Airway remodeling and RELM-β

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TYPE 2 INFLAMMATORY RESPONSES are characterized by differentiated CD4+ T helper type 2 (Th2) cells that secrete a panel of cytokines including IL-4, IL-5, IL-9, and IL-13 with the recruitment of multiple effector cells, including B cells producing IgE, mast cells, eosinophils, and basophils. Although inflammation per se attracts a great deal of attention, it is the effects of inflammation on tissue that actually induce disease. Recent gene profiling studies in murine model systems have identified a number of novel molecules that are highly upregulated during type 2 inflammation and that may be involved in tissue injury (21). Among these are members of the resistin-like molecules/found in inflammatory zone (RELM/FIZZ) family that includes RELM-α/FIZZ1, RELM-β/FIZZ2, and RELM-γ, all of which share sequence homology to resistin, an adipocyte-secreted factor that can regulate responsiveness to insulin (6, 16). All RELM proteins are secreted, contain highly conserved COOH-terminal cysteine residues, and are expressed during type 2 inflammation (15). Although a RELM-α ortholog has not been identified in the human genome, human resistin shows a greater similarity in expression pattern to ortholog has not been identified in the human genome, human resistin shows a greater similarity in expression pattern to murine RELM-α than murine resistin and is expressed by leukocytes and myeloid cells. Thus the putative functions for murine RELM-α may be shared with resistin in humans (20).

The best-studied member of this family is RELM-α/FIZZ1, which is expressed in the lung and gastrointestinal (GI) tract in pulmonary epithelial cells, dendritic cells, B cells, macrophages, and GI tract goblet cells under a variety of conditions, including parasite infection, Th2 inflammation, and pulmonary fibrosis (15). Expression of RELM-α is a defining feature of murine alternatively activated macrophages along with expression of arginase and Ym1 (3). RELM-α is also upregulated in a STAT6-dependent fashion in the alveolar epithelium during allergic and fibrotic conditions. In both cases, it may mediate fibrosis through induction of myofibroblast differentiation, proliferation, and protection from apoptosis (2, 6, 10, 11, 14, 17, 21). Hypoxia upregulates RELM-α in the lung where it has mitogenic activity for smooth muscle and epithelium (9, 18). RELM-α has angiogenic activity, which is at least partly mediated through VEGF and VEGFR2 (19). Finally, RELM-α has been shown to have activity against nerve growth factor-induced neural survival as well (6). Thus RELM-α is a multipotent molecule involved in multiple aspects of tissue remodeling.

RELM-β has similar properties in that it is induced in a Th2 cytokine-dependent manner in the lung and GI tract. In the GI tract, RELM-β has a more restricted expression pattern than RELM-α in that it is uniquely expressed by goblet cells and requires IL-13 for expression (1). In the context of GI parasite infection, worm expulsion correlates with RELM-β expression (1, 15). RELM-β is also upregulated during bacterial coloni-
including transforming growth factor-β, to RELM-β-induced fibrosis. The result with the RELM-β-deficient mice is somewhat difficult to interpret since there is little known about the effect of RELM-β on the development of a Th2 response. At baseline, these mice are not grossly immunologically abnormal, and we are told that there are equivalent numbers of eosinophils upon allergen challenge (5, 13). However, it will be important to formally exclude a role of RELM-β in eosinophils upon allergen challenge (5, 13). However, it will be of interest to look for effects of RELM-β on other aspects of airway remodeling, such as effects on smooth muscle or vascularity.

Despite these areas of uncertainty, RELM-β potentially appears to belong to a family of mediators that may be downstream of the immune response and both amplify the inflammatory response and mediate some of its effects. The ability to produce fibrosis is particularly intriguing. All in all, these data implicate RELM-β as a mediator dependent on Th2 responses that is also implicated in airway remodeling.

REFERENCES


