The Polymorphonuclear Leukocyte and the Abdominal Aortic Aneurysm
A Neglected Cell Type and a Neglected Disease

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Atherosclerotic occlusive disease (AOD) and AAA share 2 risk factors: smoking and hypertension. There is 1 risk factor that is divergently shared; diabetes mellitus is a positive risk factor for AOD and a negative risk factor for AAA. There has been little scientific evidence that the 2 positively shared risk factors operate through the same molecular mechanisms. When a probable cause has joint observable effects, the conclusion that one observable effect has caused the other has been called the “fallacy of spurious causation.” The Joint Committee of the Society for Vascular Surgery and the North American Chapter of the International Cardiovascular Surgery on “Reporting Standards for Aortic Aneurysm” took the positive step in 1991 of recommending that the usual term “atherosclerotic aneurysm” be replaced by the term “nonspecific aneurysm” because there was so little evidence that atherosclerosis actually causes aneurysmal disease.9

The contemporary period of AAA research may have been initiated by the editorialist in a publication in 1980, which compared profiles of 50 patients with AAA with 50 patients with AOD.10 The characteristics of these 2 populations were so divergent that the author speculated that AOD and AAA were 2 different disease processes. It was unwritten knowledge at the time that vessels that are aneurysm susceptible (eg, the internal iliac artery and the popliteal artery) are relatively AOD resistant, whereas vessels that are aneurysm resistant (eg, the external iliac artery) are highly AOD susceptible. It is interesting that aneurysm-susceptible versus aneurysm-resistant vessels have different embryological anlage, which has become a new subject for molecular aneurysm research. There are not only artery-specific antigenic proteins but also segment-specific arterial proteins.11 The conclusions of the editorialist in 1980 had been anticipated in an article by R.M. Greenhalgh and coworkers in 1975, who noted differences in the lipid profiles of patients with “atherosclerotic dilating” versus “atherosclerotic stenosing” disease12; however, these authors did not make the leap to considering the possibility that there might be fundamental differences in the pathogenesis of AOD versus AAA.

Another anticipatory communication was the report by Clifton in 1977 that 3 brothers had died of ruptured AAAs.13 In the early 1980s, there were publications that took a more general approach to the possibility that there were genetic susceptibility factors for AAA. The editorialist initially reported 16 situations of familial clustering of AAA and then 50 more collected family histories.14 Shortly thereafter, there was a more rigorous report by Johanson and coauthors that left little doubt about the importance of genetic susceptibility factors. That study included a control group in which the
families of patients with aortic AOD were also studied. A positive family history was 6 times more common among the AAA probands than among the AOD probands. The race was then on among several laboratories in the United States and abroad to find the “the aneurysm gene.”

As most readers know, there are 2 approaches to gene discovery in relation to diseases. The “reverse” approach is based on genome-wide screening in large kindreds who manifest the disease of interest at a young age or sibling-pair analysis in diseases of older age. One by one, chromosomes are ruled out, and then the focus narrows to the so-called hot spots on the chromosomes with the highest LOD scores. Helena Kuivaniemi and colleagues have been leaders in this field. Dr Kuivaniemi tells the editorialist that there may be 6 or more hot spots in the human genome for aneurysm susceptibility (H. Kuivaniemi, oral communication, November 2002). Recently, this group reported that a locus at chromosome 19q13.3 is a susceptibility factor for both cerebral aneurysm and AAA.16,17 This locus alone is neither necessary nor sufficient to cause either disease, but it may increase susceptibility for both. The gene at that locus is the ferritin light chain, and our research group has reported 3 nucleotide substitutions in the mRNA of the ferritin light chain (resulting in 2 codon changes) in a cDNA expression library derived from fibroblasts of an AAA surgical specimen (Genbank accession No. AY207005).

The other method is the “candidate gene” approach, which is more feasible for a small laboratory like our own. The TIMP-1 gene was ruled out in 1993.18 Meanwhile, as several publications began to appear on the role of inflammation and autoimmune mechanisms in AAA,19–22 the laboratory of the editorialist made a preliminary communication on the possible role of HLA DR-2 as a risk factor.23 This candidate, presently known as HLA DR-B1-15, based on molecular typing, has been confirmed by 2 larger studies.24,25 Thus, if 2 candidates are tentatively identified, at least 4 more remain to be discovered.

The companion articles in this issue of Circulation1,2 on the role of the PMN use the elastase-infusion technique for initiating aortic injury in small animals (rats and mice), which is often referred to as the Anidjar/Dobrin model. The initial invasive insult leads to AAA formation, which develops over a period of 4 days to 4 weeks, dependent on experimental conditions. A cascade of inflammatory events with multiple molecular messages (some of which are known, whereas others remain unknown) results in the failure of adventitial collagen and permits enlargement to aneurysmal dimensions. The importance of the adventitial collagen in preventing aortic ballooning, even after nearly complete destruction of the integrity of the media (by either surgical endarterectomy or enzymatic elastolytic activity) is supported by clinical experience and experimental evidence. Although little elastin is detectable by histochemical techniques within 24 hours after elastase-infusion treatment, the time period for aneurysmal dilatation is generally ≈1 week.26

As in the case of the adventitial fibroblast and its collagen products, the role of PMN has been neglected in research on the pathogenesis of the AAA. The importance of the aneurysm-infiltrating macrophage cell has been recognized for more than a decade, in particular for its production of the elastin-destructive enzyme matrix metalloproteinase-9.27,28

The present communications in this issue of Circulation lift the level of the discourse on the role of PMN to a new plateau. 1-Selectin–knockout mice were significantly more AAA resistant than were wild-type controls. Fewer macrophages appear to have been recruited to the injured aorta, and aortic dilatation was either prevented or delayed. Convergent conclusions may be drawn from the companion work.1 PMN depletion in C57BL6 mice by pretreatment with an anti-PMN antibody induced neutropenia and also conferred AAA resistance in the Anidjar/Dobrin model. For reasons that are unclear, there was also the surprising finding that there were no differences in matrix metalloproteinase-2 or matrix metalloproteinase-9 mRNA expression, protein levels, or immunostaining patterns.

Although we still see through the glass darkly, the view is slowly becoming less opaque. PMN has become an exciting subject of renewed interest in the pathobiology of AAA, and further studies of its role may add important new pieces to the puzzle. As other investigators are intensifying the search for AAA susceptibility genes in humans, the regulation of PMN recruitment becomes a new candidate for molecular analysis. For example, if there is heterogeneity for 1-selectin in the genome or if there are tissue-specific splicing events for variants of 1-selectin, allowing some PMNs to bind more avidly to the aorta than others, then another aspect of the AAA enigma may come to light.

References


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