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Inflammatory Vascular Disease: A Unifying Hypothesis

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From many, one.
Endless seas distilled.
All stars a single sun.
Droplets frozen still
Consumed in unlimited flame,
Burning with a single name.
Old pathways unite
In flight

Anonymous, 2012

Research scientists and physicians alike describe many different forms of inflammatory vascular disease, reporting each separate pathological entity in terms of individual causes, symptoms, signs, and physical findings Atherosclerotic plaque, recurrent plaque growth after angioplasty and stent implant, transplant rejection, arthritic disorders, and the inflammatory vasculitic syndromes such as giant cell arteritis or Takayasu's disease, are all associated with increased inflammatory cell activation and severe arterial disease. Viewing these vasculitic disorders autonomously, as separate entities, leads to a risk of misdiagnosis, longer treatment, increased mortality, and in short limits treatment options. This has significant implications for morbidity and mortality. The very classifications on which we rely prevent us from seeing that inflammatory arterial disorders actually represent a continuum. We propose here that these separate classifications of vascular disease are artificial, that these vascular diseases represent a continuum of inflammatory arterial disorders, rather than separate pathological entities. We postulate that the underlying central cause for a wide spectrum of occlusive arterial diseases is an up-regulation of innate immune responses that drive ongoing arterial damage.

Inflammation or innate immunity is now proven to have a central role in many disease processes from infections to degenerative joint disease to cancers and finally arterial disease. Metchnikov first describes innate immunity or inflammation (1845-1916). The innate immune response occurs long before an antibody-mediated defense is mounted by a mammalian host. Metchnikov made his discovery, through observing a rapid cellular response after inserting a splinter into a transparent starfish. Innate immune responses clear the majority of infections, clearing over eighty percent of infections, before antibody mediated defenses arise. Conversely, when excessive, this same innate immunity can cause ongoing damage to the arterial wall and can affect organs after injury from differing causes, such as trauma, infection, and toxins as found in cigarette smoke. We now believe this inflammation driven collateral damage to be a leading cause for atherosclerotic arterial disease. These same inflammatory responses may also alter the balance in the coagulation (clot forming) pathway inducing platelet and serine protease activation with sudden plaque rupture and thrombotic vascular occlusions. Davies et al reported that acute inflammatory cell invasion into the surface of atherosclerotic plaques leads to plaque rupture. The thrombotic occlusions often occur in lesions that are less than seventy percent occlusive for the arterial lumen. It is this same systemic innate immune response that drives ongoing damage in the many differing vasculitic disorders classified under differing names.

Research now clearly demonstrates that this same inflammatory response system with activation of monocyte/macrophage cells and T lymphocytes drives atheroma formation. The injurious agents include hyperlipidemia, hypertension, diabetes mellitus, smoking, and also of course various iatrogenic injuries such as balloon angioplasty and stent implant or even cardiac transplant. In native atherosclerosis when the inflammatory system is activated these cells can attach to the plaque surface or erode the plaque from within causing sudden rupture and thrombotic occlusion. Russell Ross first proposed a similar 'Response to Injury' hypothesis 1977, suggesting that many differing causes for damage to the arterial inner lining, the intimal layer of endothelial cells, can induce the rapid growth of atherosclerotic plaque. It is the sudden rupture of an unstable plaque with inflammatory macrophage invasion which causes sudden arterial clot formation that blocks blood flow and causes for heart attacks and strokes or even peripheral vascular occlusions and gangrene.

What causes the sudden increased inflammatory cell response leading to cell invasion, connective tissue breakdown, plaque rupture and local clot formation is not completely defined, however inciting events such as recent upper respiratory infections have been correlated with increased incidence of myocardial infarctions (heart attacks). Recent reports further indicate that the acute inflammatory changes seen in atheromata with erosion and rupture of the plaque surface may be accelerated by acute infections. Upper respiratory bacterial infections as well as influenza are now known to be associated with acute heart attack and stroke. One study even detected a reduction in acute MI with vaccination against influenza. Similar associations between ongoing periodontal disease and increased atherosclerotic vascular disease (ASVD) are also reported and confirmed by the American Heart Association.

These same inflammatory responses also are responsible for roughly fifty percent of the ongoing arterial damage seen after transplants, an ongoing damage that can begin at the time of organ transplant with damage produced by donor ischemia, surgical trauma and even infections. Infectious organisms such as cytomegalovirus (CMV) have been associated with both transplant vasculopathy and organ scarring, also called chronic rejection, as well as with the more common atherosclerotic lesions. Oral bacteria that cause periodontal

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disease are implicated in systemic disorders such as endocarditis, ASVD, rheumatoid arthritis, adverse pregnancy outcomes, and Alzheimer's disease. Oral pathogens are associated with advanced plaque growth although work continues to determine the precise roles for oral pathogens in atherosclerotic plaque growth. Significant associations between oral pathogens and atherosclerotic plaque were reported beginning in the 1990s, however a direct causative role has yet to be proven nor is it known whether the association is due to systemic up-regulation of inflammatory responses of is limited to a true direct infectious process. Gene sequences for specific organisms such as *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Agrigatibacter actinomycetemcomitans*, *Prevotella intermedia*, and *Streptococcus mutans* have been reported in atherosclerotic plaques and more recent work has demonstrated increased plaque growth with oral and systemic oral pathogen infections in animal models.

Inflammatory vasculitic syndromes (IVS), which include Takayasu's disease as well as giant cell arteritis among others, are very aggressive forms of inflammatory vascular disease. These IVS cause widespread arterial narrowings as well as aneurysm formations and Takayasu's disease is also called pulseless disease for this reason. These arterial lesions are characterized by activated T lymphocyte and macrophage infiltrates, as well as thrombosis. The vascular narrowing leads to extensive organ ischemia and in some cases strokes, sudden blindness, cardiomyopathies and severe claudication in the extremities. This severe diffuse arterial blockade is reminiscent of the peripheral arterial disease seen in Berger's disease. While specific etiological causes or infections are not known for these medium to large vessel syndromes e.g. Takayasu's and Giant cell arteritis, hepatitis viral markers have been associated with another IVS called polyarteritisnodosa. Of interest, when first described the polyarteritisnodosa was believed to be cause by small worms infecting the arterial wall – this theory was later retracted.

In each of these arterial diseases or syndromes the same inflammatory cells are found associated with disease progression. T lymphocytes as well as macrophage abound, invading the arterial wall from the lumen and intimal layers from the circulating blood and also are seen migrating into the intimal layers from the outer adventitial layers. Similar changes in the balance between pro-inflammatory CD4+ T helper (Th) cells between pro-inflammatory Th1, and Th17 to more inflammation suppressing Th2 and Treg, have been reported in many of these vasculitic states. Recent work has detected altered levels of the newly-coined pro-inflammatory macrophage 1 and the predominantly anti-inflammatory macrophage 2. These innate immune system activators release cytokines, chemokines, and growth factors that further activate inflammatory mononuclear cells in turn activating the clot forming and clot dissolving cascades.

Platelets are small cell fragments that initiate clot formation at sites of endothelial injury, carrying stores of inflammatory cytokines and clotting factors that are released to further stimulate these processes and exacerbate local inflammatory responses. Coagulation proteases can also activate the innate immune response. Both thrombotic (clot forming) and thrombolytic (clot dissolving proteases are expressed at sites of arterial and tissue damage. The thrombotic factor X and thrombin factor II activate receptors called Protease Activated Receptors (PAR) on inflammatory mononuclear cells. Similarly the thrombolytic proteases, tissue- and urokinase-type plasminogen activators (tPA and uPA) and their receptors (PAR and uPAR)increase cell adhesion, and cell migration through activation of matrix degrading enzymes called matrix metalloproteinases (MMPs).

Serine protease inhibitors named serpins, such as anti-thrombin III (ATIII) and plasminogen activator inhibitor-1 (PAI-1) regulate these proteases, and also alter inflammatory responses. While atherosclerotic plaque is often described as limited to the intimal (endothelial luminal) layer of the arterial wall, in fact many reports now have indicated marked inflammatory cell infiltrates in the adventitial and medial layers as well. Moreover, parallels in gene expression, cytokine and protease activators and inflammatory cell infiltrates are detected in vascular disease progression whether it is the more common atheroma or the less common IVS.

We suggest that each of these pathologic disorders representvariants of similar, if not identical, disease processes, and that in fact the variations in the pathology represent different causative events. These events include, but are not limited to, selected infections, host susceptibility and host responses. Certainly the arterial tree is the gateway through which inflammatory cells, clotting factors, and infections can spread systemically and reach downstream organs, causing damage. The arterial system is thus not simply a potential site for pathological change, as in inflammatory vascular disorders, but also supplies many of disease-driving factors throughout the human body. We propose that these inflammation-based arterial diseases be classified together under a broad label of inflammatory arterial disease (IAD). Within this encompassing definition we can then proceed to investigate the shared etiologies such as potential triggers that may drive these devastating and widespread disorders.