Invited Editorial on “Reduction of allergic airway responses in P-selectin-deficient mice”

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DURING THE PAST TWO DECADES the field of immunology has witnessed a technical and scientific revolution that was accompanied by a parallel explosion in related literature. Ground-breaking studies have heralded a new day in understanding the potential role of various proteins, including cytokines, chemokines, growth factors, and receptors. This has been particularly relevant to research in bronchial asthma. The prevalence of this heterogeneous and serious condition is lamentably on the increase in both children and adults (5). Research efforts by various laboratories around the world are accelerating and increasing our understanding of the mechanisms regulating the inflammatory response with a view to better therapy. It is now generally recognized that inflammation may be responsible for the damage to the airways. Eosinophils, regulated by various cytokines including interleukin-5, interleukin-3, and granulocyte/macrophage-colony-stimulating factor, appear to be key effector cells in this condition (10). In pursuit of this, a number of viable animal models of airway hyperresponsiveness and allergic inflammation have been established and tested. Despite the tremendous breakthroughs in understanding immunological processes in general and inflammation in particular, asthma remains a mystery, an unresolved jigsaw puzzle. Scientists are stymied by their relative inability to provide conclusive, as opposed to circumstantial, evidence that ascribes precise roles for each component of the inflammatory response associated with it.

The events leading to leukocyte migration from sites of hematopoiesis to blood and ultimately to tissue are central in maintaining the integrity of the immune system as well as in regulating inflammation (5, 10). In asthma, for instance, the selective recruitment of eosinophils and memory T cells to the site of allergic reaction is a prominent feature (1). Adhesion molecules are key in the influx and recruitment of immune and inflammatory cells to the site of reaction and their ultimate effector function. The discovery of these molecules, their characterization, and the gradual elucidation of their potential role are seen as turning points in our understanding of inflammation (7).

The adhesion molecules involved in this process include integrins, immunoglobulin-like molecules, and selectins (7). It is thought that selectins, a family of three carbohydrate-rich adhesion receptors, are involved in regulating the initial attachment and rolling of leukocytes in capillaries, leading to their margination (6). Three different types of selectin molecules have been described: P-selectin, E-selectin, and L-selectin (platelet, endothelium, and leukocyte, respectively) (6). A number of chemoattractant molecules have been implicated in initiating leukocyte activation, leading to their firm anchoring on the endothelium (1, 7). Members of the immunoglobulin family of adhesion receptors (including integrins) are thought to play a role in subsequent migration (diapedesis and extravasation) of these cells and in interaction with various extracellular matrix proteins. The precise role(s) played by each of these adhesion molecules is currently the subject of intensive studies.

The collaborative study by an internationally respected team of researchers in this field (2), represents a major contribution to our current understanding of the role of P-selectin in airway inflammation. The study was conducted in a P-selectin-deficient mouse model of allergen (ovalbumin) -specific sensitization and challenge. De Sanctis et al. (2) found that ovalbumin-sensitized and -challenged P-selectin-deficient mice exhibited significantly reduced airway eosinophilia and lymphocyte infiltration in bronchoalveolar lavage fluid compared with similarly treated wild-type controls, whereas immunoglobulin E response was unaffected. Airway hyperresponsiveness to methacholine was also diminished in the knockout mice. These are fascinating data that confirm studies that employed monoclonal antibody treatment to downregulate P-selectin responses in vitro, ex vivo, and in vivo (8, 9).

It is, however, important to take stock of these new observations and see what can be learned from the use of transgenic mice, in which a selective protein is overexpressed, and in mutant knockout mice, in which expression for specific proteins is selectively deleted at the molecular level. Both of these systems have provided important, but not conclusive, answers to intractable questions about the role of specific protein(s) in regulating immunological and inflammatory reactions (3, 4).

There are lessons for us from the data generated by the use of these knockout and transgenic mouse models. The first is a confirmation that phenotypes are ultimately the product of many ingredients, including, among others, genetic expression and environmental factors. Second, there is a high degree of redundancy...
within biological systems, which has the potential to compensate for the loss of a particular protein. We have witnessed that cells, their receptors, and mediators have a remarkable capacity, under certain circumstances, to switch paths and become involved in interactions beyond their identified roles. What is needed is a better understanding of the intricate manner in which cells and their proteins communicate with each other.

With the aid of new technologies, multidisciplinary research in such fields as physiology, pathology, immunology, and cell and molecular biology is turning up myriads of novel observations. The challenge is to make sense of these data that are at once exciting and confusing. The technique of differential display of mRNA is a case in point. It opened new vistas for appreciating the potential inherent in the genomic capacity of various biological systems. However, it also raised more questions than it answered and led to its designation by some as “differential dismay” technique. That being said, biotechnological advances are critical if we are to unravel the secrets of DNA protein synthesis and function.

Finally, a couple of points in regard to this and similar studies. Although the data present clear a role for P-selectin in cell recruitment and hyperresponsiveness in this model, we should exercise caution while extrapolating from mice to humans. In addition, not all the pieces of this jigsaw puzzle are in place yet. Many new molecules are being discovered and characterized that are relevant to the complex process of inflammation associated with asthma.

These studies continue to spur us on toward the goal of arriving at a more sophisticated and safer treatment for asthma. In this quest, the road is long and winding, and while there may be many signposts pointing the way to our destination, only some of these will eventually lead to "Rome"!

REFERENCES