resistance TF which extends lifespan in *Caenorhabditis elegans* (Dutta et al., 2012; Lopez-Otin et al., 2013; Canto and Auwerx, 2011; Potus et al., 2014; Kim et al., 2014).

Additionally, SIRT1 is also activated under stress conditions and has the ability to confront the stress and apoptosis by deacetylating a number of enzymes and transcriptional switchers, specially PGC-1α, NF-kB, FOXO, p53, and histones (Zhao et al., 2010; Canto and Auwerx, 2011; Csiszar et al., 2005; Bai et al., 2011). In contrast to p53, deacetylated/activated state of PGC-1α/FoxO causes transcription activation of mitochondrial biogenesis or its renovation. Noteworthy, SIRT1 regulates energy homeostasis by controlling the acetylation status and activity of a number of enzymes and transcriptional regulators (Dutta et al., 2012; Lopez-Otin et al., 2013; Menghini et al., 2009; Bai et al., 2011).

PARP acts as the sensor waking up DDR machinery to maintain chromatin integrity, while SIRT acts a sensor controlling trophic and bioenergetic pathways for mitochondrial biogenesis and removal of aged ones (Gorospe and Abdelmohsen, 2011; Tessitore et al., 2014; Bai et al., 2011; Zhang and Kraus, 2010). DDR/telomere erosion damps mitochondrial function through decreasing the activity of SIRT1/PGC-1α, a master transcriptional regulatory pathway in mitochondrial biogenesis and activity versus p53. This new pathway involves specially the inside interplay of SIRT1/PARP1 system (Pacher and Szabo, 2007; Canto and Auwerx, 2011; Potus et al., 2014).

Notable, SIRT activity is controlled by upstream PARP in three ways, 1) at SIRT promoter, 2) by post-translational modifications and 3) by NAD + availability. Notable, the Km of SIRT1 for NAD+ is considerably higher than concentration range of NAD + for PARP Km, implying that PARP over-activation can intriguingly compete and rate-limit SIRT1 activity (Canto and Auwerx, 2011).

Noteworthy, p53 activation as the most important DDR, is completely repressed by PARP1/SIRT1 system, while miR-34a as the

product of alternative ARF pathway, a stress-dependent response. (B) Over-expressed miR-217, 199, 181/182, 34, 15 targets a complex of several proteins essential for the DDR SIRT signaling. SA-miR-217, 19, 181/182, 34, 15 over-expression switches off the DDR and PARP/SIRT1 system completely, and leads cells to confront genome instability and permissive to senescence. Whereas in response to DNA damage and in relevance to aging processes, miR-17-92 and 29 acts for maintenance of genome integrity, through activating a wide variety of DDR proteins such as Chk1/2, p38, γ-H2AX and ATM, specially over-activating SIRT1 pathway. Activated deacetylase SIRT1 inhibits p53/p21/p16 pathway, while in a tight interconnection with PARP **e**specially in the heart orchestrating a complex of events including mitochondria biogenesis, enhanced antioxidant defenses, energetic metabolism to improve regeneration process.

main effector of p53 leads to down-regulation of SIRT1 (van Almen et al., 2011). Therefore, there is a double negative feed-back loop between p53/miR-34a and PARP1/SIRT1 system. Intriguingly, PARP over-activation activates p53/p16 versus SIRT1, while its moderate activation activates SIRT1 versus p53/p16. SIRT1 in turn as switcher inactivates p53 through deacetylating p53, thereby subsequently represses miR-34. An area worthy of interest is the relationship of SA-mit-miRNAs with aging switcher system SIRT1/PARP1 (Rippo et al., 2014; Zhao et al., 2010; Tabuchi et al., 2012; Ito et al., 2010; Zhang and Kraus, 2010).

Therefore, reactivation of SIRT can act as a protective switcher in CVS aging and related disorders. Furthermore, PARP-1 moderate activation holds on cardiomyocyte senescence while leads to heart failure protection, as well as, inducing SIRT1 activity (Zhang and Kraus, 2010; Yao and Ventura, 2011; Bai et al., 2011).

## 3. MicroRNAs as fine-tuner switchers of the cell pathways

Accordingly, cell fate decisions and development of cellular phenotypes are controlled by a regulatory system of small ($\approx$22 nt) non-coding miRNAs which usually inhibit but may rarely increase gene expression at the posttranscriptional levels (Menghini et al., 2009; Magenta et al., 2011; Tabuchi et al., 2012).

Via partial complementary of the 5′-seed sequence ($\approx$7 nt) to the 3′-UTR of the mRNA target, miRNAs bind their targets which guides to the loading of miRNA-mRNA-protein complex, the miRNA-induced silencing complex (Fig. 2A and B). In the silencing complex, the mRNA target is degraded or its protein translation is inhibited (Leung et al., 2011; Guo et al., 2010). Theoretically, a specific miRNA can target different mRNAs that each is a part of a shared pathway, which makes great versatility to miRNA-mediated gene regulation (Schraml and Grillari, 2012; Guo et al., 2010). Noteworthy, the repression by some miRNAs is especially strong when the level of the intracellular target mRNA is low, but weak when the level is high, meaning a miRNA can act as a switcher or a fine-tuner depending on the mRNA target level (Zhao et al., 2010; Matkovich et al., 2010; Noren Hooten et al., 2010). Moreover, the protein level of a target mRNA can be much lower when it is co-targeted to multiple miRNAs than when it is targeted to a single miRNA (Ugalde et al., 2011; Tessitore et al., 2014).

In addition, different mRNAs that share the same target site for a specific miRNA can compete for binding to the miRNA and thereby mutually influence the expression of each other. This may result in the different outcomes of the same miRNA in distinct cell types, due to expression of a diverse set of mRNA targets (Wei et al., 2013).

The miRNA targets are commonly the key regulatory proteins which function as switchers for distinct pathways, including transcription factors which are a major component of a feed-forward loop, a mutually negative or positive feedback loop (Rippo et al., 2014; Menghini et al., 2009; Sharma et al., 2013; Tabuchi et al., 2012). Thus, small changes in the target level can have large physiological influence. A special miRNA can thereby confer robustness to biological processes, such as cell fate switchers, by suppressing aberrant transcripts (Gorospe and Abdelmohsen, 2011; Ugalde et al., 2011; Lafferty-Whyte et al., 2009). Hence, miRNA deregulation would lead numerous biological disorders, including premature aging and age-related pathological diseases (Zhang et al., 2012; Sharma et al., 2013; Maes et al., 2009; Ito et al., 2010; Martinelli et al., 2014; Zhu et al., 2011).

Even more, epigenetic modifications, such as DNA methylation or histone acetylation, is controlled by miRNAs, by directly/indirectly targeting components of the epigenetic machinery, to induce global changes in the gene expression pattern. All these mechanisms may need to be considered to interpret the effects of miRNAs in atherosclerosis (Lopez-Otin et al., 2013; Gorospe and Abdelmohsen, 2011; Ugalde et al., 2011; Tessitore et al., 2014).

For example, miR-29 induces DNA hypomethylation by targeting distinct DNA methyltransferases (DNMT3) that links miR-29 to aging, since epigenetic alterations are characteristic features of aging and atherosclerosis process (Ugalde et al., 2011; Limana et al., 2005; Varga et al., 2013).

MiRNAs are able to induce DDR and cell cycle arrest or apoptosis. They take part actively in regulating DDR machinery to preserve the genomic integrity via regulating a network of DDR signaling pathways (Tessitore et al., 2014; Neijenhuis et al., 2013).

Moreover, miR-34 and miR-15 as switchers to cellular senescence, repress the key longevity pathway SIRT1/PCG-α/FOXO/IGF-1 (Fig. 2B) (Dutta et al., 2012; Lopez-Otin et al., 2013; Gorospe and Abdelmohsen, 2011). Over-expression of SIRT improves the regenerative capacity of aged human stem cells. Also, data implies the essential role of SIRT1 in compelling with IGF-1 system for healthy aging (Maes et al., 2009; Zhang and Kraus, 2010; Canto and Auwerx, 2011).

Even more, IGF-1 is a direct target of miR-1 which in ventricular cells can induce CPC apoptosis in a mechanism mediated by miR-1/oxidative stress (Li et al., 2012).

Finally, in vivo profiling of miRNAs over-expressed in old versus young humans defines differentially expression patterns in old individuals. The putative targets of the most differentially expressed miRNAs are now identified to be in particular the components of H2AX, c-Kit, IGF-1/PI3K pathway, mitochondrial biogenesis and DDR pathway, all of which must be up-regulated with advancing age (Seeger et al., 2013; Motohashi et al., 2013; Li et al., 2012; Staszel et al., 2011; Menghini et al., 2009; Tabuchi et al., 2012; Tessitore et al., 2014; Neijenhuis et al., 2013; Ikeda et al., 2007; Chen et al., 2012a).

### 3.1. The important role of miRNAs in DDR pathway of aging

To counteract age-related chromatin disturbances and senescence, cells have evolved multiple interacting DNA repair mechanisms, while PARP activation stays upstream of which is needed (Leung et al., 2011; Pacher and Szabo, 2007; Yao and Ventura, 2011; Moskwa et al., 2011a; Csiszar et al., 2005). In response to oxidative stress and inflammatory injury, DNA repair involves PARP1 activity to recruit and assemble the components of DDR machinery, but its over-activation in a feed-forward loop manner can eventually confront SIRT1 activation (Canto and Auwerx, 2011; Potus et al., 2014; Kim et al., 2014).

Contemporary, PARP over-activation depletes cells from NAD the cofactor needed for SIRT1 activity, which ultimately leads to senescence responses and apoptosis. Otherwise upon PARP over-activation, cells undergo apoptosis due to over-expression of senescence-associated (SA) miRNAs such as miRNA-34a through p53 activation. There is a double-positive feedback loop between SA-miRNAs over-expression and PARP over-activation (Canto and Auwerx, 2011; Potus et al., 2014; Kim et al., 2014).

However, SIRT1 try to control cell functions by linking NAD + metabolism to signaling pathways, besides regulating the chromatin structure and transcription factors (Zhang and Kraus, 2010).

SIRT1 has a tight interconnection with DDR switcher PARP (Canto and Auwerx, 2011; Kim et al., 2014). Especially in the heart, the mechanisms of mitochondrial free radical generation is controlled by SIRT1, which deacetylates and activates PGC-1α pathway for orchestrating a complex of events including mitochondria biogenesis, enhanced antioxidant defenses, energetic metabolism and improved fatty acid oxidation to regenerate NAD+/ATP (Lopez-Otin et al., 2013; Magenta et al., 2013; Zhang and Kraus,

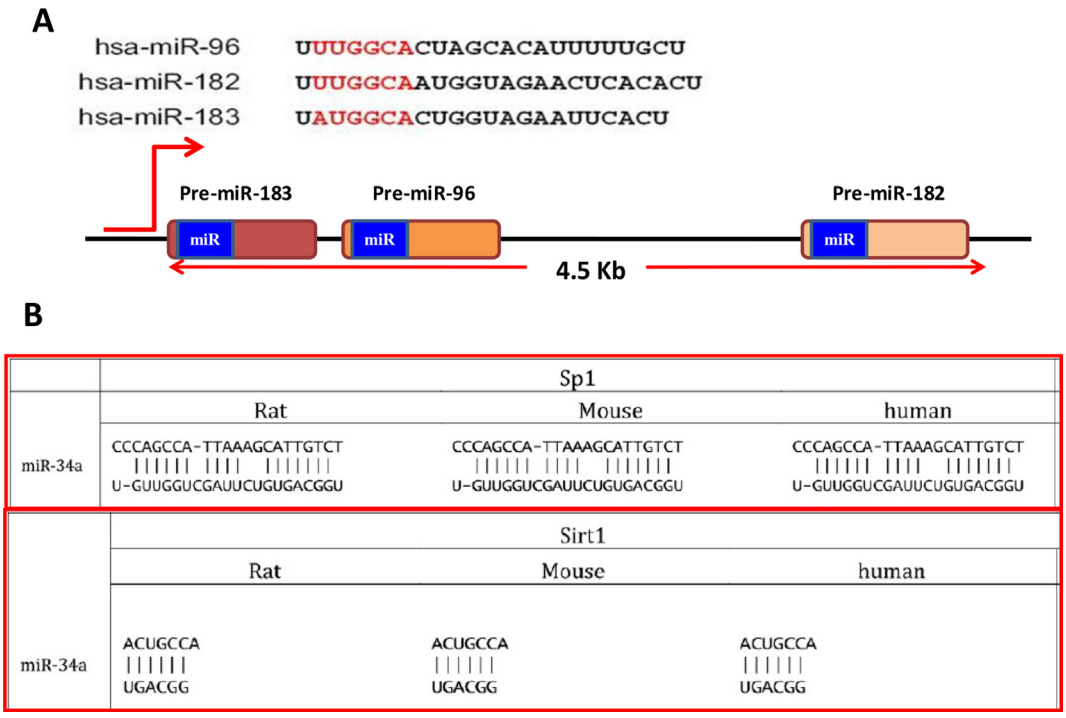


**Fig. 2.** Here is a Schematic representation of miRNA 5′-seed sequences which target sequences on 3′-UTRs of mRNAs cross species. A) The possible target sites of Sp1/Sirt1 (rat, mouse and human) by miR-34a. B) The sequences of mature miR-182 cluster (miR-182, -96, -183). Accordingly, color-coded boxes are pre-miRNAs in the cluster, while blue boxes indicate mature miRNAs. The 5′-seed sequences highlighted in red are also shown in represented miR-182s [The picture is taken from Yao and Ventura (2011)].

2010).

At this point, if DNA lesions have been adequately repaired, cells can proceed to proliferate again and to inactivate DNA damage checkpoints (Rodier and Campisi, 2011; Konstantinidis et al., 2012; Tsirpanlis, 2008).

Importantly, the ATM/ATR-dependent p53 pathway is a moderate and relatively DDR slow response, which consequently switches on different cell cycle checkpoint kinases and genes involved in cell renovation (Tessitore et al., 2014). In response to DNA damage, the mRNA expression patterns undergo significant modifications which can be due to miRNA-mediated gene regulation and their fundamental role in posttranscriptional regulation of mRNAs. The SA-miRNAs target DDR machinery directly/indirectly (Tessitore et al., 2014; Chen et al., 2012a). Interestingly, among SA-miRNAs that prevent genomic renovation and cell viability, miR-15, 34, 181/182, 199, 217 are associated with dysfunction of PARP/SIRT1 system (Fig. 1B) (Ugalde et al., 2011; Tessitore et al., 2014; Martinelli et al., 2014; Moskwa et al., 2011b; Bisso et al., 2013a). The senescence-associated (SA) miR-15, 34, 181, 199, 217 are all the major repressors of SIRT1 in mammalian cells (Fig. 2B), all of which are mainly associated with CVD in humans (Kim et al., 2014; Staszel et al., 2011; Menghini et al., 2009; Tabuchi et al., 2012; Song et al., 2010).

Among them, SA-miR-181/182 is highly expressed miRNAs in cardiac mitochondria, even more than 2-fold abundant than total heart-mitochondria RNAs (Tessitore et al., 2014; Moskwa et al., 2011a; Bisso et al., 2013a; Das et al., 2012). SA-miR-181/182 is a potential signature for their ability to target multiple components of DDR pathway, whose over-expression represses PARP/SIRT1 function and causes cells to confront genome instability and permissive to senescence (Fig. 1B) (Li et al., 2009; Yao and Ventura, 2011; Bisso et al., 2013a; Krishnan et al., 2013). Other validated mRNA targets of miR-181/182 have been identified to include RGS, FOXO and Chk1/2 kinases, all of which are enriched in stem cells and key components of cell cycle progression (Krishnan et al., 2013). Notable, the miR-181/182-related signaling is the main inducer of p53/p21/RB pathway. They arrest cells at G1/S transition, by targeting CDK6/CDK4 the in-activators of RB and inducers for G1/S transition.

Remarkable, repression of the CDKs by normal concentration of miR-15, 34, 181/182 would lead to the activation of RB and the cell cycle arrest, enabling efficient DNA repair. But, over-expressed miR-181/182 targets a complex of several proteins essential for the DDR (p27, REV1 and RAD51), which make cells ready for progression to senescence (Tabuchi et al., 2012; Rippo et al., 2014; Krishnan et al., 2013; Wang et al., 2012a).

In such circumstances accordingly, human miR-15, 23, 34, 30, 106, and 181/182 are even more up-regulated by senescence p53 pathway. Among them, miR-217, 34 and 15 directly target the SIRT1 pathway, versus p53/p21 pathway (Zhao et al., 2010; Tessitore et al., 2014; Maes et al., 2009; Porrello et al., 2011; Zhu et al., 2011).

Over-expression of miR-217, 181, 34, 15 switches off the PARP/SIRT1 system completely, whereby leading to p53 over-activation and aggravating ROS production pathways (Canto and Auwerx, 2011; Bai et al., 2011).

Conversely, miR-29 and miR-17-92 act as key regulators of genome integrity in response to DNA damage and in relevance to aging processes, through activating a wide variety of DDR proteins such as Chk1/2, γ-H2AX and ATM (Fig. 1B) (Zhao et al., 2010; Tessitore et al., 2014; Ugalde et al., 2011).

In mouse model of muscle oxidative stress and mitochondrial dysfunction, miR-149 could rescue mitochondria and induce its biogenesis, by keeping on PARP/SIRT1 activation, whereby strongly activates SIRT-1/PGC-1α pathway (Mohamed et al., 2014).

Otherwise in human vascular system, down-regulation of miR-204 in contemporary to reduced miR-126 levels has been attributed to switching off SIRT1 activity (Potus et al., 2014).

Concluding, a low concentration of a discrete set of human

miRNAs such as miR-15, 34, 181/182, 199, 217 would lead to the efficient DNA repair, while their over-expression targets several proteins essential for DDR and PARP/SIRT pathway and damps its activity and subsequently causes cells to confront genome instability and permissive to senescence (Fig. 1) (Tessitore et al., 2014; Leung et al., 2011; Neijenhuis et al., 2013; Chen et al., 2012a; Pacher and Szabo, 2007; Moskwa et al., 2011a; Csiszar et al., 2005; Moskwa et al., 2011b; Bisso et al., 2013a; Krishnan et al., 2013; Wang et al., 2012a; Wu et al., 2013).

### 3.2. The important role of miRNAs in redox signaling pathway of aging

The oxidative stress and mitochondrial damage are responsible for triggering the increased cardiomyocyte death which is accompanied by hypertrophy of remaining cells and impaired structure of extracellular matrix (ECM), thereby leading to ventricular remodeling and reduced cardiac contractility (Dutta et al., 2012; Magenta et al., 2013; Topkara and Mann, 2011). Meanwhile, cardiac hypertrophy leads to a mismatch in oxygen supply and demand, which further contributes to dysfunction of cardiomyocytes. In response to these chronic stressors, the aged heart undergoes a complex pathophysiological changes that finally progresses to symptomatic heart failure (Chimenti et al., 2003; Menghini et al., 2013; Huang et al., 2013).

In premature model of aging, oxidative stress links mitochondrial to telomere shortening and to p53/SIRT-dependent repression of PGC-1α and PGC-1β pathway. As a consequence, telomere attrition represent a primary instigator of mitochondrial decay, which in turn would lead to further ROS production and sustained p53 activation (Dutta et al., 2012; Lopez-Otin et al., 2013; Rippo et al., 2014; Magenta et al., 2013).

SIRT1 activates components of the respiratory chain, tricarboxylic acid cycle, ketogenesis, and fatty acid b-oxidation (Dutta et al., 2012). SIRT1 also directly control the rate of ROS production by deacetylating manganese superoxide dismutase, a major mitochondrial antioxidant enzyme would increase maximum life span in virtually every species (Lopez-Otin et al., 2013; Csiszar et al., 2005).

SIRT1 is a well-established enzyme for its role as the longevity-associated protein in coronary artery disease (Canto and Auwerx, 2011; Staszel et al., 2011; Tabuchi et al., 2012; Menghini et al., 2009).

In the other side, lines of evidence indicate a discrete set of miRNAs (mir-17-92, 29, 34 146, 155, 181 and 217) as “inflame-aging” signatures whose deregulation is specifically linked to mitochondria dysfunction. The “inflame-mit-miRNAs” cause systemic chronic inflammation and provide a biological background favoring susceptibility to age-related diseases (Rippo et al., 2014; Li et al., 2009; Qin et al., 2012; Vasa-Nicotera et al., 2011).

The mit-miRNAs are expressed in all human cell types and regulate mitochondrial-mediated aging, through targeting a large number of mitochondrial proteins crucial in energy metabolism, mitochondrial transport and apoptosis (Rippo et al., 2014; Menghini et al., 2009). However, some other studies has additionally introduced let7, mir-15, 133, 106, 182 and 221 as mit-miRNAs, to modulating mitochondrial activity in different species and cell types (Gorospe and Abdelmohsen, 2011; Menghini et al., 2013). Looking at each individual miRNA, we can see those that have more support for their roles in senescence than others (Magenta et al., 2013; Menghini et al., 2013; Noren Hooten et al., 2010; Tian et al., 2014).

A special panel of inflam-mit-miRNAs consisting of miR-146a, 181a, 34a, has been proposed to induce mitochondria aging (Rippo et al., 2014). Otherwise, inflame-miR-146a in combination with miR-25 has been assumed anti-aging by suppressing over-activation of NOXs (Varga et al., 2013; Vasa-Nicotera et al., 2011). NOXs act as putative signaling enzymes which show strong up-regulation during CVS senescence and are causative of oxidative/nitrosative stress (Braunersreuther et al., 2013). Remarkable, over-expressed inflame-miR-155 is also upstream regulator of NOXs and is required to induce oxidative/nitrosative stress and is needed for lipid uptake in oxLDL-activated macrophages (Tian et al., 2014).

SA-miR-15, 34, 181, 199, 217 are all the major repressors of SIRT1 in mammalian cells, all of which are mainly associated with CVD in humans (Kim et al., 2014; Staszel et al., 2011; Menghini et al., 2009; Tabuchi et al., 2012; Song et al., 2010). SIRT1 in turn as switcher has the ability to confront the stress and apoptosis by deacetylating a number of enzymes and transcriptional switchers, specially PGC-1α, NF-kB, FOXO, p53, and histones (Zhao et al., 2010; Canto and Auwerx, 2011; Csiszar et al., 2005; Bai et al., 2011). In contrast to p53, deacetylated/activated state of PGC-1α/FOXO causes transcription activation of mitochondrial biogenesis or its renovation pathways. Noteworthy, SIRT1 regulates energy homeostasis by controlling the acetylation status and activity of a number of enzymes and transcriptional regulators (Dutta et al., 2012; Lopez-Otin et al., 2013; Menghini et al., 2009; Bai et al., 2011).

Finally, the area worthy of interest is the relationship of SA-mit-miRNAs with aging switcher system SIRT1/PARP1. The tight association of PARP1/SIRT1 system with inflame-mit-miRNAs which was mentioned earlier, emerges them as key modulators of oxidative/nitrosative stress progressed to CVS dysfunction (Pacher and Szabo, 2007; Csiszar et al., 2005; Bai et al., 2011). Both of them are key modulators of inflame-mit-miRNAs expression and vice versa. PARP1/SIRT1 system is influenced directly/indirectly by inflam-mit-miRNAs whose deregulation would afterwards exhibit pathology conditions, due to PARP over-activation in a feed-forward loop manner which depletes CVS cells from ATP/NAD (Tessitore et al., 2014; Neijenhuis et al., 2013; Chen et al., 2012a; Moskwa et al., 2011a; Csiszar et al., 2005; Krishnan et al., 2013; Bisso et al., 2013b; Mohamed et al., 2014).

Besides regulating longevity and gene expression, PARP1/SIRT1 system gives a reasonable expectation that they are central players in cell senescence and pathogenesis of age-related diseases (Leung et al., 2011; Canto and Auwerx, 2011; Pacher and Szabo, 2007; Csiszar et al., 2005; Kim et al., 2014; Potus et al., 2014; Bisso et al., 2013b).

## 4. The expression patterns of miRNAs in CVS aging

With advancing age, there is a gradual change in the expression of some special miRNAs, whose abrupt deregulation is tightly associated with senescence and age-related diseases (Chimenti et al., 2003; Torella et al., 2004; Motohashi et al., 2013; Noren Hooten et al., 2010). In profiling miRNA expression in PB from healthy individuals, researchers found that in older participants (~60 y) compared to younger participants (~30 y), the miRNA signatures; miR-15, 17-92, 23, 29, 34, 145, 181/182, 199, 302 are most progressively down-regulated in aged-healthy humans, which is interestingly consistent with data from C. elegans (Noren Hooten et al., 2010). Whereas, a clinical study aiming to analyze SA-miRNA signatures in PB of young healthy controls (~25 y) versus aged healthy controls (~64 y), and age-matched chronic heart failure (CHF) patients (64 + 11y), observed that SA-miRNAs are merely changed in aged-healthy individuals versus young healthy ones, while, the changes in SA-miRNA signatures are far more profound in aged-matched CHF patients, in comparison to y/o/healthy individuals (Seeger et al., 2013).

In age-advancing humans according to consistent evidence, miRNA signatures (hsa-miR-1, 133, 17-92, 34, 15, 29, 181/182, 199,

155, 217), appear with distinct patterns of expression. The signatures are demonstrating a high level of concordance between experimental/animal models of CVD with those in humans (Seeger et al., 2013; Topkara and Mann, 2011; Noren Hooten et al., 2010; Bonifacio and Jarstfer, 2010; Chilton et al., 2014; Tan et al., 2009; Naga Prasad et al., 2009).

For instance, genome-wide profiling of miRNAs in human heart failure obtained from left ventricular samples belonging to control healthy, ischemic cardiomyopathy (ICM), dilated cardiomyopathy (DCM) individuals, confirms the results of other studies. There is marked over-expression of SA-miR-15, 34, 181, 199, 214 in compare to under-expression of miR-1, 17-92, 29, 126, 133 in patients prone to heart failure (ICM & DCM subjects). Importantly, miRNA profiles correctly grouped samples by their clinical diagnosis, indicating that miRNA expression profiles are distinct between diagnostic groups (Ikeda et al., 2007).

Plus the combined effect of multiple miRNAs could pose a notable impact on a broad range of targets in aging pathway, the majority of miRNA signatures display similar expressing pattern, likely to be regulated by a common signaling mechanism (Zhang et al., 2012; Maes et al., 2009; Martinelli et al., 2014; Ikeda et al., 2007).

The ratio between over/under-expressed miRNAs is generally far higher in clinical/experimental model of CVD than healthy ones, showing aberrantly deregulated SA-miRNAs with advancing in senescence (Zhang et al., 2012; Noren Hooten et al., 2010; Seeger et al., 2013; Bagnall et al., 2012).

In agreement, heart samples from end-stage heart failure patients in compare with healthy ones, exhibited highly up-regulated SA-miRNAs such as miR-181, 145 and 214 versus miR-29, in all failing hearts (Seeger et al., 2013). Also, in global miRNA profiling of the mouse ventricles during development of severe hypertrophic cardiomyopathy and progression to heart failure, fold change expressions show abruptly up-regulation of SA-miR-34, 146, 199, 214 versus miR-1, 133, 150 (Bagnall et al., 2012).

Despite some exceptions, abruptly under/over-expressed miRNAs in premature senescence or late in heart failure, have been generally revealed to be (miR-1, 17-92, 29, 133)/(miR-15, 34, 146, 155, 181/182, 217), respectively (Figs. 1B and 3A & B) (van Rooij et al., 2008; Ikeda et al., 2007; Seeger et al., 2013; Schroen and Heymans, 2012; Rippo et al., 2014; Naga Prasad et al., 2009).

Notably, miR-29 and miR-17-92 act as key regulators of chromatin structure in response to DNA damage and in relevance to SIRT1-PGC-1α pathway, through activating a wide variety of chromatin-associated proteins such as Chk1/2, γ-H2AX and ATM (Fig. 3A and B) (Zhao et al., 2010; Tessitore et al., 2014; Ugalde et al., 2011).

Considerably, two inflam-miR-155 and 146 that modulate inflammatory responses in macrophage-derived foam cells and ECs during early atherogenesis, showed no significant differences between y/healthy and o/healthy volunteers, while their expression levels have been reported to be markedly reduced in CHF patients (Seeger et al., 2013; Schroen and Heymans, 2012; Vasa-Nicotera et al., 2011; Tian et al., 2014).

Additionally, several reports implicate markedly increased expression of miR-181 and miR-146 in both the plasma and PBMCs from patients with acute coronary syndrome, as well as, in atherosclerotic plaques and PBMCs from patients with CAD (Seeger et al., 2013; Menghini et al., 2013). Conversely, miR-126 and miR-17-92 are down-regulated in samples from CAD patients. Therefore the number of EPCs is reduced in atherosclerotic plaques of CAD patients due to deregulation of these miRNAs (Schroen and Heymans, 2012; Rippo et al., 2014; Menghini et al., 2013). In cardiac biopsies obtained from young (~30 y) and old (~60 y) healthy humans in comparing to old patients (~60 y) with cardiomyopathy, moderately decrease of miR-17-92 family was observed in old (~60 y) healthy participants in compare to young subjects, while markedly reduction was found in old patients. The expression changes are specific for cardiomyocytes and are absent in cardiac fibroblasts (van Almen et al., 2011). Noteworthy, the miR-17-92 cluster (miR-17, 18, 19, 20 and 92), has been implicated as switcher not only in cellular proliferation, but also in cellular senescence. Abrupt down-regulation of the cluster miR-17−92 has been implicated in failure-prone mice plus in human failing heart, but not in healthy aging heart (Zhang et al., 2012; Ikeda et al., 2007; Bagnall et al., 2012).

### 4.1. The important role of miRNAs in senescence of CVS

Data imply that miRNA expression changes are associated with aging and senescence, such as gradual up-regulation of miR-34a in aging, and or gradual down-regulation of miR-17-92. Cellular senescence is characterized with an irreversible growth arrest and is defined as a markedly decreased expression of the cluster family miR-17-92, 23, 29 which target SA-genes such as p21 (miR-17-92), MKK4 (miR-24, miR-25) and p16 (miR-24) (Fig. 1A and B) (Li et al., 2009; Noren Hooten et al. (2010); Lafferty-Whyte et al. (2009)). Assuming, the cluster miR-17-92 in a negative feedback loop suppresses the senescence (Lopez-Otin et al., 2013; Li et al., 2009; Noren Hooten et al., 2010; Bonifacio and Jarstfer, 2010; Chilton et al., 2014). Additionally, the senescence-specific pathway p16/RB and p53/p21, is switched off by proliferating-associated cluster miR-17-92 and miR-23 (Rodier and Campisi, 2011; Seeger et al., 2013; Gorospe and Abdelmohsen, 2011). Whereas, miR-34a as an established tumor-suppressor potentially switching on both pathways to trigger senescence (Gorospe and Abdelmohsen, 2011; Zhao et al., 2010; Staszel et al., 2011; Tabuchi et al., 2012). Also in combination with other miRNAs, miR-15 contributes to progression toward senescence via the p16/RB pathway (Figs. 1B and 3) (Gorospe and Abdelmohsen, 2011).

Senescence is associated with the increased levels of p16, whereby leads to inhibition of HDAC activity (e.g. SIRT1). The p16/RB pathway contributes to up-regulation of miR-15, 34, 181/182, 199, which in turn induces senescence pathways (Figs. 1B and 3A & B) (Tsirpanlis, 2008; Lafferty-Whyte et al., 2009; Bonifacio and Jarstfer, 2010; Bagnall et al., 2012).

Particularly, the best-characterized miRNAs assumed to be up-regulated during SIPS of CVS is supposed to be miR-181/182 (Li et al., 2009; Motohashi et al., 2013; Leung et al., 2011; Pacher and Szabo, 2007; Yao and Ventura, 2011; Moskwa et al., 2011a; Csiszar et al., 2005; Das et al., 2012).

Interestingly, abrupt up-regulation of miR-181/182 has been implied in skin aging, whereby contributes to reducing levels of mRNA encoding retinoic acid receptor-γ (Li et al., 2009; Gorospe and Abdelmohsen, 2011).

In addition, results from young senescent human cells declare that the ratio of up/down-regulated SA-miRNAs in reversible cell cycle arrest increases stepwise to 1.6, whereas in irreversible cell cycle arrest/premature senescence elevates to 4.4. Whereby, each growth arrest state can be defined by its own distinct set of miRNA expression and some of them are shared among two states.

Noteworthy, among those shared in all growth arrest states, miR-34a is the most significant, followed by up-regulation of miR-15, miR-181/182, respectively (Gorospe and Abdelmohsen, 2011; Maes et al., 2009). Fold change in miR-34 levels specifically correlates, with senescence and with increase in the p21/p16 expression levels, beside the additional synergistic effect of miR-15 along with miR-181. Likewise, the similar sets of miRNAs represses IGF-1 pathway along with predicted targets functioning in DNA repair (Fig. 3A and B) (Rippo et al., 2014; Motohashi et al., 2013; Li et al.,

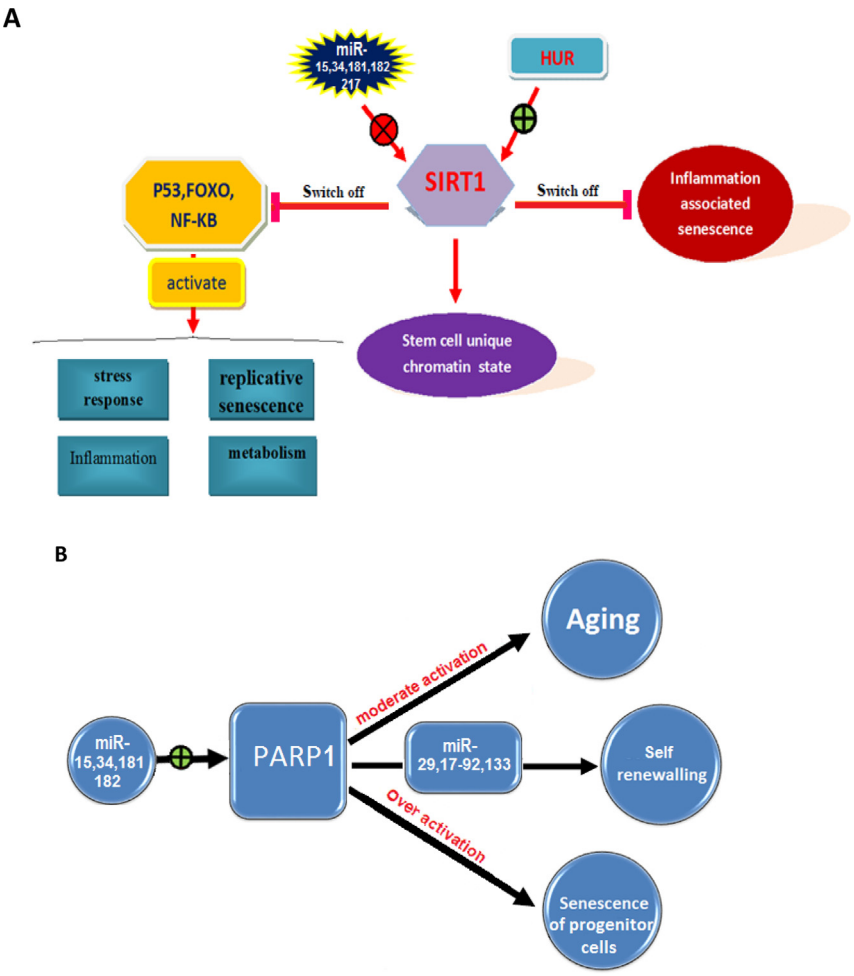


**Fig. 3.** The scheme illustrates functions of the well-known chromatin-remodeling system PARP1/SIRT1. (A) The function of SIRT1 and (B) PARP1 is regulated by inflame-mit-miRNAs. The intrinsic aging pathway involves mitochondrial/DNA damage responses that ultimately mediated senescence progression. (A) DNA damage/telomere erosion damps mitochondrial function through inhibiting the SIRT1-mediated PGC-1α pathway. SIRT1 has the ability to induce mitochondria biogenesis and renovation to confront senescence and apoptosis by deacetylating a number of transcriptional switchers; PGC-1α, NF-kB, FOXO, p53, and histones. (B) Defect of PARP1 is characterized by genomic instability, and causes the premature aging diseases. Otherwise, over-activated PARP1 causes impairing in SIRT1/mitochondrial function and progressive in senescence while, its moderate activation facilitates the efficient DNA renovation and is intended to rescue organ from the pathological consequence of an uncontrolled aging. SIRT1/PARP-1 coordinated activation acts as a protective switcher in CVS aging to holds off senescence and protect against heart failure. The inflame-mit-miRs (miR-15, 34, 181, 182, 217), but not chromatin-remodeling associated miRs (miR-17-29, 29, 133), are potential signatures targeting multiple components of SIRT1/PARP-1 system, which conferring PARP versus SIRT1 over-activation.

2012; Maes et al., 2009).

Noteworthy, some inflame-mit-miRNAs directly target DNA repair pathway and its components which lead to accelerating premature senescence of CVS (Figs. 1 & 3B) (Sharma et al., 2013; Pacher and Szabo, 2007; Tessitore et al., 2014; Menghini et al., 2009; Chen et al., 2012a; Krishnan et al., 2013; Mohamed et al., 2014).

Analysis of several studies demonstrate a discrete set of age-related miRNAs as inflam-mit-miRNAs (mir-15, 17-92, 29, 34, 146, 181/182, 199), which are differentially expressed during CVS aging and are tightly associated with its senescence (Figs. 1 & 3B) (Rippo et al., 2014; Qin et al., 2012; Menghini et al., 2013; Lafferty-Whyte et al., 2009).

Other miRNA signatures that have been associated with CVS senescence in human can be miR-143/145/146. Up-regulated miR-146 has been connected to growth arrest while miR-143 and miR-145 in a negative feedback loop, have been assumed suppress senescence (Vasa-Nicotera et al., 2011; Bonifacio and Jarstfer, 2010; Cha et al., 2013; Rangrez et al., 2011; Khanna et al., 2014).

## 5. The important role of miRNAs in CVD

The pathological change of the vessel wall of arteries caused by atherosclerosis is the underlying mechanism of CVD. It is widely accepted that ECs dysfunction mainly contributes to atherosclerosis (Menghini et al., 2013; Qin et al., 2012).

The NOX family, the major players in oxidative stress-induced vascular disorders as well as in pro-inflammatory cytokine-mediated myocardial dysfunction, has been now emerged to be regulated by miRNAs (Magenta et al., 2011; Varga et al., 2013; Braunersreuther et al., 2013). Some miRNAs have been specially defined to be involved in endothelial function and angiogenesis (hsa-let-7, miR-130, 150, 17-92, 217, 222), vascular remodeling (miR-21, 126, 150), as well as immune response (miR-17-92, 146, 150, 106a, 181a and 223) (Menghini et al., 2013; Das et al., 2012; Tan et al., 2009). Accordingly, key biological pathways that are affected by these differentially regulated miRNAs include MAPK/TGF-β/Wnt signaling and Focal Adhesion pathway. Presumably, these pathways are involved in important regulatory processes that lead to restoration and repair mechanisms (Tan et al., 2009).

Among them, miR-155 and miR-221/222 directly target angiotensin II receptor that plays an essential role in endothelial inflammation and CVD (Qin et al., 2012).

The miR-200, 217 and 34a is known to induce senescence in human ECs by targeting SIRT1 pathway and have linked atherosclerosis to autophagy process, while miR-146/155 relate it to NOX activity (Magenta et al., 2013; Ito et al., 2010; Menghini et al., 2009; Vasa-Nicotera et al., 2011; Tian et al., 2014).

Interestingly, all miRNAs that display deregulation in endothelial senescence in vitro and in human atherosclerotic plaques, also display a potential role in vivo (Menghini et al., 2013; Staszel et al., 2011; Menghini et al., 2009; Tabuchi et al., 2012; Ito et al., 2010). Between them, miR-217 seems potentially pro-atherosclerotic since its over-expression is observed clearly in human atherosclerotic lesions and is inversely relating to SIRT1 expression and directly correlating with FOXO1 acetylation status (Menghini et al., 2009).

In addition, combination of miR-182/155 certainly contributes to oxidative damage of CVS and apoptosis due to targeting heme oxygenase-1 that play antioxidant, anti-inflammatory, and anti-apoptotic roles in CVS (Magenta et al., 2013). Elevated miR-155 levels are a marker of proinflammatory macrophages in atherosclerotic lesions and ROS production (Tian et al., 2014). A panel of miR-126/145/155 has been assumed to control atherosclerosis in vivo (Wei et al., 2013), whereby miR-126 represses the expression of VCAM-1 in ECs, inhibits leukocyte adherence to ECs and protects against inflammatory reactions in atherosclerotic plaques. MiR-126 are able to induce chemokine CXCL12/CXCR4 axis **in stem cells** (Rippe et al., 2012; Schraml and Grillari, 2012; Qin et al., 2012). However, down-regulation of miR-145/155 versus miR −126 is proposed to positively prevent atherosclerosis disorders when protecting against lesion formation. The panel is believed to orchestrate various cell types in human atherosclerotic plaques; ECs, SMCs, and macrophages (Wei et al., 2013; Tian et al., 2014).

Similar to heart-aging analysis, miRNAs that show aberrant expression pattern in CVD include; miR-15, 21, 23, 34, 29, 30, 150, 181/182 and 199, among them there is a set of miRNAs generally over-expressed in hypoxic conditions consisting of; miR-23, 107, 181 (Zhang et al., 2012; Ikeda et al., 2007; Bagnall et al., 2012; Tan et al., 2009). The SDF-1α/CXCR4 axis is highly implicated in EPC mobilization from the bone marrow, homing to vascular lesions and revascularization (Magenta et al., 2013). The miR-150 down-regulation in both hypoxic conditions as well as in cardiomyopathic conditions impairs SDF-1a/CXCR4 signaling which results in reduced revascularization capacity of EPC in patients with ischemia disease (Tan et al., 2009).

### *5.1. The important role of miRNAs in cardiac hypertrophy and heart failure*

In response to mechanical or pathological stress, the adult heart undergoes hypertrophic growth, a process defined as an increase in cardiomyocyte cell size without an increase in cell number (Topkara and Mann, 2011). Physiological cardiac hypertrophy (PH) is a common adaptation that occurs in the heart during exercise training and leads to molecular and morphological changes without overall ventricular dysfunction (Martinelli et al., 2014). A distinct set of fetal genes which are responsible for cardiomyocyte expansion, and include α-MHC, β-MHC, ANF, SERCA2 etc. is switched on in cardiac hypertrophy. However, PH and pathological cardiac hypertrophy both require the reactivation of this specific set of fetal genes to be switched on by miRNAs (Zhang et al., 2012; Zhao et al., 2010; Matkovich et al., 2010; Jazbutyte et al., 2013; Abonnenc et al., 2013; Duisters et al., 2009a, 2009b; Wang et al., 2012b).

Nevertheless, in pathological condition, changes in cardiomyocyte gene expression ultimately result in impaired cell survival and contraction, and heart failure is occurred (Ikeda et al., 2007).

At early stage of PH in the mouse model, 20 miRNAs (e.g. 290 mouse analogues to has-302 and 23) have been found to be up-regulated versus 15 down-regulated miRNAs (consist of 150, 145, 101, 29, 21). Interestingly, at the settle stage of PH, up-regulated miRMAs reduced to 15 (consist of miR-214, 199, 133, 30, 22) and down-regulated miRNAs became 10 (consist of let7, miR-150, 126, 26, 23). In particular, the study of PH could not confirm any changes in the expression pattern of miRNAs that have been associated with pathological cardiomyocyte growth, including miR-1, 15, 34, and 17-92 (Topkara and Mann, 2011; Martinelli et al., 2014). While in sever model of pathological hypertrophy, the well-known miR-1 and miR-133 along with co-transcribed miR-206 are the major down-regulated miRNAs commences at the pre-disease stage of sever HCM, then precedes up-regulation of target genes causative of cardiac hypertrophy and ECM remodeling (Topkara and Mann, 2011; Bagnall et al., 2012). Notable at end-stage of sever HCM, miRNA signatures are more considerably deregulated resembling the expression profile of the other cardiac hypertrophy studies (Bagnall et al., 2012).

Similarly, the miR-17−92 cluster is down-regulated in mice failure-prone heart plus in human failing heart **whereas,** up-regulation of miR-17-92 has been observed in old mice free of disease, which has been attributed to health-related hypertrophy of cardiomyocytes in old heart (Zhang et al., 2012; van Almen et al., 2011). The signatures of miR-17-92 and 23 clusters have also been found positively pro-hypertrophic (Topkara and Mann, 2011; Dong and Yang, 2011). Notably, the miR-23 cluster (miR-23, 27, 24), may be up-regulated to different degrees in healthy old heart, as well as, in initiating the hypertrophic response to pressure overloads (Topkara and Mann, 2011; Bagnall et al., 2012).

In agreement, expression profiling of miRNAs in human LV samples belonging to ischemic and dilated cardiomyopathy (ICM, DCM) patients versus healthy controls, revealed aberrantly under-expression of miR-1, 17-92, 21, 126, 133, 222 versus over-expressed let7, miR-15, 23, 34, 143, 145, 130, 150, 199, 181/182, 214. Accordingly, miR-214 was the most strongly up-regulated miRNA in all forms of cardiomyopathy (Ikeda et al., 2007). In tissue samples from patients at end-stage of heart failure and with DCM, miR-1, 29, 125 was markedly down-regulated in contrast to miR-214/181, when compared to healthy hearts from individuals with normal ventricular structure and function. End-stage heart failure is characterized by transitioning from maladaptive hypertrophy into DCM which leads to remodeling of the heart (Naga Prasad et al., 2009). For instance, miR-29 not only targets ECM protein deposition but also its further deregulation contributes to development of cardiac hypertrophy by targeting important growth factors and inflammatory mediators, IGF-1, LIF, and PTX-3 (Abonnenc et al., 2013; Duisters et al., 2009a; Wang et al., 2012b). Levels of miR-29 family beside miR-30, has been significantly reduced in a mouse model of pathological but not physiological hypertrophy (Abonnenc et al., 2013; Chen et al., 2012b).

Or, the other targets of overly down-regulated miR-1 and 133a are components of ECM remodeling and the TGF-β signaling pathway all of which contributing to pathologic cardiac hypertrophy, electrophysiology, calcium signaling and fibrosis disorders (Zhang et al., 2012; Bagnall et al., 2012).

Indeed, data analysis demonstrates a subset of differentially expressed miRNAs in human heart failures; miR-1, 15, 23, 29, 25, 181, 214. Accordingly, miRNA families; let-7, 15, 23, 125, 199, and 214 have been found to be predominantly up-regulated in human heart failure studies (Topkara and Mann, 2011; Ikeda et al., 2007; Naga Prasad et al., 2009; Dong and Yang, 2011).

Notable, up-regulated miRNAs at early stage of sever pathologic hypertrophy in mice consist of mir-21, 132, 214 which proceeding to mir-34, 199, 222 over-expression in sever pathologic hypertrophy at the end stage of disease. Down regulated miRNAs at early stage are miR-1 and mir-133a plus miR-30 and mir-150 at the end stage of disease. The decreased levels of miR-1, 133, 150 cause down-regulation of transcription switcher FOXO the major component of SIRT/p53/IGF-1 pathway and result in inhibition of cardiomyocyte proliferation (Fig. 4) (Bagnall et al., 2012). Moreover, down-regulation of miR-150 beside up-regulation of miR-181 causes reduction in myocyte size (Bagnall et al., 2012; Duisters et al., 2009b). In particular in rat hypertrophic hearts, there was seen 10-fold up-regulation of miR-199 which disrupts the increased size of cardiomyocytes (Song et al., 2010).

Noteworthy, miRNAs are even more differentially expressed in the failing myocardium and in progressive heart failure. They target genes that govern diverse functions in cardiac processes including myocyte hypertrophy, excitation-contraction coupling, increased myocyte loss, and myocardial fibrosis (Topkara and Mann, 2011; Matkovich et al., 2010; Schroen and Heymans, 2012).

In progression to heart failure and in persisting of cardiac stress, however, irrespective to pathological stimulus, HCM-signature miRNAs have been reported to include; down-regulated miR-1, 29, 30, 133, 150 versus up-regulated miR-15, 22, 23, 34, 125, 132, 146, 199, 214, 222 (Fig. 4) (van Rooij et al., 2008; Bagnall et al., 2012; Dong and Yang, 2011).

Among them, muscle-enriched miR-22 is required for adaptation to hemodynamic stress in pressure overload in mice (Dong and Yang, 2011) In the mouse model of cardiac hypertrophy, up-regulated miR-22 inhibits cell cycle progression, in part, by targeting ERRα, CDK6, SIRT1, HDAC4 and Sp1 (Fig. 4) (Jazbutyte et al., 2013; Huang et al., 2013). Otherwise, the putative targets of down-regulated miR-26, 23, 143 and 150 are identified to be up-regulated genes IGF-1R, NFAT, GATA4, GSK3B and C-Myb (Wei et al., 2013).

Noteworthy, profound inhibition of HDACs such as SIRT1 increases the levels of miR-23, miR-26 and miR-30, which in turn repress anti-apoptotic protein HMGA2 and precede increased expression of p21, thereby triggers senescence of human multipotent stem cells (Fig. 4) (Gorospe and Abdelmohsen, 2011). Accordingly, over-expressed miR-22 is sufficient to provoke dilated cardiomyopathy, a cardiac remodeling, in response to stressors, by repressing directly SIRT1 and HDAC4 (Huang et al., 2013; Dong and Yang, 2011).

Otherwise, the central regulators of Ca2+ transients and contractile work are respectively PLN, RYR2, SERCA2a and α-MHC, which are positively influenced at the level of transcription by the PGC1α/ERR switchers whose expression is consequently repressed by over-expressed miR-22. In addition to interfering with transcription of PGC-1α/PPARα/ERRα genes, mechanistically over-expressed miR-22 impairs the Ca2+transient and its reloading into SR (Takaya et al., 2009). Interestingly, miR-1 at the early stage of aging is able to suppress aging process through marked down-regulation of α-MHC and Ncx1 versus ATPase pomp Serca2a for efficient Ca2+ uptake into SR. In the aging heart, α-MHC and Ncx1 genes are up-regulated which are associated with progression in aging while, aging-suppressing gene ATPase pomp Serca2a is gradually down-regulated, as well as, Ca2+ uptake into SR (Lafferty-Whyte et al., 2009).

Intracellular Ca2+ overload is a dangerous signal of stressors which relays by the calcium/calmodulin-dependent protein kinase (CaMKII) (Cha et al., 2013). Conversely, miR-145 over-expression represses CaMKIId protein expression and Ca2+ overload by inhibiting ROS-induction of PMCA-1, NCX, PLB, and RyR2, besides elevating mRNA levels of SERCA2a (Cha et al., 2013). The critical kinase CaMKII that relays Ca2+ signaling is responsible for heart hypertrophy, apoptosis, arrhythmia, and failure (Cha et al., 2013). At first, the increased levels of miR-22 induces a pro-hypertrophic program for adaptation and to confront stress, while continuous stress leads to its over-expression which eliciting contractile dysfunction, leading to cardiac dilation and heart failure (Takaya

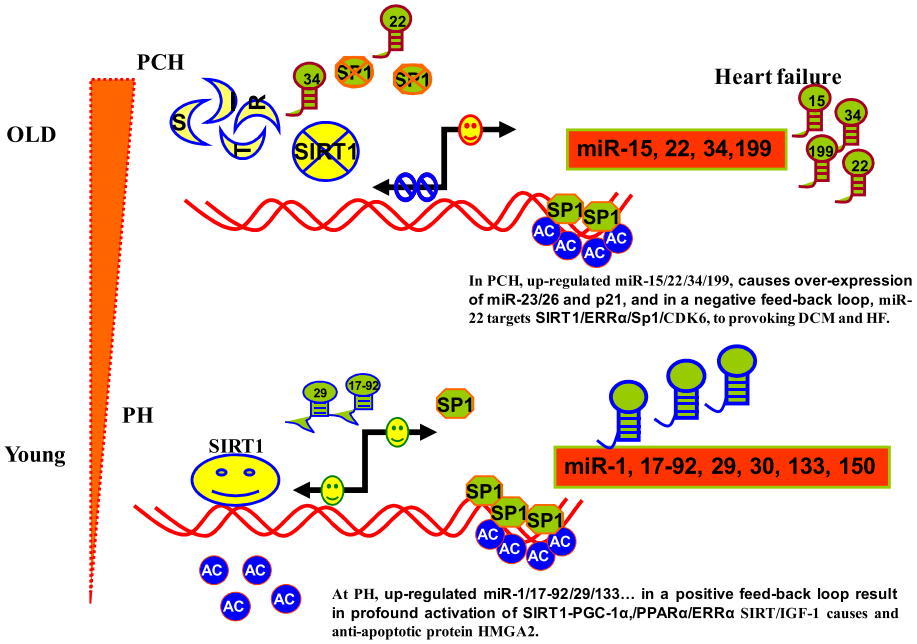


**Fig. 4.** A schematic model for miRNA/SIRT mechanism to switch on/off reprogramming of progenitor cells obtained from old humans. Here, there is a positive feedback loop between chromatin remodeling-associated miR-1, 17–92, 29, 133, 150 whereby causes SIRT/PGC-1α/IGF-1 pathway up-regulation in young humans versus old humans, while there is a negative feedback regulatory loop between SA-miR-15, 22, 34, 199 and SIRT axis. SIRT1 ensures deacetylation of the SA-miRNA promoters, which results in the low expression of SA-miRNA. Decreased level of SIRT in o/h, results in hyperacetylation of SA-miRNA promoter and subsequent over-expression of SA-miRNA which in turn in a negative feedback loop versus chromatin remodeling-associated ones, represses the expression of SIRT1 (Picture taken from Sharma et al. (2013)).

et al., 2009). Similarly, miR-1 negatively regulates calcium/calmodulin signaling through down-regulation of calcineurin/NFAT pathway, as well as, the growth inducers Mef2a/GATA4, to control cardiomyocyte growth (Bagnall et al., 2012; Dong and Yang, 2011). Therefore, miR-1 and 145 by decreasing ROS-induced intracellular Ca2+ concentration and CaMKIId expression, are closely associated with Ca2+ signaling (Bagnall et al., 2012; Cha et al., 2013). A change in intracellular free Ca2+ is a common signaling mechanism of cardiomyocyte death (Cha et al., 2013). MiR-214 has also been identified as a central regulator of Ca2+ transients, which represses Ca2+ overload and cell death by targeting NCX1, BIM, CaMKIId, and Cyclophilin D, directly (Cha et al., 2013). Accordingly, miR-214 is the most strongly up-regulated miRNA at both stages of human ischemic- and dilated cardiomyopathy (Zhang et al., 2012; Bagnall et al., 2012).

Signaling pathways associated with predicted targets of PH-associated miRNAs, are known to be IGF-1, GnRH and neurotrophin signaling (Martinelli et al., 2014). Special transcription factors and co-regulators such as nuclear factor of activated T-cells (NFAT), GATA4, SIRT1, estrogen related receptor (ERR-α,β,γ), PPAR-α, β, γ, and PGC-1α that contribute to PH process, have been found to be targets of hypertrophic miRNAs (Jazbutyte et al., 2013; Huang et al., 2013; Takaya and et al., 2009). However, miR-1 and 133 respectively target IGF-1 and FGF-R1, the former is hypertrophy factor and the later is to induce cardiac proliferation (Bagnall et al., 2012).

According to models, miRNA signatures that contribute to cardiac hypertrophy in a positive manner include miR-1, 17-92, 21, 29, 133, 145, 150 versus miR-15, 23, 181, 199 which act in a negative manner to induce apoptosis (Zhang et al., 2012; Topkara and Mann, 2011; Gorospe and Abdelmohsen, 2011; van Rooij et al., 2008; Ikeda et al., 2007). Notable, miR-15 family members are up-regulated across mouse models of heart failure (pathological cardiac hypertrophy) as well as human heart failure (Zhang et al., 2012; Topkara and Mann, 2011).

Conclusively, miRNAs not only switch on physiologic hypertrophy in healthy individuals but also bring on severe age-related heart disease by switching on gradual changing of aging to abrupt deregulation of miRNAs (Zhang et al., 2012; Noren Hooten et al., 2010; Martinelli et al., 2014; Ikeda et al., 2007; Chilton et al., 2014; Bagnall et al., 2012).

### 5.2. The important role of miRNAs in cardiac fibrosis

Age-related cardiac remodeling is known to be partially a consequence of changes in extracellular matrix (ECM) gene expression and its protein levels (van Almen et al., 2011; Duisters et al., 2009a, 2009b). Cardiac fibrosis plays a key role in regulating heart function and in the development of heart failure. Excessive fibrosis leads to ventricular dilation, infarct expansion, and heart failure (Topkara and Mann, 2011). ECM is mainly secreted by cardiac fibroblasts (CFs) (Abonnenc et al., 2013), which during aging via TGF-β pathway, differentiate into myofibroblasts and lead to excessive matrix accumulation (Topkara and Mann, 2011). The TGF-β pathway has the major role to induce fibrosis phenotype, and to promoting FCs for ECM deposition in the infarcted zone (Topkara and Mann, 2011; Abonnenc et al., 2013; Wang et al., 2012b). Nowadays, miRNAs are known as the major players in all aspects of remodeling, growth, fibrosis, cell death, vascularization and contraction of cardiac tissue (Topkara and Mann, 2011; Dong and Yang, 2011). For example, miR-21 is found to regulate CF proliferation and fibrosis (Gurha et al., 2013). Three key miRNAs; miR-133/30/29 are involved in cardiac fibrosis. While, miR-30/29 is enriched in CFs, miR-133 is expressed specifically in cardiomyocytes. All three miRNAs are down-regulated in cardiac hypertrophy which leads to scar formation and fibrosis (Abonnenc et al., 2013).

The miR-29 family directly targets a number of ECM components related to myocardial fibrosis including collagens, fibrillins, and elastin (Topkara and Mann, 2011). Intense interest is present on miR-29. Since unlike most miRNAs that are only present in the cytosole, miR-29 is also found in the nucleus (Topkara and Mann, 2011; Dong and Yang, 2011; Chen et al., 2012b). Besides ECM proteins, miR-29 alters secretion of CF growth factors and cytokines such as; LIF and IGF-1, also blocks the response of CFs to TGF-β, and exhibits a much stronger effect on the ECM proteome of CFs (Abonnenc et al., 2013; Duisters et al., 2009a, 2009b). Additionally, down-regulation of miR-29 in CVS, leads to down regulation of miR-149 in contrast to up-regulation of miR-21/214/222 (Dong and Yang, 2011). Anti-aging miR-149 rescue mitochondria and induce its biogenesis, by holding off PARP over-activation, whereby strongly activates SIRT-1/PGC-1α pathway (Wei et al., 2013).

In vitro experiments show that TGF-β is interestingly an inducer of miR-24 expression, whereby its over-expression represses the pathway by reducing TGF-β secretion and Smad2/3 phosphorylation in CFs (Fig. 5). Besides decreasing the synthesis of ECM proteins, miR-24 reduces the conversion of CFs to myofibroblasts and attenuates the serum-mediated migration of CFs (Wang et al., 2012b). The miR-24 belongs to the miR-23 cluster (miR-23, 24, 27), which is abundant in the heart to positively regulate cardiac hypertrophy through NFATc3 versus the TGF-β pathway (Topkara and Mann, 2011), and is able to improve heart function through reduction of the infarct size. But, miR-23 is accordingly down regulated in after myocardial injuries (Topkara and Mann, 2011). The TGF-β signaling is targeted by both miR-23/29 clusters through several mechanisms for example, by suppressing smad2/3 phosphorylation and depressing furin function. The findings indicate that furin gene is involved in angiotensin II-induced TGF-β activation, and causes in collagen production during fibrosis (Fig. 5) (Topkara and Mann, 2011; Tessitore et al., 2014; Wang et al., 2012b). MiR-30/133 has been identified to directly target connective tissue growth factor (CTGF), and further decrease production of collagen (Matkovich et al., 2010). Interestingly, CTGF is upstream inducer of TGF-β and its up-regulation in age-induced cardiac disease correlates with TGF- β induction, cardiac fibrosis, and left ventricular stiffening (van Almen et al., 2011). Data analysis reveals that the miR-133, 30, 29, 17-92, each controls cardiac fibrosis by targeting ECM components such as CTGF and TSP-1 that are up-regulated in old failing hearts (Jazbutyte et al., 2013; van Almen et al., 2011). However, miR-133, 30, 29, 23 are generally down-regulated at the end stage of myocardium hypertrophy (Duisters et al., 2009a, 2009b).

Conversely, miR-22/21 is important regulators of cellular senescence, and the main parts of their effects are directly mediated via CF regulation (Jazbutyte et al., 2013; Duisters et al., 2009a, 2009b; Wang et al., 2012b).

Besides fibrosis, increased expression of miR-22/21 exhibits increased tendency towards hypertrophic growth, ventricular dilatation and cardiac dysfunction in response to pressure overload in mice in the pathogenesis of HF, then their down-regulation could therefore be a beneficial approach to block CF proliferation in heart disease to inhibit secondary cardiac remodeling (Huang et al., 2013; Wang et al., 2012b; Dong and Yang, 2011; Gurha et al., 2013).

### 5.3. The important role of miRNAs in cardiac remodeling

The morphological changes observed in the old heart are usually associated with senescence that occur during the aging process (Konstantinidis et al., 2012; Torella et al., 2004; Gonzalez et al., 2008), which is characterized by the loss of cardiomyocytes with subsequent hypertrophy of the remaining viable ones,

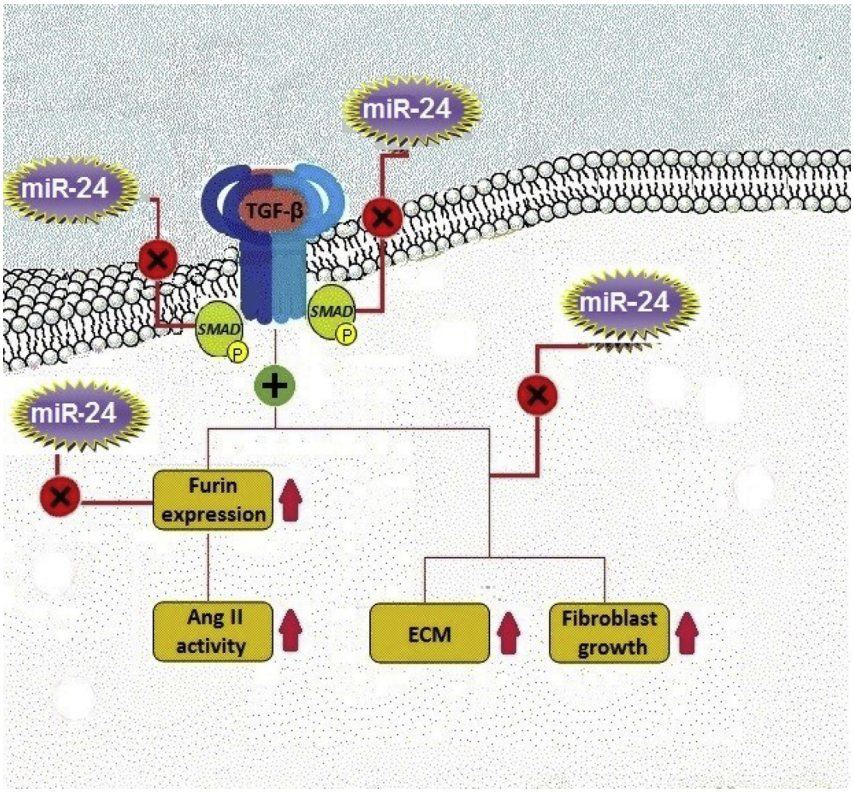


**Fig. 5.** A proposed model to explain the major positive role of miR-24 in prevention of injuries-induced fibrosis of myocardium through the suppression of TGF-β signaling pathway. The miR-24 up-regulation leads to decreases of smad2/3 phosphorylation and either directly or indirectly depressing furin function.

accompanied with the proliferation of CFs (Table 1) (Zhang et al., 2012; Topkara and Mann, 2011). As myocytes are lost and CFs continues to proliferate and produces collagen matrix, the physical properties of the aging heart become altered (Zhao et al., 2010; Matkovich et al., 2010; Jazbutyte et al., 2013; Abonnenc et al., 2013; Duisters et al., 2009a, 2009b; Wang et al., 2012b).

The constant remodeling and accumulation of ECM are recognized as a key feature of cardiac aging in humans and animal models (Topkara and Mann, 2011; Abonnenc et al., 2013). In particular, the expression of ECM proteins TSP and CTGF increases with aging and causes development of spontaneous age-related cardiomyopathy (Matkovich et al., 2010; van Almen et al., 2011). It has been increasingly clear that progressive cardiac remodeling plays a critical role in disease progression of heart failure (Huang et al., 2013; Abonnenc et al., 2013; Gurha et al., 2013).

In the remodeled aged heart, remarkable-switched on of the "fetal gene program" is observed to potentially contribute to the subsequent heart failure phenotype (Huang et al., 2013; Gurha et al., 2013; Patrick et al., 2010). The cause of senescent failing heart is due the abruptly changes in gene expression of cell cycle regulators/chromatin remodeling (van Almen et al., 2011).

In cardiac remodeling and in response to stressors, miR-21 is up-regulated but it is not directly involved in inducing cardiac hypertrophy (Patrick et al., 2010). Hence it is involved directly in fibrosis in response to pressure overload. MiR-21 is specifically over-expressed in fibroblasts of the failing myocardium, which leads to augmentation of ERK/MAPK signaling, thereby to increasing fibroblast survival, secretion and fibrosis (Schroen and Heymans, 2012; Topkara and Mann, 2011; Patrick et al., 2010). In contrast, miR-22 is essential to regulate directly cardiac hypertrophy and remodeling in response to stress. Over-expression of miR-22 is sufficient to induce pathologic cardiac hypertrophy (Huang et al., 2013). Specifically, miR-150 is another novel marker affecting both cellular and extracellular elements of the myocardium in remodeling heart after acute myocardial infarction. Low circulating level of miR-150 is a marker of left ventricular (LV) remodeling and development of heart failure versus marker Nt-proBNP (Devaux et al., 2013).

The cardiac remodeling is especially associated with decreased levels of miR-17–92, 24, 29, 30, 133 families, which targets the ECM proteins CTGF and TSP-1. Aging induces increase in the ECM proteins CTGF and TSP-1 which trigger TGF-β signaling (Matkovich et al., 2010; Jazbutyte et al., 2013; Duisters et al., 2009a, 2009b; Wang et al., 2012b). Interestingly, failure-resistant mice show an opposite expression pattern for both the ECM proteins and the microRNAs (van Almen et al., 2011).

Notable, according to the recent report, miR-133/29 are able to switch genetic reprogramming of myocardium toward preventing cardiac apoptosis and hypertrophy while modulating electrical re-

**Table 1**
Features of cardiac remodeling.

| |
|---|
| **Changes in excitation contraction coupling of myocytes** |
| α-myosin heavy chain (fetal) gene expression in myocytes |
| β-adrenergic receptor desensitization in myocytes |
| Hypertrophy with loss of myofilaments and loss of cytoskeletal proteins |
| Myocyte loss |
| **Alterations in extracellular matrix** |
| Matrix degradation and fibrosis replacement |
| **Alterations in left ventricular chamber geometry** |
| Left ventricular dilation |
| Increased LV wall stress |
| Mitral valve incompetence |
| Wall thinning with after load mismatch |

polarization by specially targeting Kv4-encoded fast transient outward (Ito) K channels (*Kcnip2*) and protecting myocardium against fibrosis (Matkovich et al., 2010; Ikeda et al., 2007; Abonnenc et al., 2013). In vivo cardiac remodeling is prevented by increased levels of miR-133/29 which would abrogate hypertrophy-induced down-regulation of $I_{to,f}$ channel in cardiac-hypertrophic mice (Matkovich et al., 2010; Jazbutyte et al., 2013).

Up-regulation of miR-29 family can revert DNA aberrant methylation by targeting the DNMT3a and DNMT3b genes, and thereby causing global DNA hypomethylation. DNA hypomethylation of MMP-2/MMP-9 genes is associated with up-regulation of MMP-2/9 and subsequent ECM degradation which promoting either regeneration processes or in chronic action, neointimal formation (Topkara and Mann, 2011; Chen et al., 2012b). Finally, protein HMGB1 that is released from damaged myocytes is able to improve left heart function via inducing miR-206 over-expression in the myocardium. MiR-206 is in turn able accordingly to provoke cardiac regeneration by stimulating ckit + -cell reactivation/reprogramming, in an IGF-1 signaling-depended manner (Limana et al., 2011). Noteworthy, the co-transcribed miR-1/133/206 is the major down-regulated miRNA cluster that commences at the pre stage of sever HCM, that precedes cardiac hypertrophy and ECM remodeling (Topkara and Mann, 2011; Bagnall et al., 2012).

## 6. The important role of miRNAs in cardiovascular cell differentiation & reprogramming

Observing that hearts in respond to specific miRNAs as small switchers to go under genetic reprogramming termed “cardiac remodeling.”, encourage researchers to use these biological switchers to direct changes in protein compositions that modify cardiac cell geometry, function, and viability (Li et al., 2012; Matkovich et al., 2010; Noren Hooten et al., 2010; Jayawardena et al., 2012).

On the basis of in vitro/in vivo studies, it has been recently reviewed that diverse miRNAs play roles in the CVS remodeling by establishing ECs and CPC senescence via cell type-specific regulatory networks (Staszel et al., 2011; Menghini et al., 2009; Magenta et al., 2011).

Comparative profiling of human/animal cardiac adult cells with those of embryonic heart cells has specially exhibited gradual up-regulation of the miRNA families; let-7, miR-15, 22, 34, 181/182, 199 as well as miR-217, 222 in vascular system and somehow miR-214 in the heart (Rippo et al., 2014; Topkara and Mann, 2011; Gorospe and Abdelmohsen, 2011; Sharma et al., 2013; Ikeda et al., 2007; Naga Prasad et al., 2009; Patrick et al., 2010). Among them, generally down-regulated miR-1, 17-92, 23, 29, 133 and 214 are associated with pathological cardiac hypertrophy whereas up-regulated miR-15, 34, 181/182, 199, as well as miR-217 are known as apoptotic and senescence associated signatures (Rippo et al., 2014; Topkara and Mann, 2011; Gorospe and Abdelmohsen, 2011; Bonifacio and Jarstfer, 2010).

In one side, SA-miRNAs as very small biological switchers, are able to orchestrate cardiac remodeling by targeting specific mRNAs that have central role in genetic reprogramming (Sharma et al., 2013; Li et al., 2012; Matkovich et al., 2010; Chilton et al., 2014), **in the other side** they impact different cellular pathways, specially those involved in senescence; mitochondrial dysfunction/DDR/anti-apoptotic pathway IGF-1 (Lopez-Otin et al., 2013; Motohashi et al., 2013; Li et al., 2012; Pourrajab et al., 2014a, 2014b). In this aspect and according to the data analysis, miR-17-92, 29, 133, 34, 15, 181/182 are specifically assumed to affect cell cycle progression with either proliferating or apoptotic functions (Gorospe and Abdelmohsen, 2011; Ugalde et al., 2011; Lafferty-Whyte et al., 2009; Maes et al., 2009; Bonifacio and Jarstfer, 2010; Moskwa et al., 2011b; Bisso et al., 2013a; Wang et al., 2012a; Wu et al., 2013). Accordingly, while miR-17-92 and miR-29s is observing generally to hold off senescence by switching off main CDK inhibitors p53/p21/p16, miR-15, 34, 181/182, 199, in contrast, progress cells toward senescence (Zhao et al., 2010; Tabuchi et al., 2012; Lafferty-Whyte et al., 2009).

Noteworthy and according to the several references, senescent progenitor cells can resume/switch on cell growth/reprogramming after genetic interventions repressing p16, besides inactivating p53-depended pathway (Rodier and Campisi, 2011; Gonzalez et al., 2008; Gorospe and Abdelmohsen, 2011; Zhao et al., 2010).

Otherwise, IGF-1/IRS1/PI3K/Akt signaling is well known to stimulate CPC/myoblast proliferation/differentiation, besides increasing protein synthesis (Lopez-Otin et al., 2013; Motohashi et al., 2013; Li et al., 2012). Then, in respect to the positive effect of SIRT1/IGF-1/PI3K pathway in CVS, and according to the consistent data that increased levels of miR-1/17-92/29/133/150 is associated with up-regulation of SIRT/IGF-1 pathway and the transcription switcher PGC-1α, we assume that miRNAs can be the main switcher in reprogramming of mammalians aging CVS whom is tightly associated with activation of SIRT1/PARP1/p53 and IRS1/PI3K/Akt pathways (Dutta et al., 2012; Lopez-Otin et al., 2013; Gorospe and Abdelmohsen, 2011; Ito et al., 2010; Bagnall et al., 2012).

In one side, human miRNA-up-regulated SIRT1 can switch off cellular senescence by inducing cell reprogramming pathways (Sharma et al., 2013), and in the other side, SIRT1 through FOXO/PCG-α transcription factors/miR-17-92, is able to actively delay aging with improving the mitochondria function, potentially. The miR-17-92/29/PCG-α pathway has been known to keep switch on longevity, both in humans and in model organisms (Dutta et al., 2012; Zhang et al., 2012; Gorospe and Abdelmohsen, 2011; Sharma et al., 2013; Ito et al., 2010).

SIRT1 can be functioning as the main effector in reprogramming of mammalians aging cells and is tightly associated with inactivation of deacetylated p53/SA-miRNAs, and activation of IRS1/PI3K/Akt pathway through deacetylated state of FOXO/PGC (Dutta et al., 2012; Lopez-Otin et al., 2013; Gorospe and Abdelmohsen, 2011; Ito et al., 2010). The IRS1/PI3K/Akt signaling is the major pathway well known to stimulate proliferation and differentiation of myoblasts (Motohashi et al., 2013; Li et al., 2012).

There is direct links between miR-1/17-92/29/133, PARP/SIRT, DDR, aging and epigenetic alterations. As alterations in the epigenetic factors determine chromatin architecture and redistribution of heterochromatin which constitute characteristic features of aging (Ugalde et al., 2011; Zhang and Kraus, 2010; Pourrajab et al., 2014a, 2014b; van Almen et al., 2011; Bagnall et al., 2012). For example, changes in the acetylation of DNA components especially of histones (for H3K4 and for H3K27) contribute to the aging process (Lopez-Otin et al., 2013).

Interestingly under stress conditions, activated SIRT1 act to confront the stress by deacetylating transcriptional switchers; PGC-1α, NF-kB, FOXO, p53, and histones (Zhao et al., 2010; Canto and Auwerx, 2011; Csiszar et al., 2005; Bai et al., 2011).

SIRT up-regulation is assumed to be under influence of chromatin/SA-miRNAs which induces regenerative capacity of aged hematopoietic stem cells, via regulating genomic stability, NF-kB signaling, and glucose homeostasis through histone H3K9 and mitochondrial proteins deacetylation (Fig. 3A) (Lopez-Otin et al., 2013; Sharma et al., 2013).

SIRT1 over-activation that switches on reprogramming of resistant cells obtained from old humans has been proposed as a substantial model for miRNA mechanism. According to a proposed

model for SA-miRNA mechanism, SIRT by deacetylating the promoter of SA-miRNAs switches them off whose expression contribute to aging progression. However, in presence of senescence stressors and in reduced level of SIRT activity in response to down-regulation of chromatin associated-miRNAs, SA-miRNA promoter is switched on. Thereby, hyperacetylation of SA-miRNA promoter make it over-activated, whereby in a negative feedback regulatory loop, SA-miRNA strongly represses SIRT expression and leads to accelerating aging (Fig. 4) (Sharma et al., 2013). Noteworthy, a similar switching mechanism can be proposed for other SIRT/PARP/SA-miRNAs axis which in a negative/positive feed-forward loop, a mutually negative or positive feedback loop, completely represses/fully activates SIRT (Figs. 3 and 4) (Gorospe and Abdelmohsen, 2011; Menghini et al., 2009; Tabuchi et al., 2012; Tessitore et al., 2014; Maes et al., 2009; Ito et al., 2010; Neijenhuis et al., 2013; Canto and Auwerx, 2011; Chen et al., 2012a; Mohamed et al., 2014).

In the other side, identification of ckit + progenitor cells which are able to differentiate into various types of CVS (Chimenti et al., 2003; Torella et al., 2004; Gonzalez et al., 2008), provide an approach for cardiac regeneration by a strategy using miRNA switchers for direct reprogramming of cardiac cells. The repressive actions of miRNAs on gene expression can be powerful as a single miRNA may target multiple pathways simultaneously (Rippo et al., 2014; Li et al., 2012; Guo et al., 2010; Matkovich et al., 2010; Noren Hooten et al., 2010; Chilton et al., 2014; Jayawardena et al., 2012).

Comparison of adult-CSC-miRNA profile with those of BMCs and embryonic heart cells, gives unprecedented information on the possible age-regulated miRNAs involved in establishing the CSC senescence phenotype.

Interestingly, down-regulated SA-miR-17-92 emerges as one of the major difference between adult CSCs and their primary progenitor populations (Zhang et al., 2012; Sharma et al., 2013; Noren Hooten et al., 2010; Pourrajab et al., 2014a, 2014b), which is commonly associated with stem cell re-growth and proliferation (Pourrajab et al., 2014a, 2014b). Therefore, miR-17-92 cluster appears as a reprogramming switcher whose up-regulation is clearly associated with cell renovation/proliferation or reversely its down-regulation brings heart to senescence (van Almen et al., 2011; Bagnall et al., 2012).

In Addition, miR-17-92 in combination with miR-126 are able to keep vascular repairing and maintaining its homeostasis, then contributing to EPC reprogramming (Schroen and Heymans, 2012; Rippo et al., 2014; Menghini et al., 2013).

Conversely, inflame-mit-miR-217/199/182/181/34/22/15, is tightly related to chromatin-associated factors p53/p16 to hold off reprogramming in human senescent cells (Tabuchi et al., 2012; Ito et al., 2010; Zhu et al., 2011; Porrello et al., 2011; Jayawardena et al., 2012).

Accordingly, restoration of SIRT1 activity and expression is achieved through down-regulation of miR-15/22/34/181/182/199/217 (Menghini et al., 2009; Tessitore et al., 2014; Kim et al., 2014; Huang et al., 2013; Dong and Yang, 2011). The other direct targets of miR-15/34 for example are cell cycle inducers; E2F family, CDK4/6, CCND1, and CCNE2, whereby confront cell cycle progression in mammalians (Ito et al., 2010).

MiR-34a produces a strong resistance against cell reprogramming by down-regulation of components of DNA repair machinery; RAD51AP1, Chek1, and MDC1 (Tessitore et al., 2014). Also, up-regulation of the miR-15 family is linked to in vivo repression of a number of cell cycle genes, in particular Chek1. The Chek1 plays a crucial role in the renovation of the genome, the regulation of mitosis and coordination of progression through G2/M phase, as well as correct segregation of chromosomes (Tessitore et al., 2014). Thus, in vivo miR-15 over-expression contributes to onset of premature cell senescence in myocardium of congenital heart abnormalities (Porrello et al., 2011; Krishnan et al., 2013), whose all members; miR-15a, 15b, 16-1, 16-2, 195, and 497 have a common seed region for sharing the common targets. The miR-15 family is expressed in most adult tissues, specially the heart (Chen et al., 2012a; Porrello et al., 2011).

Beside up-regulation of miR-1/17-92/29/133/150, down-regulation of miR-15/22/34/181/182/217 that potentially targets telomere genes and DNA repair machinery, shows marginal significance in preventing aging processes (Sharma et al., 2013; Tabuchi et al., 2012; Ugalde et al., 2011; Moskwa et al., 2011b; Bisso et al., 2013a; Wang et al., 2012a; Wu et al., 2013; Chilton et al., 2014).

In particular, miR-34/181 has the potential to regulate all of the aging-associated pathways, through regulating both the tumor suppressor p53/p21/p16/Rb and SIRT1 pathways (Lopez-Otin et al., 2013; Lafferty-Whyte et al., 2009; Ito et al., 2010; Zhu et al., 2011; Bisso et al., 2013a; Naga Prasad et al., 2009).

Additionally, miR-181/182 has been reported to target the homeobox protein Hox-A11 to reduce mammalian myoblast proliferation, CDK6/4 to inactivate the G1/S transition and to bring on the cell cycle arrest (Rippo et al., 2014; Motohashi et al., 2013; Tabuchi et al., 2012; Krishnan et al., 2013).

Even more, the panel miR-133/29 is recommended to switch on genetic reprogramming of myocardium toward preventing cardiac apoptosis and hypertrophy partly via modulating electrical repolarization specially by targeting Kv4-encoded fast transient outward (Ito) K channels (*Kcnip2*) (Matkovich et al., 2010; Ikeda et al., 2007; Jazbutyte et al., 2013; Abonnenc et al., 2013). In contrast, up-regulated miR-199 beside 181 causes reduction in myocyte size (Song et al., 2010; Bagnall et al., 2012; Duisters et al., 2009a, 2009b).

Remarkably, myomiR-1/133/143 is reported to be strongly expressed in developing adult heart. Then, up-regulation of this panel is in particular recommended for spontaneously differentiating embryonic stem cells toward myoblasts (Matkovich et al., 2010). While, increased level of miR-133 mediates epigenetic switching to induce myoblast proliferation through SIRT/p53/FOXO/IGF-1 pathway (Song et al., 2010; Bagnall et al., 2012; Duisters et al., 2009a, 2009b) up-regulated-PI3K/Akt pathway switches on miR-143 expression to lead mesenchymal stem cells to mitogenesis and better survival in organ niches (Pourrajab et al., 2014a, 2014b; Wei et al., 2013; Rangrez et al., 2011).

Notable, it was recently reported that miR-133 in combination with miR-29 are able to hold off cardiac hypertrophy, protecting against myocardial fibrosis, specially through modulating electrical re-polarization, by targeting Kv4-encoded fast transient outward (Ito) K channels (*Kcnip2*) (Matkovich et al., 2010; Ikeda et al., 2007; Abonnenc et al., 2013).

Now according to data, chromatin/SA-miRNAs as master switchers in senescence process, are able to regulate the pathways of aging (Lopez-Otin et al., 2013; Rippo et al., 2014; Motohashi et al., 2013; Li et al., 2012; Pourrajab et al., 2014a, 2014b; Tessitore et al., 2014; Pourrajab et al., 2014a, 2014b).

## 7. Conclusion and future prospects

The evidence for the involvement of miRNAs in regulating the pathways of cardiac aging, not only verify them as potential new therapeutic targets to rejuvenate stem cells to aid regenerative process in cell therapies, but also is useful in finding new ways to inhibit aging processes in organ cells.

For instance, therapeutic targeted delivery of SA-miRNA-

antisense oligonucleotides (antagomirs) can be employed for systemic miRNA inhibition. Also, nanoparticle-targeted delivery of anagomirs may restore anti-SA-miRNA expression which would be a potential therapeutic strategy to reverse stress-induced aging process and to prevent maladaptive cardiac remodeling. Thus, these findings provide a proof-of- concept support for application of antagomirs for silencing of SA-miRNAs expression predominantly in cells in vivo which would result in reduced stem cell apoptosis, enhanced vascularization, and improved cardiac function.

Here, we tried to introduce key miRNAs modulating aging and cellular senescence, besides examining their influence upon senescence-associated programs. Evidence discuses deregulation of mit-miRNAs as governors in senescence programs and underling mechanism in age-associated CVD (Guo et al., 2010; van Almen and et al., 2011).

The main goal of this literature survey was to provide support for the exciting new hypothesis that one or a panel of miRNAs emerging as SA-miRNAs, could play direct roles in accelerating the aging or holding it off via modulating mitochondria/DDR pathways. The pathway of free radicals from mitochondrial continues to DNA for telomere shortening and to p53/SIRT-dependent repression of PGC-1α/β pathway. PGC-1α repression causes further DNA damage and leads to PARP over-activation specially to inactivate SIRT1 pathway. PARP1/SIRT1 system are directly associated with chromatin remodeling factors.

During cellular senescence, chromatin-remodeling factors that maintain stem cells-unique states of chromatin and are required to remodeling it are down-regulated. In particular, progenitor cells get senescent chromatin-remodeling whose is unsuccessful to regenerate the failing organ, in acute and chronic diseases. But, miRNAs are strongly appeared to counteract progressive degeneration. In particular, miRNAs have been defined as master switchers in controlling proliferation and differentiation in stem cell biology, due to the highly conserved nature and their well-recognized target sites. Then understanding the molecular mechanism of SA-miRNA especially those associated with mitochondria/chromatin function, holds the grate promise in modulation/prevention of the cellular senescence and age-associated diseases.

## Acknowledgment

We would like to thanks Mr. *Mohsen Mazloomrezaei ss and fatemeh bidmeshki* for their kind help and also Shahid Rahnemun Research Center, Shahid Sadoughi University of Medical Sciences, for their kind support.

## References

Abonnenc, M., et al., 2013. Extracellular matrix secretion by cardiac fibroblasts: role of microRNA-29b and microRNA-30c. Circ. Res. 113 (10), 1138–1147.
van Almen, G.C., et al., 2011. MicroRNA-18 and microRNA-19 regulate CTGF and TSP-1 expression in age-related heart failure. Aging Cell. 10 (5), 76–79.
Bagnall, R.D., et al., 2012. Global microRNA profiling of the mouse ventricles during development of severe hypertrophic cardiomyopathy and heart failure. PloS one 7 (9), e44744.
Bai, P., et al., 2011. PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. Cell. Metab. 13 (4), 461–468.
Bisso, A., et al., 2013a. Oncogenic miR-181a/b affect the DNA damage response in aggressive breast cancer. Cell. Cycle (Georgetown Tex. 1) 12 (11), 1679–1687.
Bisso, A., et al., 2013b. Oncogenic miR-181a/b affect the DNA damage response in aggressive breast cancer. Cell. Cycle (Georgetown, Tex) 12 (11), 1679–1687.
Bonifacio, L.N., Jarstfer, M.B., 2010. MiRNA profile associated with replicative senescence, extended cell culture, and ectopic telomerase expression in human foreskin fibroblasts. PloS one 5 (9).
Braunersreuther, V., et al., 2013. Role of NADPH oxidase isoforms NOX1, NOX2 and NOX4 in myocardial ischemia/reperfusion injury. J. Mol. Cell. Cardiol. 64, 99–107.
Canto, C., Auwerx, J., 2011. Interference between PARPs and SIRT1: a novel approach to healthy ageing? Aging 3 (5), 543–547.
Cha, M.J., et al., 2013. MicroRNA-145 suppresses ROS-induced Ca2+ overload of cardiomyocytes by targeting CaMKIIdelta. Biochem. Biophys. Res. Commun. 435 (4), 720–726.
Chen, P.S., et al., 2012a. Dysregulation of microRNAs in cancer. J. Biomed. Sci. 19, 90.
Chen, K.C., et al., 2012b. OxLDL causes both epigenetic modification and signaling regulation on the microRNA-29b gene: novel mechanisms for cardiovascular diseases. J. Mol. Cell. Cardiol. 52, 587–595.
Chilton, W.L., et al., 2014. Acute exercise leads to regulation of telomere-associated genes and microRNA expression in immune cells. PloS One 9 (4), e92088.
Chimenti, C., et al., 2003. Senescence and death of primitive cells and myocytes lead to premature cardiac aging and heart failure. Circ. Res. 93 (7), 604–613.
Csiszar, A., et al., 2005. Role of oxidative and nitrosative stress, longevity genes and poly(ADP-ribose) polymerase in cardiovascular dysfunction associated with aging. Curr. Vasc. Pharmacol. 3 (3), 285–291.
Das, S., et al., 2012. Nuclear miRNA regulates the mitochondrial genome in the heart. Circ. Res. 8 110 (12), 1596–1603.
Devaux, Y., et al., 2013. MicroRNA-150: a novel marker of left ventricular remodeling after acute myocardial infarction. Circ. Cardiovasc. Genet. 6 (3), 290–298.
Dong, De-li, Yang, Bao-feng, 2011. Role of microRNAs in cardiac hypertrophy, myocardial fibrosis and heart failure. Acta Pharm. Sin. B 1 (1), 1–7.
Duisters, R.F., et al., 2009a. miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. Circ. Res. 30 104 (2), 170–178, 6pp. following 8.
Duisters, R.F., et al., 2009b. miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. Circ. Res. 104 (2), 170–178, 6p Following 8.
Dutta, D., et al., 2012. Contribution of impaired mitochondrial autophagy to cardiac aging: mechanisms and therapeutic opportunities. Circ. Res. 110 (8), 1125–1138.
Gonzalez, A., et al., 2008. Activation of cardiac progenitor cells reverses the failing heart senescent phenotype and prolongs lifespan. Circ. Res. 102 (5), 597–606.
Gorospe, M., Abdelmohsen, K., 2011. MicroRegulators come of age in senescence. Trends Genet.: TIG 27 (6), 233–241.
Guo, H., et al., 2010. Mammalian microRNAs predominantly act to decrease target mRNA levels. Nature 466 (7308), 835–840.
Gurha, P., et al., 2013. microRNA-22 promotes heart failure through coordinate suppression of PPAR/ERR-nuclear hormone receptor transcription. PloS One 8 (9), e75882.
Huang, Z.P., et al., 2013. MicroRNA-22 regulates cardiac hypertrophy and remodeling in response to stress. Circ. Res. 112 (9), 1234–1243.
Ikeda, S., et al., 2007. Altered microRNA expression in human heart disease. Physiol. Genomics 31 (3), 367–373.
Ito, T., et al., 2010. MicroRNA-34a regulation of endothelial senescence. Biochem. Biophys. Res. Commun. 6 398 (4), 735–740.
Jayawardena, T.M., et al., 2012. MicroRNA-mediated in vitro and in vivo direct reprogramming of cardiac fibroblasts to cardiomyocytes. Circ. Res. 110 (11), 1465–1473.
Jazbutyte, V., et al., 2013. MicroRNA-22 increases senescence and activates cardiac fibroblasts in the aging heart. Age Dordr. Neth. 35 (3), 747–762.
Khanna, N., et al., 2014. MicroRNA-146b promotes myogenic differentiation and modulates multiple gene targets in muscle cells. PloS One 9 (6), e100657.
Kim, H.J., et al., 2014. Augmentation of NAD(+) by NQO1 attenuates cisplatin-mediated hearing impairment. Cell Death Dis. 5, e1292.
Konstantinidis, K., et al., 2012. Mechanisms of cell death in heart disease. Arterioscler. Thromb. Vasc. Biol. 32 (7), 1552–1562.
Krishnan, K., et al., 2013. MicroRNA-182-5p targets a network of genes involved in DNA repair. RNA (New York, NY) 19 (2), 230–242.
Lafferty-Whyte, K., et al., 2009. Pathway analysis of senescence-associated miRNA targets reveals common processes to different senescence induction mechanisms. Biochim. Biophys. Acta 1792 (4), 341–352.
Leung, A.K., et al., 2011. Poly(ADP-ribose) regulates stress responses and microRNA activity in the cytoplasm. Mol. Cell. 42 (4), 489–499.
Li, G., et al., 2009. Alterations in microRNA expression in stress-induced cellular senescence. Mech. Ageing Dev. 130 (11–12), 731–741.
Li, Y., et al., 2012. IGF-1 prevents oxidative stress induced-apoptosis in induced pluripotent stem cells which is mediated by microRNA-1. Biochem. Biophys. Res. Commun. 426 (4), 615–619.
Limana, F., et al., 2005. Exogenous high-mobility group box 1 protein induces myocardial regeneration after infarction via enhanced cardiac C-kit+ cell proliferation and differentiation. Circ. Res. 97 (8), e73–83.
Limana, F., et al., 2011. HMGB1 attenuates cardiac remodelling in the failing heart via enhanced cardiac regeneration and miR-206-mediated inhibition of TIMP-3. PloS One 6 (6), e19845.
Lopez-Otin, C., et al., 2013. The hallmarks of aging. Cell 153 (6), 1194–1217.
Maes, O.C., et al., 2009. Stepwise up-regulation of microRNA expression levels from replicating to reversible and irreversible growth arrest states in WI-38 human fibroblasts. J. Cell. Physiol. 221 (1), 109–119.
Magenta, A., et al., 2011. miR-200c is upregulated by oxidative stress and induces endothelial cell apoptosis and senescence via ZEB1 inhibition. Cell Death Differ. 18 (10), 1628–1639.
Magenta, A., et al., 2013. Oxidative stress and microRNAs in vascular diseases. Int. J. Mol. Sci. 14 (9), 17319–17346.

Martinelli, N.C., et al., 2014. An analysis of the global expression of microRNAs in an experimental model of physiological left ventricular hypertrophy. PloS One 9 (4), e93271.
Matkovich, S.J., et al., 2010. MicroRNA-133a protects against myocardial fibrosis and modulates electrical repolarization without affecting hypertrophy in pressure-overloaded adult hearts. Circ. Res. 106 (1), 166–175.
Menghini, R., et al., 2009. MicroRNA 217 modulates endothelial cell senescence via silent information regulator 1. Circulation 120 (15), 1524–1532.
Menghini, R., et al., 2013. MicroRNAs in endothelial senescence and atherosclerosis. J. Cardiovasc. Transl. Res. Dec 6 (6), 924–930.
Mohamed, J.S., et al., 2014. MicroRNA-149 inhibits PARP-2 and promotes mitochondrial biogenesis via SIRT-1/PGC-1alpha network in skeletal muscle. Diabetes 63 (5), 1546–1559.
Moskwa, P., et al., 2011a. miR-182-mediated downregulation of BRCA1 impacts DNA repair and sensitivity to PARP inhibitors. Mol. Cell 41 (2), 210–220.
Moskwa, P., et al., 2011b. miR-182-mediated downregulation of BRCA1 impacts DNA repair and sensitivity to PARP inhibitors. Mol. Cell 41 (2), 210–220.
Motohashi, N., et al., 2013. Regulation of IRS1/Akt insulin signaling by microRNA-128a during myogenesis. J. Cell Sci. 126 (Pt 12), 2678–2691.
Naga Prasad, S.V., et al., 2009. Unique microRNA profile in end-stage heart failure indicates alterations in specific cardiovascular signaling networks. J. Biol. Chem. 284 (40), 27487–27499.
Neijenhuis, S., et al., 2013. Identification of miRNA modulators to PARP inhibitor response. DNA Repair 12 (6), 394–402.
Noren Hooten, N., et al., 2010. microRNA expression patterns reveal differential expression of target genes with age. PloS One 5 (5), e10724.
Pacher, P., Szabo, C., 2007. Role of poly(ADP-ribose) polymerase 1 (PARP-1) in cardiovascular diseases: the therapeutic potential of PARP inhibitors. Cardiovasc. Drug Rev. 25 (3), 235–260.
Patrick, D.M., et al., 2010. Stress-dependent cardiac remodeling occurs in the absence of microRNA-21 in mice. J. Clin. Investig. 120 (11), 3912–3916.
Porrello, E.R., et al., 2011. MiR-15 family regulates postnatal mitotic arrest of cardiomyocytes. Circ. Res. 2 109 (6), 670–679.
Potus, F., et al., 2014. Vascular remodeling process in pulmonary arterial hypertension, with focus on miR-204 and miR-126 (2013 Grover Conference series). Pulm. Circ. 4 (2), 175–184.
Pourrajab, F., et al., 2014a. MicroRNA-based system in stem cell reprogramming; differentiation/dedifferentiation. Int. J. Biochem. Cell Biol. 20.
Pourrajab, F., et al., 2014b. Application of stem cell/growth factor system, as a multimodal therapy approach in regenerative medicine to improve cell therapy yields. Int. J. Cardiol. 15 173 (1), 12–19.
Qin, B., et al., 2012. Role of microRNAs in endothelial inflammation and senescence. Mol. Biol. reports 39 (4), 4509–4518.
Rangrez, A.Y., et al., 2011. miR-143 and miR-145: molecular keys to switch the phenotype of vascular smooth muscle cells. Circ. Cardiovasc. Genet. 4 (2), 197–205.
Rippe, C., et al., 2012. MicroRNA changes in human arterial endothelial cells with senescence: relation to apoptosis, eNOS and inflammation. Exp. Gerontol. 47 (1), 45–51.
Rippo, M.R., et al., 2014. MitomiRs in human inflamm-aging: a hypothesis involving miR-181a, miR-34a and miR-146a. Exp. Gerontol. 56, 154–163.
van Rooij, E., et al., 2008. Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. Proc. Natl. Acad. Sci. USA 105 (35), 13027–13032.
Rodier, F., Campisi, J., 2011. Four faces of cellular senescence. J. Cell Biol. 192 (4), 547–556.
Schraml, E., Grillari, J., 2012. From cellular senescence to age-associated diseases: the miRNA connection. Longev. Heal. 1 (1), 10.
Schroen, B., Heymans, S., 2012. Small but smart–microRNAs in the centre of inflammatory processes during cardiovascular diseases, the metabolic syndrome, and ageing. Cardiovasc. Res. 93 (4), 605–613.
Seeger, T., et al., 2013. Immunosenescence-associated microRNAs in age and heart failure. Eur. J. Heart Fail. 15 (4), 385–393.
Sharma, A., et al., 2013. The role of SIRT6 protein in aging and reprogramming of human induced pluripotent stem cells. J. Biol. Chem. 288 (25), 18439–18447.
Song, X.W., et al., 2010. MicroRNAs are dynamically regulated in hypertrophic hearts, and miR-199a is essential for the maintenance of cell size in cardiomyocytes. J. Cell. Physiol. 225 (2), 437–443.
Staszel, T., et al., 2011. Role of microRNAs in endothelial cell pathophysiology. Pol. Arch. Med. Wewnetrznej 121 (10), 361–366.
Tabuchi, T., et al., 2012. MicroRNA-34a regulates the longevity-associated protein SIRT1 in coronary artery disease: effect of statins on SIRT1 and microRNA-34a expression. Clin. Sci. Lond. Engl.: 1979) 123 (3), 161–171.
Takaya, T., et al., 2009. MicroRNA-1 and MicroRNA-133 in spontaneous myocardial differentiation of mouse embryonic stem cells. Circ. J. Off. J. Jpn. Circ. Soc. 73 (8), 1492–1497.
Tan, K.S., et al., 2009. Expression profile of MicroRNAs in young stroke patients. PloS One 4 (11), e7689.
Tessitore, A., et al., 2014. MicroRNAs in the DNA damage/repair network and cancer. Int. J. genomics 2014, 820248.
Tian, F.J., et al., 2014. Elevated microRNA-155 promotes foam cell formation by targeting HBP1 in atherogenesis. Cardiovasc. Res. 103 (1), 100–110.
Topkara, V.K., Mann, D.L., 2011. Role of microRNAs in cardiac remodeling and heart failure. Cardiovasc. Drugs Therapy/Sponsor. Int. Soc. Cardiovasc. Pharmacother. 25 (2), 171–182.
Torella, D., et al., 2004. Cardiac stem cell and myocyte aging, heart failure, and insulin-like growth factor-1 overexpression. Circ. Res. 94 (4), 514–524.
Tsirpanlis, G., 2008. Cellular senescence, cardiovascular risk, and CKD: a review of established and hypothetical interconnections. Am. J. kidney Dis.: Off. J. Natl. Kidney Found. 51 (1), 131–144.
Ugalde, A.P., et al., 2011. Aging and chronic DNA damage response activate a regulatory pathway involving miR-29 and p53. EMBO J. 30 (11), 2219–2232.
Varga, Z.V., et al., 2013. MicroRNA-25-dependent up-regulation of NADPH oxidase 4 (NOX4) mediates hypercholesterolemia-induced oxidative/nitrative stress and subsequent dysfunction in the heart. J. Mol. Cell. Cardiol. 62, 111–121.
Vasa-Nicotera, M., et al., 2011. miR-146a is modulated in human endothelial cell with aging. Atherosclerosis 217 (2), 326–330.
Wang, Y., et al., 2012a. MiR-96 downregulates REV1 and RAD51 to promote cellular sensitivity to cisplatin and PARP inhibition. Cancer Res. 72 (16), 4037–4046.
Wang, J., et al., 2012b. MicroRNA-24 regulates cardiac fibrosis after myocardial infarction. J. Cell. Mol. Med. 16 (9), 2150–2160.
Wei, Y., et al., 2013. MicroRNA-126, -145, and -155: a therapeutic triad in atherosclerosis? Arteriosclerosis, Thromb. Vasc. Biol. 33 (3), 449–454.
Wu, C.W., et al., 2013. MicroRNA-18a attenuates DNA damage repair through suppressing the expression of ataxia telangiectasia mutated in colorectal cancer. PloS One 8 (2), e57036.
Yao, E., Ventura, A., 2011. A new role for miR-182 in DNA repair. Mol. Cell 41 (2), 135–137.
Zhang, T., Kraus, W.L., 2010. SIRT1-dependent regulation of chromatin and transcription: linking NAD(+) metabolism and signaling to the control of cellular functions. Biochimicaetbiophysicaacta 1804 (8), 1666–1675.
Zhang, X., et al., 2012. The expression of microRNA and microRNA clusters in the aging heart. PloS One 7 (4), e34688.
Zhao, T., et al., 2010. MicroRNA-34a induces endothelial progenitor cell senescence and impedes its angiogenesis via suppressing silent information regulator 1. Am. J. Physiol. Endocrinol. Metabol. 299 (1), E110–E116.
Zhu, H., et al., 2011. MicroRNA-195 promotes palmitate-induced apoptosis in cardiomyocytes by down-regulating Sirt1. Cardiovasc. Res. 92 (1), 75–84.