**Clinical Implications of Basic Research**

**ADAM-33 Surfaces as an Asthma Gene**

Asthma is thought to result from complex interactions between genes and the environment. Although allergens and endotoxins appear to be environmental modifiers of asthma, the genes involved have been harder to identify. However, progress is now being made. For example, Van Eerdewegh and colleagues conducted genetic-linkage analysis on 460 pairs of siblings affected in families in the United States and United Kingdom and identified a locus on the short arm of chromosome 20 that was linked to asthma and bronchial hyperresponsiveness. They assessed 135 polymorphisms of 23 genes in this region and identified the ADAM-33 gene as significantly associated with asthma.

What are the ADAMs, and how could they be related to asthma? ADAMs are a subfamily of metalloproteinases, which are enzymes that depend on a zinc atom within the active site of the enzyme to mediate cleavage of the peptide bonds of other proteins. Metalloproteinases are widely distributed throughout the biologic kingdom. Until now, much of the focus in humans has been on the matrix metalloproteinase (MMP) family, of which 24 members have been identified. MMPs can be subdivided into collagenases, gelatinases, stromelysins, and membrane-type MMPs.

ADAMs mediate extracellular matrix remodeling during discrete physiologic processes such as embryonic development, menstruation, wound repair, and the migration of cells through matrix barriers. Recognition of their capacity to cleave nonmatrix substrates has led to the identification of their role in additional processes. For example, MMP-7 activates defensins, thus enhancing innate immunity. Aberrant or excessive expression of MMPs results in a variety of tissue-destructive diseases, such as invasive tumors, arthritis, cardiovascular disease (rupture of coronary plaque and abdominal aortic aneurysm), and emphysema.

ADAMs were originally identified as proteins on the cell surface. Since they had two functional domains—a disintegrin and a metalloproteinase domain—they were given the acronym ADAMs. About 35 ADAMs have now been described, as well as several more that also contain a thrombospondin domain (ADAMTS) and that, unlike ADAMs, are secreted by cells. The first ADAMs were identified on the basis of their roles in sperm–egg fusion and the formation of myotubules during development.

In addition to their roles in cell fusion and proteolysis, ADAMs have roles in cell adhesion and cell signaling. Interest in ADAMs in the biomedical community heightened after several studies demonstrated that MMP inhibitors abolished the lipopolysaccharide-induced release of tumor necrosis factor α (TNF-α) and death in laboratory animals. Characterization and cloning of the enzyme responsible for this activity led to the discovery of ADAM-17 (also referred to as TNF-α convertase, or TACE). We now understand that after its synthesis, latent pro–TNF-α (a 26-kD protein) is deposited on the cell surface of monocytes and other cells. ADAM-17 cleaves pro–TNF-α, releasing an active, soluble 17-kD form. Other proteolytic functions of ADAMs include shedding of members of the family of TNF receptors and other surface cytokines, adhesion molecules, and growth factors and receptors that are involved in inflammation, cell proliferation, and cell death. MMPs are no longer thought of as just matrix-degrading proteins; rather, proteolysis should be viewed as an important post-translational mechanism capable of regulating a variety of biologic processes.

One can only speculate about the role of ADAM-33 in asthma, since the gene that encodes it was identified only earlier this year and we have no information about its biologic activities or whether the polymorphisms in the gene result in a gain or a loss of function. Van Eerdewegh et al. reported that in humans, ADAM-33 is expressed by lung fibroblasts and bronchial smooth-muscle cells. Given its structure and cellular-expression profile, we suspect that ADAM-33 is associated with small-airway remodeling in patients with asthma. ADAM-33 polymorphisms may accelerate the proliferation of smooth-muscle cells and fibroblasts, leading to bronchial hyperreactivity and subepithelial fibrosis (Fig. 1). A loss-of-function mutation in the ADAM-33 gene could impair the shedding of growth factor receptors, whereas a gain-of-function mutation could enhance the shedding of growth factors. Alternatively, ADAM-33 may regulate the shedding of cytokines, with certain polymorphisms causing increased inflammation or a shift toward an immune response mediated by type 2 helper T cells.

The identification of a proteinase involved in asthma appears to lend support to the long-standing hypothesis that asthma and chronic obstructive pulmonary disease are part of a continuum of a single disease process. However, proteinases cause emphysema by degrading elastin and other components of the extracellular matrix, leading to alveolar destruction and enlargement of the air space. It is possible, but unlikely, that ADAM-33 has similar tissue-damaging properties. If ADAM-33 is also involved in chronic obstructive pulmonary disease, its role could be related to subepithelial fibrosis, which is often observed in the small airways of both patients with chronic obstructive pulmonary disease and those with asthma.
Despite the relative infancy of the field, this is not the first time that an ADAM gene has been implicated in human disorders. Recently, the ADAMTS-13 gene was found to be responsible for congenital thrombotic thrombocytopenic purpura. ADAMTS-13 cleaves von Willebrand factor, a blood-clotting factor in plasma. Decreased ADAMTS-13 activity leads to the accumulation of unusually large multimers of von Willebrand factor, promoting the formation of the microvascular thrombi characteristic of thrombotic thrombocytopenic purpura. In addition, mutations in the ADAMTS-2 gene are responsible for Ehlers–Danlos syndrome type VII.

Despite uncertainties about the biologic functions of ADAMs in general and ADAM-33 in particular, research tools are available to address these issues. For example, the generation of knockout mice that are deficient in ADAM-33 and the use of these mice as experimental models will allow us to tease out the role of ADAM-33 in asthma. If other investigators confirm that ADAM-33 is an asthma gene, further study should enhance our understanding of the disease process and lead to new therapeutic targets for asthma.

The clinical benefits of studies that attempt to identify genes associated with a complex disease such as asthma include the possibility of genetic screening, improved disease classification, and an increased understanding of underlying disease mechanisms. When
these concepts are translated into therapeutic targets that intervene in disease processes, then our support for these costly and laborious studies will pay off by revealing something new about a disease that has been very hard to understand.

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REFERENCES