

How similar is the genetic makeup of diseased and nondiseased tissue?

Summary of: *Gottlieb B, et al. BAK1 Gene Variation and Abdominal Aortic Aneurysms. Human Mutation 2009, 30(7):1043*

Abdominal Aortic Aneurysms (AAAs), which are characterised by an inflammatory infiltrate, elastin destruction, and a decrease of medial smooth muscle cells (1), affect 6-9% of men over the age of 65 in the United States. (2). For multifactorial diseases, such as AAA, hundreds of SNPs have been identified in putative disease-associated genes. However, the difficulty is to determine which of these SNPs are involved in disease phenotypes. By using nondiseased tissue, such as blood, the basic assumption underlying most of these studies is that the genetic makeup of all cells, whether in diseased or nondiseased tissue, is the same. Nondiseased tissue is often used for gene association studies, except in the case of cancer where tumours can be evaluated following their excision from the patient.

Since chronic apoptosis activation has been linked to the development and progression of AAA, the sequence variation of *BAK1*, a gene which codes for an apoptotic-promoting protein, was examined (3). This study investigates whether intercellular variation of *BAK1* exists and how these genetic differences contribute to the penetrance, frequency and relative risk of AAA. *BAK1* abdominal aorta cDNA from 31 AAA patients with matching blood samples and five nondiseased abdominal aortic tissue samples were compared. The results found similar SNPs in the normal abdominal aortic and AAA tissue, and that these SNPs were not found in matching blood samples. These findings suggest that the genetics of AAA is more complex than the simple accumulation of somatic mutations (3). In addition, the SNPs also appeared, albeit rarely, in references sequences, suggesting that selection may be a factor in AAA ontogeny (3). The authors also suggest the possibility that the SNPs found in abdominal aortic tissues are not directly due to somatic mutational events at all, but rather due to RNA editing (4).

This study is significant as it is likely the first to study a multifactorial noncancer disease in which the sequence of a specific gene in diseased tissue was compared with the same gene in matching blood samples as well as in nondiseased tissue. The presence of SNPs in nondiseased abdominal aortic tissue suggests that they may be present prior to the appearance of disease and may be a consequence of vascular development and maturation (3). The presence of these SNPs may also be at least partially responsible for the increased susceptibility of abdominal aortic tissue to the formation of aneurysms (3). Based on this study, and others (5,6), Gottlieb and his colleagues propose a novel hypothesis postulating that multiple variants of genes may exist in “minority” forms within specific nondiseased tissues and be selected for when intra- and/or extracellular conditions change.

References

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