Airway remodeling and RELM-β

Robert J. Homer

Yale University School of Medicine, New Haven, Connecticut

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 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 multi-potent 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 colonization of the gut, suggesting a broader function in response to diverse microorganisms in the GI tract (4). RELM-β is important for maintenance of GI barrier function, but paradoxically the absence of RELM-β also protects against dextran sulfate-induced colitis (5, 12).

The authors of the companion article had previously shown that RELM-β was upregulated in a murine asthma model (21). The companion article (13) confirmed that result by Northern blot analysis and quantitative RT-PCR. Expression was primarily limited to airway epithelium and inflammatory cells. IL-4 and IL-13 themselves were each shown to directly induce RELM-β via a STAT6-dependent pathway. This is not a trivial point, since although STAT6 is the best known signal transduction mediator for IL-4/IL-13, IL-13 also signals through the mitogen-activated protein kinase pathway (8). In allergic models, the induction of RELM-β was dependent on IL-13, STAT6, and IL-4Rx as shown in the respective gene-deficient mice and as previously reported for STAT6 (17). This is consistent with previous work by the authors who previously reported that most, but not all, gene products in various allergic models (including RELM-β) were STAT6 dependent (21).

RELM-β, when directly delivered to the mouse lung, increased the number of macrophages. Direct administration of RELM-β was also able to directly induce fibrosis and a slight increase in mucus production. In addition to being sufficient to produce fibrosis, RELM-β was necessary for fibrosis since mice deficient in RELM-β were protected from airway fibrosis despite equivalent numbers of eosinophils induced. Consistent with the minor effect of RELM-β on induction of mucus, the absence of RELM-β had a minor effect on reduction of mucus. In vitro, whereas RELM-β had no effect on fibroblast mitogenesis, it did enhance fibroblast migration.

What are the future directions we can expect from this work? There is expression of RELM-β in epithelial cells, but we do not know which cell type, especially in relation to other secondary mediators induced by Th2 inflammation, including RELM-α. For comparison, chitinases are another family of Th2-induced mediators with some similar properties to the RELM family (15). Different chitinase family members, despite being expressed by “airway epithelium,” are actually expressed in mutually exclusive cells that reflect different microanatomic regions of the lung (7). Given the exclusive expression of RELM-β in goblet cells in the GI tract, this is particularly important to asthma in which goblet cell metaplasia is prominent. It will be important to determine exactly at what step (Th2 induction or response to Th2 mediators) the defect in RELM-β production lies in the IL-13-, IL-4Rx-, and STAT6-deficient mice. With respect to the direct administration of RELM-β, the mechanism of fibrosis and inflammation induced by RELM-β needs to be worked out. RELM-β has previously been shown to activate peritoneal macrophages to produce TNF-α and IL-15, thus it is would be particularly important to know if the pulmonary macrophages induced by RELM-β also show evidence for activation (12). It would also be of interest to determine the relationship of Th2 cytokines,
including transforming growth factor-β, to RELM-β-induced fibrosis. The result with the RELM-β-deficient mice is somewhat different 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 on the Th2 response. Finally, in addition to fibrosis, it would 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


