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 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. 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.

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” disease; 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. 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. 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

Companion reports in this issue of Circulation under the senior authorship of G.R. Upchurch1,2 address the possible roles of polymorphonuclear (PMN) cells in the pathogenesis of the nonspecific abdominal aortic aneurysm (AAA). As the authors observe, the AAA is the 10th leading cause of death in white men ages 65 to 74, according to the 2000 National Vital Statistics report, and there were 36,000 surgical repairs.
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. Meanwhile, as several publications began to appear on the role of inflammation and autoimmune mechanisms in AAA, the laboratory of the editorialist made a preliminary communication on the possible role of HLA DR-2 as a risk factor. This candidate, presently known as HLA DR-B1-15, based on molecular typing, has been confirmed by 2 larger studies. Thus, if 2 candidates are tentatively identified, at least 4 more remain to be discovered.

The companion articles in this issue of Circulation 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 collagen and permits enlargement to aneurysmal dimensions. 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 L-selectin in the genome or if there are tissue-specific splicing events for variants of L-selectin, allowing some PMNs to bind more avidly to the aorta than others, then another aspect of the AAA enigma may come to light.

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