Asthma is an important national health problem, affecting 6 to 8 percent of the U.S. population, with 10 percent of all asthmatics having severe disease and responding poorly to standard asthma treatment such as inhaled and systemic corticosteroids. The pathobiology of asthma involves many cell types, including the mast cell (MC), a resident inflammatory cell expressing CD34, c-kit, and the high affinity IgE receptor. Unfortunately, human mast cells remain difficult to study, because they are not present as circulating blood cells and bear little resemblance to primary cells.

Figure 1: Bronchial epithelial brushing cells stained for tryptase from a severe asthmatic. Red arrows: Tryptase-positive mast cells.

Mast cells have long been implicated in the pathogenesis of asthma through Type I hypersensitivity reactions, likely through activation of epithelial MCs. Studies in mice and humans suggest the environment is highly influential in determining the cell phenotype. In humans, the tissue environment is believed to contribute to two major MC phenotypes, identified by their protease-rich cytoplasmic granule content. The MCT contains tryptase and is thought to represent a mucosal MC phenotype. Under normal circumstances, the MCT represents the majority of lung MCs. (Figure 1, tryptase positive MCs in the epithelial brushing from a severe asthmatic.) In contrast, the MCTC phenotype is identified by chymase and smaller amounts of tryptase, and has been proposed to contain carboxypeptidase A3 (CPA3) and hematopoietic prostaglandin D synthase (HPGDS). HPGDS is the enzyme that generates prostaglandin D2 (PGD2), which acts on three G-protein coupled receptors, including chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes (CRTH2) and DP1. CRTH2 has been of significant interest as a therapeutic target in asthma. However, much remains to be understood regarding the presence and activation of these pathway elements in asthma.

Their research team has shown that the presence and activation of MCs in chronic severe asthma differs from milder asthma, with severe asthmatic airways having higher percentages of MCTC than milder asthma. This increase in epithelial MCs is associated with increases in bronchoalveolar lavage fluid PGD2.

Building on this novel finding, Dr. Fajt’s recent work, published in The Journal of Allergy and Clinical Immunology, compared the expression and activation of PGD2 pathway elements in bronchoscopically obtained samples from 107 participants, healthy controls and asthmatics, across a range of severity and control. Dr. Fajt also explored the PGD2 pathway in relationship to a phenotype of asthma with evidence for a T-helper type 2-like inflammation. Confirming their previous results, BAL fluid PGD2 was highest in severe asthma. Bronchial epithelial brushing HPGDS mRNA and cells staining positively for HPGDS protein differed among the groups.
and associated with mRNA expression for MCs. The CRTH2 receptor for PGD2 was highest in BAL cells from severe asthmatics by both mRNA and protein measures. Of clinical relevance, asthmatics with higher PGD2 levels, HPGDS, and CRTH2 had more asthma exacerbations in the past year and worse asthma control compared to asthmatics with low levels of these markers. Lastly, asthmatics with evidence for a type-2 inflammatory process (based on peripheral blood eosinophilia or elevations in exhaled nitric oxide) had higher PGD2 levels, HPGDS, and CRTH2, suggesting a possible role for this pathway in severely poorly controlled asthma with evidence of a type-2 inflammatory phenotype.

These studies suggest a highly active PGD2 pathway in poorly controlled severe asthma patients. Several recent studies, including one presented at the recent American Academy of Asthma, Allergy and Immunology meeting, have shown that CRTH2 antagonists improve lung function and asthma control, and may decrease exacerbations in milder asthma (Wenzel, AAAAI poster, 2014). Dr. Fajt’s recent studies in severe asthma, in conjunction with these early therapeutic trials, support the need for trials of CRTH2 antagonists in severe asthma. The research team at the Asthma Institute continues to enroll asthmatics in the SARP study, as well as in numerous other asthma clinical trials that will lead to better understanding of the role of the MC and its mediators in human asthma.

Figure 2: Dr. Fajt analyzing immunohistochemical-stained slides from asthmatic participants in the SARP program.