A Street-Level Look At Urban Allergy

How living in an urban environment may foster an allergic response and the potential treatments waiting in the wings.

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Allergy has been called “the 21st century disease.” The increasing prevalence of allergy has been linked to global industrialization and urbanization, with prevalence rising at the highest rates in nations where development is greatest, particularly in Asia. Urbanization has so impacted the environment that our adaptive immune system has responded with increasingly complex and severe reactions. The exposed mucosa of the eye represents a dynamic immunological system that is particularly sensitive to this changing landscape. Under these conditions, the mechanisms in place to protect the ocular surface and respond to pollutant-reinforced allergen attacks are being tested as never before.

The physiological systems that evolved to protect the ocular surface include the blink and tear reflexes, and the host of humoral factors that control the level and nature of immune responses. For patients who develop ocular allergy, antihistamines and steroids have demonstrated therapeutic value beyond the natural defenses, but there is a growing subpopulation of allergic conjunctivitis patients who respond poorly to available treatments. These patients suffer from a persistent conjunctivitis and a chronic allergic inflammation. In this month’s column, we’ll discuss the environmental and cultural factors that promote urban allergy, as well as the key mediators of the allergic inflammatory response that may provide potential therapeutic targets for new treatments.

Urban Enhancements to Allergy

Growing urbanization around the globe has led to climate change and increased local levels of airborne pollutants, primarily due to vehicle exhaust. These environmental changes have profoundly influenced adaptive immune responses in exposed individuals. Increased global temperatures have expanded the geographic migration of vegetation and have led to an accelerated onset and extended duration of the growing season. Also, urban areas are typically characterized by more plant homogeneity than rural areas, which promotes greater pollination rates and higher pollen levels per plant. These factors combine to significantly increase the antigen burden on urbanites with seasonal allergies.

Longer and more intense pollen seasons, combined with urban area pollutants, create a perfect storm for exposed mucosal tissues. The major urban pollutants include ozone, nitrogen dioxide and particulate matter. These pollutants have the capacity to interact with and structurally modify airborne pollens, thereby enhancing their antigenicity. However, of even greater interest, urban-area pollutants can function as immune system adjuvants. For example, ozone subjects the mucosal epithelium to oxidative stress and promotes a pro-inflammatory response. This is associated with epithelial barrier disruption and the local production of inflammatory cytokines. Inflammatory disruption of mucosal barrier integrity then facilitates tissue penetration by allergen and interaction with cells of the immune system. In this way, urban pollutants have the capacity to prime or sensitize the immune system for an allergic response.

However, things get even worse for the city dweller. Not only are airborne pollutants and pollens modifying immune responses, but the comparative lack of an abundant and diverse micro-
bial environment that exists in rural and underdeveloped areas, incongruously may threaten immune health. The hygiene hypothesis of atopic diseases proposes that lack of early life exposure to pathogens diverts T cells from their original *raison d’etre* of microbial defense in favor of atopy, and the recognition of harmless proteins as antigenic. Our stressful and unhealthy lifestyle is another component of urban/Western culture that predisposes toward allergy, particularly the Western diet. A recent U.S. survey found that obesity and associated systemic inflammation are risk factors for allergy in children and adolescents. The concept that systemic inflammation is associated with mucosal allergy may be related to complex immune pathways involving priming and tolerance (elucidated in November 2012’s Therapeutic Topics). Together, these factors point to the importance of general health issues as additional risk factors for atopic disease.

Patients with symptomology consistent with “urban allergy” exhibit signs and symptoms of disease which, when compared with others with allergies, are generally more chronic, more severe and more resistant to currently employed therapies. Although precise numbers are not available, these patients may represent up to 30 to 40 percent of the allergic conjunctivitis population. This subset also includes patients who are poly-sensitive, meaning they are allergic to more than one type of allergen (pollens as well as dust mites, for example). The increase in patients with multiple allergies may be part of the explanation for the growing chronic population. In addition, patients with vernal and atopic keratoconjunctivitis have chronic and severe disease that can be sight-threatening and poorly responsive to currently approved drugs. Taken together, in this substantial population of chronic ocular allergy patients, inflammation drives the intensity of the response and represents a significant unmet medical need.

### Recruits for Urban Warfare

Allergic inflammation occurs in sensitized tissues where a predominately Th2-lymphocyte immune response has established high local levels of antigen specific-IgE bound mast cells. Antigen challenge triggers release of chemotactic signaling molecules that drive the accumulation of leukocytes including neutrophils, basophils, eosinophils and lymphocytes into the sensitized tissue. The goal of most emerging therapies is to disrupt this recruitment, prevent the buildup of inflammatory cells, and allow the natural cycle of inflammation to proceed to resolution.

In sensitized individuals, antigen is captured by specific IgE bound to the high affinity receptor FcεRI on the surface of mast cells, an event that triggers degranulation and activation. Critical to this mast-cell response to antigen is activation of spleen tyrosine kinase. Mast cells deficient in Syk do not degranulate or synthesize inflammatory mediators upon antigen-induced aggregation of FcεRI. Syk-induced activation of phospholipase C generates second messengers that increase intracellular calcium, which is required for mast-cell degranulation and histamine release. In addition, phospholipase A2 is activated to liberate membrane-bound arachidonic acid for conversion into prostaglandins and leukotrienes.

Syk-induced transcription factor activation leads to transcription and translation of genes encoding several pro-inflammatory cytokines and chemokines. These essential roles played by Syk in the production of a host of pro-inflammatory mediators provide the rationale for its development as a therapeutic target for the treatment of allergic conjunctivitis and associated

### Emerging Drug Candidates for Chronic Allergy

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allergic inflammation. The potent Syk inhibitor R343 (Rigel Pharmaceuticals) is currently in development for the treatment of patients with allergic asthma.

While mast cells are primarily thought of as suppliers of the histamine that elicits the classic signs and symptoms of allergic conjunctivitis, they are also a source of cytokines and chemotactic factors that are key to subsequent recruitment of inflammatory cells. One such chemo-attractant is histamine itself, which exerts an attractant effect via histamine H4 receptors expressed on eosinophils, T-lymphocytes and other mast cells.9 Alcaftadine (Allergan), a dual antihistamine/mast-cell stabilizer, is known to also have H4R-antagonistic properties that may contribute to its anti-inflammatory effects. Part of this effect may also be based upon an ability to stabilize epithelial tight junctions and maintain the barrier function of the epithelium.10 Selective H4R antagonists including UR-63325 (Palau Pharma S.A.) have entered clinical trials for the treatment of allergic respiratory diseases, including asthma.

Like histamine, PGD2 is involved in both the early and late phases of allergy. Mast-cell derived PGD2 activates receptors on Th2 cells to promote eosinophil chemotaxis and cytokine production. Antagonists of the PGD2 receptors have been effective in animal models of ocular allergy11 and several compounds in this class, including QAW039 (Novartis), are now in clinical trials for the treatment of asthma.

Eosinophils are the hallmark cell type of allergic inflammation, and are of particular concern due to the tissue-destructive properties of their cationic granule proteins. Major basic protein is the most abundant eosinophil-derived granule protein, and it is a potent disruptor of cell membranes. Eosinophil peroxidase enzymatically generates oxidants that are also cytotoxic. In the eye, eosinophilic mediators contribute significantly to the breakdown of protective barriers, promoting tissue remodeling and further lymphocyte accumulation.

Eotaxin is a potent chemotactic factor for eosinophils that is produced by fibroblasts, epithelial cells, endothelial cells, T-lymphocytes and eosinophils. Exposure of corneal fibroblasts to the Th2 cytokines, IL-4 and IL-13, is a major stimulus for local production of eotaxin. TNFα also induces eotaxin release and synergizes with IL-4 and IL-13.12 Recently, several compounds have been developed that interfere with eotaxin signaling by blocking activation of the eotaxin receptor (also referred to as CCR3). ICo Therapeutics recently announced plans to initiate a clinical trial of bertilimumab, a human anti-eotaxin-1 monoclonal antibody, for treatment of vernal keratoconjunctivitis.

The Th2 cytokines IL-4 and IL-13 are the major agents of inflammation in the urban allergy battle; this makes the IL-4 receptor a key potential target since it acts as receptor for both cytokines. Pitrakinra (Aerovant) is a recombinant human form of IL-4 that functions as an IL-4R antagonist that demonstrated efficacy in asthma clinical trials.13 Another IL-4R antagonist now in clinical trials as an anti-allergic is dupilumab (Sanofi/Regeneron).

Urban allergens in action: The American Lung Association says the Los Angeles/Long Beach/Riverside area has the fourth-worst air quality in the United States.20 The JAK kinase inhibitor R256 (Rigel Pharma), which also acts to suppress IL-4 and IL-13 signaling, is entering clinical trials as well.

Another key Th2 cytokine, IL-5, mediates the differentiation, proliferation, activation, and chemotaxis of eosinophils and synergizes with IL-4, IL-13 and eotaxin to promote allergic inflammation.14 Anti IL-5 (mepolizumab; GSK) and anti-IL-5R (bencilizumab; AstraZeneca) are in clinical development for allergic asthma.

A link between innate and adaptive immunity has been the subject of much recent immunology research. Resident tissue cells respond to immune cell mediators by producing factors that further modulate immune responsiveness. Epithelial-cell derived cytokines such as IL-25, IL-33 and thymic stromal lympho-protein play key roles in chronic allergic inflammatory responses. TSLP promotes Th2 differentiation and proliferation, directly enhances effector functions of Th2 cells and activates mast cells and eosinophils.15

It has been reported in animal studies that short ragweed pollen stimulates epithelial TSLP production and triggers Th2 allergic inflammation by activating Toll-like receptor 4.16 Toll receptors are widely expressed pattern recognition receptors that bind molecular sequences conserved by a variety of pathogens, including bacteria and viruses. Activation of TLRs leads to production of cytokines and chemokines that stimulate an immune response. In addition, activation of TLRs can synergize with FcεRI signaling, potentially enhancing the response of mast cells to antigen.17 Antibodies that target TSLP (AMG157, Amgen; MEDI-9929, AstraZeneca) and a TLR modulator (AZD8848, AstraZeneca) are in early development for the treatment of asthma, and may be future therapies for severe or chronic allergic conjunctivitis.
Outlook for the Urbanite

The variety of emerging therapies for allergic inflammation reflects the complexity of the pathophysiology of these conditions. Currently available immune-modulators may provide an option but these drugs inhibit all T-lymphocytes, including suppressor T-regulatory cells. More selective targeting could improve the therapeutic index of drugs to help fill this unmet medical need.

There is a clear rationale for evaluating therapies originally developed for respiratory allergy as treatments for ocular allergic inflammation. For example, the anti-IgE drug omalizumab (Xolair, Novartis), approved by the Food and Drug Administration for the treatment of allergic asthma, has been shown to be effective in reducing ocular symptoms and rhinitis, has been shown to be effective in reducing ocular symptoms in severe allergic conjunctivitis.18 The same may be true for marketed anti-TNF and PDE4 inhibitor compounds that have demonstrated efficacy in respiratory inflammatory diseases. In addition, local administration of anti-allergy drugs provides ocular efficacy and pharmacokinetic advantages over systemically delivered treatments.19

The picture of ocular allergic disease we’re left with is one that is more akin to a Los Angeles freeway interchange than a rural crossroad. As our understanding of the immune system’s complex networks of signaling checks and balances expands, we recognize that changes in the nature and prevalence of ocular allergy are, in large part, a result of an immunological response to a moving target. It’s vital to remember that the best way to treat allergy is to remove the irritant, whether it’s pollen or pollution. In addition, our goal should also be to identify one or more new therapeutic approaches to the problem of chronic, urban allergy from either new or repurposed biologicals or small molecules; combining these with new drug delivery paradigms will be key to fighting urban allergy in the 21st century.

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