

Mites, ticks, anaphylaxis and allergy: The Acari hypothesis

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ABSTRACT

Anaphylaxis is a poorly understood immune process in which a Th2/IgE-mediated adaptive response commandeers cellular machinery, typically reserved for defense against multicellular ectoparasites, to activate against otherwise benign molecules. Its clinical manifestations consist of rapid pathophysiological reflexes that target epithelial surfaces. The galactose- α -1,3-galactose hypersensitivity response is a compelling model of anaphylaxis for which causation has been demonstrated. At the core of the model, a tick bite sensitizes a recipient to a tick foodstuff. As proposed herein, the model likely informs on the origin of *all* allergic inflammation; namely, allergy is not intended to protect against seemingly harmless and irrelevant materials, but is, instead, intended to rid epithelial surfaces of pathogen-bearing Acari, *i.e.*, mites and ticks. The demonstrated adjuvant activity of acarian gastrointestinal secretions, when paired with the polyphagous diet of mites, renders acarians eminently suited to accounting, mechanistically, for many, if not all, human allergies.

Anaphylaxis, the type 1 hypersensitivity reaction, manifests as a constellation of pathophysiological responses mediated by IgE. When triggered, it elicits in affected individuals urticarial rash, bronchospasmic cough, mucous expectoration, vomiting, diarrhea, oropharyngeal edema, and hypotension. Importantly, considerable overlap exists between anaphylaxis and allergic reactions of lesser clinical consequence, *e.g.*, urticaria, rhinitis and asthma. All of these conditions confound clinicians, both because their global prevalence is increasing [1–8] and because therapeutic options, albeit improving, remain limited [9].

For good reason, clinicians perceive allergic conditions to be pathological processes. This perception derives from incomplete understanding of allergic ‘drivers’ and from a sense that if these conditions represent an attempt by the immune system to rid epithelial surfaces of allergens of molecular dimensions, then the mechanical reflexes intended to achieve that end are ill-suited.

Because much about allergy remains unknown, various theories attempting to account for its etiology have been proposed. One theory postulates that Th2/IgE-mediated immune responses evolved to protect against epithelial assault by multicellular helminths, ectoparasites and venomous creatures [10–12]. Inasmuch as the histopathology of allergic inflammation resembles that of cutaneous lesions elicited by bites of ectoparasites [13,14], it has been hypothesized that allergy is a consequence of the immune system having mistaken an otherwise benign allergen for an ectoparasite [10]. An alternative theory holds that

allergy represents a general defense against non-infectious, chemically dissimilar, environmental materials [15,16]. Of the two theories, the former seems more likely correct for the following reason: the bite of a particular group of ectoparasites, the tick, is capable of sensitizing a human against tick foodstuffs [17]. Although ticks are hematophagous and, consequently, the items against which they might sensitize humans are limited, the diet of the tick’s ubiquitous relative, the mite, is expansive, and includes most, if not all, human allergens, Fig. 1. It follows that *allergic inflammation is an attempt by the immune system to rid epithelial surfaces of mites.*

Mites and ticks, sole members of the phyletic subclass Acari [18], are especially and intimately associated with allergic inflammation [19–25]. Inhalation and/or ingestion of acarian-associated proteins trigger both asthma and food-related anaphylaxis, and cellular reactants mediating allergic inflammation – mast cells, eosinophils and basophils – protect against acarian infestation [26–37]. Especially noteworthy, mites and ticks also harbor and transmit a number of pathogenic bacteria, most significantly, Rickettsiales [38–40].

In addition to eliciting allergic inflammation, mites and ticks are able to enhance immune responsiveness to materials not otherwise allergenic [41–43]. As a well-documented example, hypersensitivity to galactose- α -1,3-galactose (α -gal) can follow the bite of a Lone Star tick, *Amblyomma americanum* [44]. Briefly, clinical trials involving the drug cetuximab revealed a cohort of patients at risk for lethal hypersensitivity to α -gal, a disaccharide epitope expressed on non-primate red

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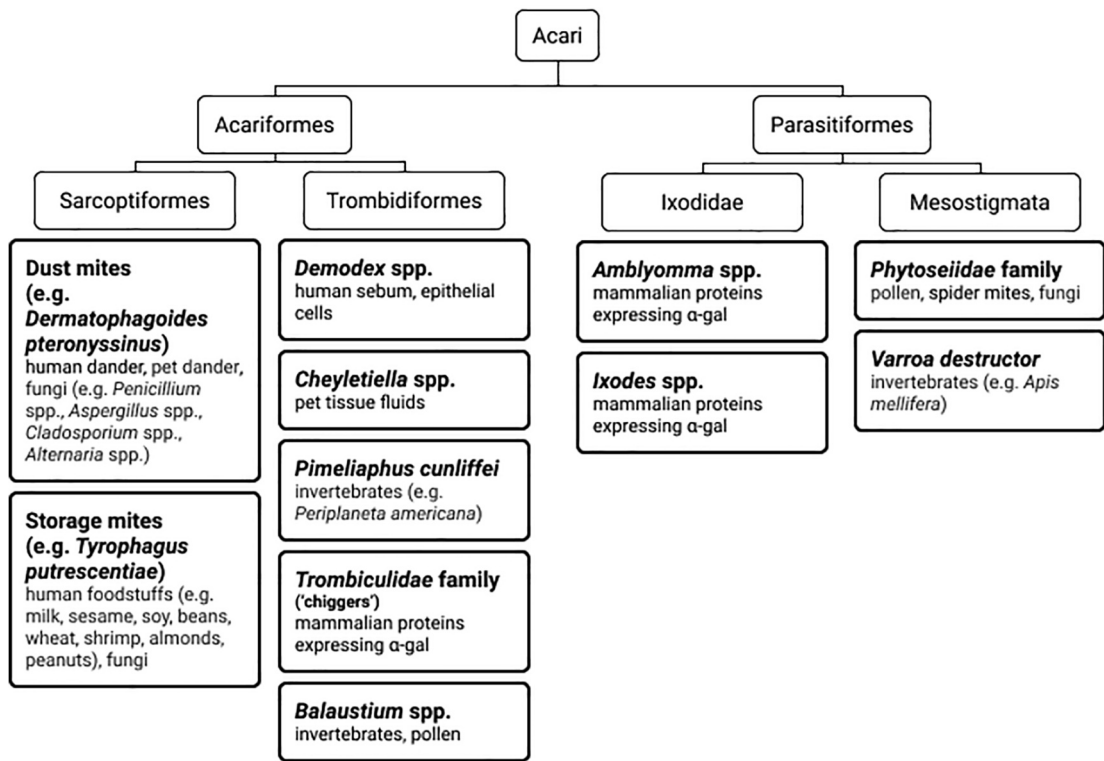


Fig. 1. Members of Acari, and their Diets.

Table 1
Food Stores and the Mites that Infest Them.*

Allergen Source	Mites that Inhabit and/or Consume Allergen Source
Almond	Glycyphagus domesticus, Acarus siro, Carpoglyphus lactis
Egg (dry storage pet food)	Dermatophagoides farinae, Tyrophagus putrescentiae
Fish (dry storage pet food)	Dermatophagoides farinae, Tyrophagus putrescentiae
Milk	Mycetoglyphus fungivorus, Tyrophagus putrescentiae
Peanut	Rhizoglyphus callae, Lardoglyphus konoi, Euroglyphus maynei
Sesame	Tyrophagus putrescentiae, Aleuroglyphus ovatus, Lardoglyphus konoi, Dermatophagoides farinae
Shrimp	Tyrophagus putrescentiae, Tyrophagus longior
Soy Bean	Tyrophagus putrescentiae, Acarus siro, Tyrolichus casei, Lepidoglyphus michaeli
Wheat	Acarus siro, Tyrophagus longior, Lepidoglyphus destructor, Chortoglyphus arcuatus, Aleuroglyphus ovatus

* Adapted from “The Density and Species of Mite Breeding in Stored Products in China.” Li C, Zhan X, et. al, 2014, Nutricion Hospitalaria, 31(2), p. 799–804.

blood cells and some proteins from non-primates [45]. The cohort had a curious geographic distribution, with susceptible patients clustering within regions of the United States endemic for Rocky Mountain spotted fever. Those regions, in turn, corresponded to the geographic distribution of the American dog tick, *Dermacentor variabilis*, the primary vector of the causative bacteria of Rocky Mountain spotted fever, *Rickettsia rickettsia*. Further investigation linked α -gal hypersensitivity to the Lone Star tick [46], a tick having a distribution very nearly the same as the dog tick. It has been theorized that the bite of a tick harboring a molecular species that expresses α -gal is responsible for hypersensitivity to the disaccharide [47]. More recent analyses indicate that the development of this hypersensitivity is not limited to encounters with *A. americanum*, but also to encounters with other ticks endemic to different continents [44]. In Europe, *Ixodes ricinus* has been implicated [48–49], and, within the United States, case reports suggest species of mites of the order Trombidiformes are also able to sensitize against α -gal [50]. It appears the mammalian immune system can generate an allergic response to an exogenous molecular species pre-existing within acarian saliva, a potentially adjuvant-active principle. Although data regarding mites are less robust, the relatedness of

mites and ticks makes it likely the two have similar adjuvant capabilities. That capability, along with an exceedingly diverse diet, render mites in particular ideally positioned to sensitize against human allergens, Fig. 1 and Table 1 [51–58]. In this regard and not unexpectedly, mites in frequent close proximity to humans, e.g., dust and storage mites, feed on materials to which humans are most commonly allergic, i.e., milk, eggs, sesame, wheat, pet dander and fungi, including *Penicillium chrysogenum*. Other mites that bite humans feed on pollens [59], while still others feed on invertebrates such as cockroaches [60], helminths [61] and bees [62]. It is entirely reasonable to suppose that complexation of these many dietary materials with relevant acarian salivary or gastrointestinal secretions leads to misidentification of the foodstuffs as mite representations, directing a specious adaptive immune response. Then, ubiquity and size ensure aerial dispersion of mites from abundant environmental stores, which, in turn, ensures frequent, albeit under-appreciated, contact of mites with human epithelia [63–65]. Aspects of allergy are conducive to eliminating the pathological threat posed by acarians. Firstly, many structural families of allergens are well-represented in acarian saliva, e.g., serpins, tropomyosins and

Table 2
Inductive Reasoning in Support of the Acari Hypothesis.

Observation	Supposition
Anaphylaxis – indeed allergic inflammation in general – triggers physiological reflexes that target epithelial surfaces. Even allergens introduced intravenously produce epithelium-directed responses.	The presence of an allergen informs the body of a perceived threat – such as an ectoparasite – on an <i>external</i> surface of the body.
Reflexes triggered during the acute phase allergic response are not effective at removing molecular-sized targets from epithelial surfaces, but they are effective at removing arthropod-sized targets.	The objective of allergic reflexes is to remove a target associated with a molecular-sized allergen, but orders of magnitude larger than the allergen itself.
The late phase of an allergic response is largely effected by eosinophils, cells involved in defense against multicellular organisms.	The objective of allergic inflammation is to defend against multicellular organisms, such as ectoparasites.
Ticks are able to sensitize humans against α -gal, a molecular species present in tick gastrointestinal content.	An agent within the gastrointestinal content of the tick is adjuvant-active and able to induce an allergic response against substances with which it is associated.
Mite materials are able to induce an allergic response against otherwise non-allergic substances, <i>i.e.</i> , they are adjuvant-active.	An agent within the gastrointestinal content of the mite is adjuvant-active and able to induce an allergic response against substances with which it is associated.
Allergens can be organized into molecular families, many of which are well-represented in tick gastrointestinal content.	The allergic response is uniquely suited to recognizing and responding to the gastrointestinal content of ticks and mites.
Allergic responses occur very rapidly.	The speed of the allergic 'defense' is commensurate with the vectorial threat of acarians, which can transmit a pathogen payload within minutes of initiating a blood meal.
The polyphagous diet of the mite includes many, if not all, human allergens.	Mites are ideally positioned to sensitize humans against many, if not all, allergens.
The diet of synanthropic mites includes the most common human allergens.	Synanthropic mites are responsible for the bulk of allergic disease.

EF-hand domains [66,67]. (As a relevant example, *A. americanum* expresses within its saliva at least 17 serpins) [68]. Secondly, the rapidity of the early onset acute phase allergic response is commensurate with the rapidity with which acarians transfer their pathogenic payloads [69]. Thirdly, any allergenic challenge that occurs via intravenous route elicits a pathophysiological reflex consistent with an attempt to remove an ectoparasite from an epithelial surface.

From a teleological perspective, the Acari hypothesis proposed herein brings rationale to the otherwise confounding nature of the pathophysiological reactions that constitute allergic conditions, including anaphylaxis, Table 2. Should an allergen, *e.g.*, penicillin, be detected, the immune system of a sensitized individual elicits responses intended to expel a pathogen-laden acarian: scratching, spitting, coughing, vomiting and defecating.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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