Abdominal aortic aneurysms (AAAs) affect up to 9% of persons over 65 years of age in the United States, and ruptured AAAs are responsible for approximately 15,000 deaths each year in this country alone. Although the means to reduce deaths caused by ruptured AAAs are readily available, the overall mortality from this condition is unlikely to change in the absence of more comprehensive diagnostic screening. Unfortunately, population-based screening for AAAs has met with limited enthusiasm because most AAAs detected in screening programs are too small to warrant repair and because there are no known forms of treatment for patients with small asymptomatic AAAs. The lack of therapeutic options and our inability to predict the natural history of AAAs reflect our limited understanding of the clinical and biologic factors that influence aneurysmal degeneration. Fundamental knowledge of the pathophysiology of AAAs therefore remains an important gap in the basic science of vascular disease, and understanding the mechanisms that underlie this condition is a critical goal of vascular surgery research.

One of the aims of contemporary basic research is to delineate how different disorders are distinguished at the tissue, cellular, and molecular levels. Although this may involve hypothesis-driven studies on individual gene products, investigations to detect broad changes in gene expression are also of great importance. In the past, such studies involved laborious and time-consuming techniques, with the results requiring characterization of numerous (often unknown) gene products. As a “spin-off” of technologies developed to help complete the human genome sequence, complementary DNA (cDNA) microarrays now permit such large scale investigations to be performed with a remarkably high degree of efficiency. Thus, membrane-based or microchip-based cDNA arrays have made it possible to examine the expression of thousands of genes in the same experiment. With robust statistical analysis for the characterization of different patterns of altered gene expression, microarray-based studies provide information frequently described in terms borrowed from forensics (ie, molecular “signatures,” “fingerprints,” or “profiles” of a given disease process). Whereas the use of cDNA microarrays has been especially fruitful in cancer research (see Khan et al and references therein), this technology has also begun to yield basic information about healthy and diseased blood vessels, including aortic aneurysms.

In this issue of the Journal of Vascular Surgery, Armstrong and colleagues present the results of a study that contributes new information to our understanding of AAAs. With tissues obtained from patients with AAAs and atherosclerotic occlusive disease (AOD), they used a microarray that contained 265 genes to begin developing molecular profiles of these diseases. This is an especially important goal with respect to AAAs in that the development of a more comprehensive description of genes that exhibit altered expression—both qualitatively and quantitatively—may help illuminate molecular pathways that warrant further investigation.

The results presented by Armstrong et al indicate that 11 of 265 genes present on the array (4.1%) were expressed at different levels between healthy and diseased aortic tissues. With respect to individual genes, they found increased expression for matrix metalloproteinase–9 (MMP-9), intercellular adhesion molecule–1, and tumor
necrosis factor receptor-β in both AAAs and AOD and decreased expression of integrin α5, ephrin A5, and rho/ rac guanine nucleotide exchange factor. There was also increased expression of laminin α4 and insulin-like growth factor receptor-2 in AOD and decreased expression of collagen VI α1, glycoprotein IIIa, and α2-macroglobulin in AAAs. Because there were no genes specifically increased in AAAs as compared with AOD, these findings were interpreted to support the notion that AAAs and AOD are similar disease processes. Emphasis was also placed on the common alterations in genes that reflect the role of inflammation and matrix-degrading proteinases in both types of aortic disease.

The conclusions reached in this paper need to be considered in the context of other observations, many of which reveal important distinctions between AAAs and occlusive atherosclerosis. For example, the inflammatory response in these conditions is similar in cellular composition but is quite distinct in tissue distribution, being transmural in aortic aneurysms and confined to the intimal plaque in AOD. Second, although aneurysms are typified by the destruction of the cellular and matrix components of the elastic media, the tunica media is usually undamaged in occlusive atherosclerosis. Increased expression of MMP-9 has been particularly well documented in AAAs, with approximately 10-fold elevations being consistently measured at both the messenger RNA and protein levels. In another recent study using cDNA microarrays, MMP-9 was also found to be one of 18 genes (of 1181) upregulated in AAAs versus healthy aorta.7 Perhaps most importantly, the expression of MMP-9 is consistently localized to mononuclear phagocytes in the outer aortic wall of AAAs, where its capacity for mediating elastic fiber degradation may be particularly relevant to the pathophysiology of aneurysm degeneration. In contrast, expression of MMP-9 in occlusive atherosclerosis is largely confined to macrophages and smooth muscle cells within the diseased intima. Thus, in determining the functional role of MMP-9 in AAAs versus AOD, differences in regional localization may be far more important than differences in the overall level of messenger RNA expression.

The observations by Armstrong et al suggest a number of important avenues for further research. One obvious direction is the use of microarrays that represent a broader spectrum of genes. Although these techniques can involve considerable expense, commercially produced microarrays that contain more than 10,000 genes are now available. Secondly, it is customary to confirm the differential expression of genes identified in microarray experiments with complementary techniques, such as Northern blot analysis or quantitative reverse transcription-polymerase chain reaction assays, and to show whether alterations in gene expression are reflected at the protein level. Third, genes that exhibit altered expression in AAAs need to be localized within aortic wall tissue, especially considering the substantial differences in histopathology between AAAs and occlusive disease. Finally, additional approaches to the statistical analysis of microarray data are needed to make optimal progress in this area. Thus, diagnostic algorithms based on hierarchical “clustering” might be used to identify gene expression patterns capable of distinguishing AAAs from AOD. This approach will also be valuable in the examination of molecular alterations at different stages of aneurysmal degeneration. The aforementioned success of these approaches in cancer research offers a valuable model for studies of vascular disease, where gene expression profiling might be used in the classification of different subsets of aneurysmal or occlusive disease on the basis of their molecular patterns.

Given the current expense of cDNA microarrays and the many issues that need to be addressed in exploiting their potential, investigators in other fields have formed multidisciplinary research groups to facilitate progress. An excellent example of this is the multiinstitutional Consortium for Expression Profiling Studies in Sepsis organized by the Genomics Group of the Trauma Research Network. Because of their unique clinical understanding of vascular diseases and direct access to pathologically relevant tissues, vascular surgeons can play a key role in embracing the “microarray revolution,” thereby helping develop a comprehensive molecular understanding of AAAs and other vascular disorders. Efforts like those reported by Armstrong et al are surely an important step towards profiling some of our most common adversaries.

REFERENCES


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Please see the related article by Dr Armstrong et al on pages 346-55.