The Mechanism of a Pollinosis Diagnosis

An update on how allergens attack the eye and how that knowledge can help us develop better treatments for allergy.

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Some people seem to go through life with the attitude that the world is out to get them. But those of us with seasonal allergies know this to be a fact. While others cheer the arrival of birds, flowers and all the assorted harbingers of spring, allergics prepare for another round of battle with pollens, armed only with eye drops and nasal spray. Just what makes pollens such efficient vectors of misery? This month we will examine the nature of pollinosis, a condition more commonly known as hay fever, rhinitis or, in its ocular incarnation, seasonal allergic conjunctivitis.

A Peek Inside Pollination

Pollens are the male gametes of plants, and as such, they are engineered for reproduction. It turns out that plants have evolved three distinct mechanisms for pollen transfer: by insect; animal; or through the air. Pollen transfer by air, or anemophily, is predominant in temperate regions and is the mechanism employed by most grasses and weeds, and by many tree varieties. The dominance of insect and animal-based pollination mechanisms in the tropics is one factor in the lower prevalence of pollinosis in those regions.

The morphology of airborne pollens shows remarkable convergence across a wide diversity of species. This convergence means that without sophisticated protein or DNA analysis, it is often impossible to identify pollens by plant species. When fully mature, most airborne pollens are near spherical in shape, range from 10 to 30 μm in diameter, and typically feature an arrangement of spikes or points distributed uniformly across their surface. The precise function of these spikes is the subject of much speculation: They may improve aerodynamics (in the way the dimples of a golf ball create a turbulent layer that reduces drag and enable the ball to fly farther) or enhance attachment of the pollen grain once it reaches its destination. Studies of nanoparticle-based delivery of drugs suggest that airborne pollen morphology may increase the capacity of the particle to deliver compounds coating the exterior surface.

While the actual function of pollen morphology is probably some combination of these or other factors, an unintended consequence of their irregular surface is that the pollen grains are likely to be greater irritants when they reach the soft tissue surfaces of their unsuspecting victims.

An important factor in the prevalence of pollinosis is the prodigious capacity of many species of plants to synthesize and distribute pollens. For example, an acre of ryegrass is
capable of producing nearly 200 kg of pollen in a single bloom.3 Pollen production, particularly with tree species (such as birch, cedar and oak) is synchronized with flower production and so is optimized to generate bursts of pollen release and dispersal.4 As with all forms of reproduction, airborne pollination is a competition, so plants are compelled to produce large pollen yields in short time frames in order to be successful. Unfortunately, allergenic pollen producers appear to have organized their assault on our immune systems with a well-designed schedule of pollination that provides allergen nearly year-round, from spring trees to summer grasses to fall weeds.

Perhaps the most important aspect of pollen biology is that all pollen are decidedly not equal when it comes to eliciting allergic signs and symptoms, and it is the nature of the allergens carried by each pollen that determines whether it will elicit an allergic response.

**Pollens Aren’t Created Equal**

Despite the tremendous diversity of plant species around the globe, there are relatively few that release pollens capable of eliciting allergic reactions (See Table 1). Of an estimated 200,000 known species of plants, only 50 are listed as airborne allergen sources by the International Union of Immunological Societies.5 While many grass pollens are allergenic, only a handful of tree species, including birch, alder, cypress and cedar are responsible for the majority of pollen-evoked allergies. Similarly, a few species of weeds, including mugwort and, of course, ragweed, dominate the fall allergy season. When a limited number of species produce the majority of allergenic pollens, it means that atopic individuals can benefit by a careful consideration of their landscaping choices. For example, grasses such as St. Augustine (genus *Stenotaphrum*) reproduce primarily by stolons (runners) and so are far less allergenic than bermuda or ryegrasses.

Pollen allergens are soluble glycoproteins that may function in the early steps of pollination. While the precise function of many remains to be determined, at least some pollens’ allergens have enzymatic activity that allows them to degrade starches, proteins or nucleic acids. Several recent studies have demonstrated that pollen contains proteases that are capable of degrading the intercellular structural proteins in ocular epithelial tissue.6 This proteolytic activity has been proposed as a possible source of enhanced, non-immunological allergenicity via disruption of the cell-cell junctions of epithelia, facilitating the passage of allergens across tissue barriers. Another study examined proteases extracted from the pollens of several tree species, as well as ragweed.7 The serine protease activity extracted from all these pollens was similar in both substrate specificity and specific activity.

These observations suggest that some pollen constituents have the capacity to elicit pathological effects distinct from their action as immunogens. Alternatively, some proteases may also evoke immune responses in addition to their enzymatic activity.8

Another recent series of studies has shed light on causes of increased prevalence of allergies, including allergic conjunctivitis. There is growing evidence that pollutants can interact with pollen allergens; the result is a greater antigenicity and increases in allergic disease. For example, controlled studies showed that increased atmospheric carbon dioxide can cause a significant increase in the amount of pollen produced by several species of grasses.9 Hydrocarbons and other components of exhaust can also interact with pollens, acting as adjuvants to increase their antigenicity and potentiating the immune responses elicited by a given pollen allergen.

For clinicians it’s important to realize that there is considerable cross-reactivity in immune responses to
some pollen allergens, and this can significantly impact both the severity and duration of the allergy season for many patients. A well-documented example of this is seen in Japan, where increased incidence of rhinitis and allergic conjunctivitis is blamed primarily on pollens from two species, the Japanese Cedar (Cryptomeria japonica) and the Japanese Cypress (Chamaecyparis obtusa). Both C. japonica and C. obtusa trees produce prodigious amounts of pollen, but just as important is the timing of these events: C. japonica flowers first, in early February to March, while C. obtusa blooms from March to late April. And where there are flowers blooming, there is pollen. To make the situation worse, subjects allergic to C. japonica pollen typically exhibit a cross-reactivity making them susceptible to C. obtusa as well. Thus, the most important factor isn’t the specific pollen species or the maximum pollen levels on a particular day, but the fact that the susceptible individuals are exposed to high levels of pollen over a protracted period of time.

Most recent efforts to classify allergens according to antigenicity have been developed to address the observed cross-reactivity that goes beyond the level of related plant species. For example, many patients who are allergic to fruits such as apples and pears also suffer from allergic conjunctivitis in response to birch or alder pollens. A newer set of allergen families contained within a group termed panallergens represent allergens classified according to three-dimensional molecular structures and feature functions that sometimes aren’t immediately apparent from isolated analysis. Three well-defined families include profilins (cytoskeletal binding proteins), polcalcins (calcium binding proteins, such as calmodulin or cyclophilin) and lipid transfer proteins. Another large, diverse group that shares functional traits includes allergens with catabolic activity, including pectin- and sugar-degrading enzymes. Most allergenic plant species produce allergens from multiple groups (See Table 1), adding to the complexity. One value of such classifications will be in future efforts to use immunotherapy treatments: In theory, it should be possible to use the knowledge of these panallergens to produce family-specific immune therapies.

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**Keeping Up the Fight**

For those of us who are particularly interested in ocular allergy, it’s comforting to see that the most recent developments in studies of pollen and pollen allergens provide further validation for the conjunctival allergen challenge model. The CAC model was designed to provide a way to elicit allergic responses that were predictable and reproducible so that they could be used to develop new therapeutics for allergy treatment and prevention. During the screening process in a typical CAC study, each subject receives a skin test which qualitatively identifies the allergens to which the subject is sensitized. One of these allergens is then instilled in the eye, and the redness and itching responses are quantified. If the response doesn’t reach the protocol-defined threshold, a higher concentration of the same allergen is tried. This process is repeated until an adequate response is achieved, and a different allergen may eventually be used if the first doesn’t produce the desired response. At the end of this allergen titration process, each qualified subject has demonstrated a similar response within a pre-defined range. The key features of the CAC that have been validated by subsequent years of studies are that the specific allergen and allergen concentration may differ from subject to subject, but the mechanism of the allergic response is the same regardless of the allergen used. As our knowledge of pollens and the allergens carried by pollens has advanced, we have seen that the nature of the immune responses elicited by different pollens is the same, as experience with the CAC would predict.

The prevalence of allergic disease has been on the rise in recent decades, and during this time clinicians have also realized that, for a growing subpopulation of allergy sufferers, the conventional antihistamine-mast cell stabilizer medications are insufficient as treatment. It’s likely that this trend results both from increases in the amounts of pollen produced and from the effects of environmental pollutants discussed above. Despite these factors, it seems worth asking if, at some level, this trend reflects a qualitative change in allergic responses to the same varieties and concentrations of allergens. Emerging evidence suggests that this growing population of non-responders reflects an increase in prevalence of late-phase allergy.

Manifestations of late-phase allergic reactions occur approximately six to 24 hours after allergen exposure,
and are characterized by prolonged ocular signs and symptoms as well as a greater degree of a cellular aspect of the response: preformed mediators of the acute phase elicit an influx of inflammatory cells, particularly eosinophils, into the conjunctiva. In the eye, the cellular late-phase reaction may only be present in a subset of patients and, when present, is generally asymptomatic, except in relatively rare cases.\textsuperscript{14}

As with all ocular diseases, a key approach to development of improved therapies for late-phase allergy is to design and validate models that accurately reflect disease signs and symptoms. For the example of the CAC described above, one would simply modify the assay in order to elicit some or all of the features of late-phase allergy in a particular patient. These modified models employ a repeated exposure to titrated amounts of allergen to elicit the inflammatory reaction characteristic of the non-responder population. With the understanding that the prevalence of this condition is on the rise, these efforts are under way and should lead to new treatments in the near future.\textsuperscript{15,16} \textbf{REVIEW}

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