

Tissue response to injury: Ubiquity of cell injury makes inflammation-mediated disorders ubiquitous

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“Tissue response to injury”, this is the most concise and perfect definition for “inflammation.”

With time, more aspects of inflammation become clear and new windows open. Inflammation could be secondary to any internal or external insult leading to potential tissue or cell injury. Cell injury by definition is any level of cell (tissue) damage from any kind of adverse stimuli which disrupts the normal physiology of affected cells (tissue).¹

When a known causation is established, for example a microorganism, the complexity of the diseased condition is reduced and the category of diseases is shifted to fields other than autoimmunity and rheumatology. However, when no culprit agent is found, then we confront different ideations and conceptual debates. This covers the general term for rheumatism.

If we believe the unique definition for inflammation, i.e. “tissue response to injury,” then most unwanted cryptogenic events that happen continuously in the body become easy to understand from a philosophic point of view.

Understanding all aspects of inflammation could be difficult and interesting; it could be either tiny and to a milieu with limited clinical significance (low-grade inflammation) or huge enough to devastate the host organ systems with prominent clinical presentation (high-grade inflammation). Moreover, idiopathic inflammatory reaction could be of short duration with minimal clinical significance or long-lasting with resultant tissue injury. This immune-mediated tissue response to the injury could be associated with known immunologic makers such as rheumatoid factor, ANA, ANCA, or other surrogates of autoimmunity or not. Tissue injury may expose some hidden antigens to immune system following corrupted self-tolerance.

Inflammation, in general terms, denotes engaging the immune system in any type of injured tissue. So, infiltration of, for example, eosinophils in response to putative insulting agents (allergens) could be a feature of inflammation, as well as infiltration of lymphoplasma cells as occurred in most chronic rheumatic diseases or neoplastic cells in a cancer.² Immune cell activation and cytokine production in response to tissue injury without prominent cell infiltration also seems to be covered by the term inflammation.

It seems that there is no clear-cut border between the definition of rheumatism and allergic reactions at the extreme end of their spectrum.^{3,4} We can hypothesize that if an inflammation or immune aberrancy is limited to body surfaces (i.e. skin and mucosal membranes), we are most likely facing an “atopy.” On the other hand, when immune responses attack more deeply the viscera and organs, we should use the term “rheumatism;” and if atypical cells are infiltrated anywhere a “neoplasm” is in place.⁵

Understanding that some seemingly bland events like osteoarthritis cannot be free from inflammation and different interpretations may arise based on our individual backgrounds and conceptualization. In the definition of “injury,” we should consider any kinds of injuries including mechanical (osteoarthritis), autoimmune (known and unknown collagen vascular diseases), or even emotional insults (role of emotional factors on immune system). So, theoretically, with the basic notions above, we have no pure mechanical disease or any other types of tissue

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injury in a “multicellular living organism” without an inflammatory reaction. But this definitely does not mean that all medical conditions necessarily need anti-inflammatory therapy. Supposing the systemic reaction to an inflammation (elevated CRP or ESR or possibly humoral mediators of inflammation) is sine qua non for the definition of rheumatism and managing it as an inflammatory condition, we have a number of serious rheumatic diseases with systemically negative profiles but devastating results without aggressive therapy. Single organ vasculitis like isolated CNS vasculitis or normal ESR giant cell arteritis/Takayasu arteritis are good examples. On the other hand, several studies and clinical observations showed overt clinical responses with systemic or local anti-inflammatory therapy in so-called mechanical diseases.^{6,7} Therefore, the borders of these definitions are no longer inviolate.

More interestingly, the role of foods is more emphasized recently in the induction, perpetuation, and dampening of inflammation.⁸ It means that individual foods per se or over-feeding (obesity) may cause a vicious cycle of tissue injury and consequent inflammation.^{9,10} However, potentially bad foods “based on individual people” may act as a “Trojan horse” and may be hard to be accepted as an etiology of persistent inflammation by most clinicians. Obesity as a result of imbalance between calorie intake and metabolic demand, on the other hand, may badly effect the immune system, even resulting in the impairment of some brain functions.¹¹

Taken together, giving a comprehensive and also comprehensible definition for inflammation and rheumatism is a rather difficult task and it should be considered in making definitions for so-called inflammatory and non-inflammatory conditions.

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