Disease Patterns in Vasculitis—Still a Mystery

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Abstract

In the field of autoimmunity, much has been learned from studying circulating and tissue bound immune-reactive cells, cytokines and antibodies. However, what has brought those cells to the site of injury, for most forms of vasculitis remains a mystery. Might the etiology of at least certain forms of vasculitis be related to generation of neoantigens in the native vessel, making that vessel the target of a pathogenic immune response? How might one explain organ targeting and patterns of disease that are so critical to the diagnostic process? Embryologists have demonstrated great diversity in the vasculature of different organs. Unique quantitative and qualitative features become apparent in vascular territories as early as the third week of gestation. These differences are later amplified by the effects of further development, aging, infection, spontaneous mutations and other co-morbidities. Based on data from these observations a testable hypothesis would be that many forms of vasculitis may begin with emergence of new antigens within affected vessel walls and the resulting immune response may in fact be a normal reaction to perceived foreign protein(s).

Traditional thought regarding the pathogenesis of diseases such as rheumatoid arthritis, systemic lupus erythematosus, myositis, vasculitis, and similar conditions has favored a primary role for acquired aberrancies of immune function. Indeed until recent times, this has been my thinking about vasculitis. Being a clinician, it has not been a particular observation from my laboratory or discoveries from biopsy materials that have swayed me. Rather, clinical observations of many patients who represent a broad spectrum of vascular inflammatory diseases, especially vasculitides that affect single organs, have shaped my opinion. These experiences have suggested that primary abnormalities in the affected tissue (i.e., modifications in their molecular, cellular, or matrix content) should be considered as early factors in disease etiology and subsequent pathogenesis. I will try to support this argument with data from studies of single-organ autoimmune diseases, associations of infection with autoimmunity, alterations of native tissues and subsequent immune responses in malignancy, protein modifications that occur with aging, and lessons learned from embryogenesis of the vascular system.

Autoimmune diseases of single organs such as the thyroid, pancreas, adrenal gland, or brain are well known. Research in these areas has lead to discoveries of immune reactions to unique antigens and focal alterations in immune response within affected organs. Examples of targeted antigens in single-organ disease include thyroglobulin, thyroid peroxidase, the TSH cell surface receptor, the pancreatic islet cell protein glutamic acid decarboxylase, insulin, intracellular myelin oligodendrocyte glycoprotein epitopes, and the acetylcholine receptor at neuromuscular junctions.1 In some instances, disease susceptibility may be enhanced by modifications of the target organ or native proteins as the result of spontaneous mutations or organ injury, such as that associated with infection2 or radiation.3 Experimental studies with cytomegalovirus infection of human thyroid tissue have demonstrated induction of expression of MHC (major histocompatibility complex) class II molecules on thyroid cells, which may act as antigen-presenting cells (APCs), thereby initiating a thyroid autoimmune response.4

In the seemingly unrelated area of oncology, tumor-specific neoantigens have been recognized to elicit unique

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immune responses. In this setting, artificial means to enhance the immune response has had therapeutic benefits. Tumor-associated antigens have been used to expand populations of cytotoxic T cells, which can then be deployed as therapeutic agents. While enhancement of autoimmune responses may not be a sound strategy, this example illustrates how aberration in cell development may produce neoantigens that lead to unique immune responses. It would not appear far-fetched to consider whether mutations that produce changes in cell proteins, but not malignancy, may be the first step in generating certain autoimmune diseases.

Are these observations relevant to vasculitis? The comparisons with single-organ autoimmune diseases are most compelling in regards to single-organ vasculitides (SOV), a group of diseases that are known to affect many different unique organs and for which surgical resection is often curative. We have questioned whether these most simple forms of vasculitis might provide a key to better understanding of the pathogenesis of systemic vasculitides. The SOV have reminded us of the unique properties of vascular beds within each organ, a point emphasized by embryologists, but not widely appreciated in the field of autoimmunity.

The early embryo, at about 3 weeks' gestation (gastrula stage), is differentiated into three distinct cell layers, ectoderm, mesoderm, and endoderm. Mesoderm is responsible for most, but not all, of the developing vasculature. The ectoderm, in becoming ectomesenchyme and later neural crest cells, plays a critical role in the development of head and neck structures as well as the aortic root, arch, pulmonary artery trunk, and proximal components of the arch vessels. In these vascular regions, ectoderm-derived smooth muscle cells (SMCs) differ from similar appearing SMCs derived from mesoderm. In the descending aorta VSMCs are a mosaic of cells derived from mesoderm and ectoderm. The abdominal aorta VSMCs are mesoderm derived.

vascular distinctions within organs are not unique to regions of the aorta; they differ in most organs that have been compared to date in regards to endothelial junctions, basement membrane composition, pericytes, and quantity and quality of their matrix. Vascular beds differ in regard microanatomical structures. The terms “continuous,” “fenestrated,” “diaphragmatic,” and “discontinuous” (also known as sinusoidal) reflect unique structure-function roles (Fig. 2). Vascular SMCs of have been found to be remarkably “plastic” in their responses to numerous stimuli. While

**Figure 1** Mesoderm is responsible for most, but not all, of the developing vasculature. The ectoderm (x), in becoming ectomesenchyme and later neural crest cells, plays a critical role in the development of head and neck structures as well as the aortic root, arch, pulmonary artery trunk, and proximal components of the arch vessels. In these vascular regions, ectoderm-derived smooth muscle cells (SMCs) differ from similar appearing SMCs derived from mesoderm. In the descending aorta VSMCs are a mosaic of cells derived from mesoderm and ectoderm. The abdominal aorta VSMCs are mesoderm derived.

**Figure 2** Diagrammatic representation of tissue and organ specific structures in capillaries and post-capillary venules. Endothelial cells are a source of platelet derived growth factor, which plays a key role in recruitment of pericytes, which in conjunction with basement membrane provides for unique functional microvascular properties in each organ. A continuous barrier is associated with a tight seal and highly selective transport, as found in large arteries and veins, skin, tongue, skeletal muscle, heart, lung, retina and brain. Other microvascular arrangements are associated with less selectivity. For example, fenestrated capillaries allow rapid passage of large molecules in endocrine and exocrine glands, gastrointestinal mucosa and renal glomeruli.
plasticity may be adaptive, it may also be maladaptive in regards to new production of proteins, matrix, proliferation, and migration. Indeed, embryologists maintain that vascular networks in individual organs are as dynamic and unique as their parenchyma.

In addition to native vascular territories having unique qualities, vessels, like all other tissues, are modified by events such as aging or infection. Examples of the latter are herpes and other viral infections that may or may not be clinically apparent, but persist in varying degrees of latency throughout life. The affects of aging on elastic arteries includes increased vessel wall thickening and stiffness. This is in part related to fragmentation and depletion of elastica, an increase in collagen, increased production of advanced glycation end (AGE) products by cross-linking proteins with reducing sugars, increased smooth muscle growth and migration, and increase in matrix formation. AGE can change function and perhaps antigenicity of surface proteins. Aging is also accompanied by varying degrees of endothelial cell dysfunction, e.g., decreased production of nitric oxide, prostacyclin, and loss of selective permeability.

Observations from embryologists and vascular biologists have taught us that the vascular network is highly variable from the time of birth. Over a lifetime, that variability may be enhanced by aging, diet, disease, mutations, and environmental factors. Might some of these changes lead to unique antigens that set the stage for disease-producing immune responses?

There are many different forms of vasculitis, yet the patterns of involvement for specific diseases are to a large degree stereotypic. This is not unlike certain other vascular diseases. For example, aortic aneurysms in the arch region are most often related to cystic medial degeneration, whereas abdominal aneurysms are overwhelmingly due to atherosclerosis. Gene expression studies of the arch and abdominal aorta reveal similarities of about 83%. However, about 17% of genes expressed in each site (about 100 genes of 1185 evaluated) are unique and not expressed in the other part of the aorta. The result is that there are unique differences in matrix profiles of the arch, compared to the abdominal aorta. Students of vasculitis may benefit from what has been learned about vascular substrate differences, gene expression, and disease vulnerability.

It is likely that these observations bear on an animal model of aortitis produced by infection. A study of a usually harmless herpes virus in wild type mice had much different outcomes in animals genetically deficient in IFNγ or IFNγR. The latter groups experienced sudden death from aortic aneurysm rupture or dissection. Vessel injury was limited to the aortic arch; the remainder of the vascular tree being spared.

The notion of a primary modification(s) in the target tissue initiating autoimmunity would not detract from the well-known effects of genetic susceptibility or gender on the expression of some autoimmune diseases. The concepts presented in this essay merely emphasize how endogenous and environmental factors may generate stimuli that potentially may produce disease in a single organ. For this model to be relevant to multisystem autoimmune diseases would require expansion of the immune response to other organs, though mechanisms, such as molecular mimicry or, in the case of an infectious trigger, selective binding to common or similar ligands in multiple organs in which neoantigens or modified antigens are generated.

These observations suggest a number of interesting hypotheses:

1. Vessel infrastructure plays a key role in determining patterns of vessel targeting.
2. Inherent and acquired properties of vessels, including those related to age, environmental pathogens (e.g., prior infection), and spontaneous mutations are important factors in defining substrate risk.
3. In some vasculitides, the immune response may be “normal” and substrate abnormalities may drive injury-response patterns.
4. Acquired immunologic abnormalities may be important but local immune responses that are not the same in all organs may be critical in determining site vulnerability and disease phenotype.

Throughout the past 20 years, very important studies have served us well in delineating components of the immune response in vasculitis and other autoimmune diseases. I believe that the time has come for our community to take a closer look at how unique features of affected vascular substrate may influence pathogenesis.

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