An update on oral immunotherapy for the treatment of food allergy

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Abstract

Food allergy is an important public health concern, affecting 10% of infants, 5–6% of children and 2% of adults in westernized countries. Current management involves food avoidance, education of patients and carers in the emergency management of allergic reactions and in some cases provision of an adrenaline autoinjector. Oral immunotherapy (OIT) has recently been explored as a potential treatment for food allergy. This review will discuss mechanisms of oral tolerance and summarize clinical and immunologic effects of OIT.

Keywords desensitization; food allergy; oral immunotherapy; sustained unresponsiveness; tolerance

Introduction

Prevalence of food allergy and food anaphylaxis has increased significantly in recent decades. Over a 10–15 year period leading up to 2005, anaphylaxis admissions were reported to increase 2-fold, 5-fold and 7-fold in Australia, US and UK, respectively. A continued increase in food anaphylaxis admissions has been documented since 2005 in both the UK and Australia. While allergies to egg, milk, wheat and soy generally resolve during childhood, the age at resolution appears to be increasing with many cases resolving in adolescence. Furthermore, peanut, tree nut, shellfish and fish allergies tend to persist throughout life. Therefore, the burden of disease or disease prevalence is expected to increase unless either a curative treatment can be identified or the incidence can be reduced through prevention strategies.

Prevention of allergic disease may be possible. The LEAP study (www.leapstudy.co.uk) demonstrated proof of concept that early introduction of peanut can significantly reduce the early incidence of peanut allergy, and studies are underway to determine if a similar approach to early introduction of other allergenic foods may be effective for prevention of other food allergies. Nevertheless, given that disease prevalence will only stabilize when the rate of disease resolution is equal to the incidence rate, the search for a curative treatment remains a priority.

Current management of food allergy centres on allergen avoidance and education of the patient and parent/carer in the emergency management of allergic reactions, and may also include the provision of an adrenaline auto-injector. Despite food labelling laws and constant vigilance to avoid allergens, accidental ingestion is common, resulting in high levels of fear and anxiety and reduced quality of life for children and their families. Novel treatment approaches that can establish or restore oral tolerance to food allergens would offer a long-term curative treatment and improve the lives of patients with food allergy.

Mechanisms of oral tolerance

Oral tolerance is an active immunological process that involves coordinated interactions between intestinal epithelial cells, macrophages, dendritic cells, and lymphocytes. The healthy intestinal epithelium forms a dynamic barrier that excludes antigens and microorganisms, representing an important first line mechanism for maintenance of immune homeostasis in the intestine. In addition, epithelial cells possess immunoregulatory functions that can direct mucosal immune responses towards tolerance or inflammation. There is close cross-talk between intestinal epithelial cells and antigen presenting mononuclear phagocytes and dendritic cells (DC), allowing these populations to co-ordinately direct appropriate homeostatic responses.

For successful oral tolerance, luminal antigens must be sampled without disruption of the epithelial barrier; this can be achieved by one of four pathways (Figure 1a–d). Each pathway can preferentially sample antigens with specific characteristics and direct immune responses towards either inflammation or tolerance accordingly.

Immune responses to luminal antigens are directed by two populations of antigen-presenting cells within the intestinal lamina propria – CD103+ DC and CX3CR1+ DC (Figure 2). Intestinal FoxP3+ iTreg induced by CD103+ DC are critical for the induction and maintenance of oral tolerance; whereas natural T-regulatory cells (nTreg) do not appear to be required or sufficient for successful oral tolerance induction.

Food allergy: a manifestation of failure or loss of oral tolerance

Food allergy is suggested to occur as a result of failure or loss of oral tolerance. The balance between allergen-specific Treg and T-helper(Th)-2 cells provides a critical factor determining progression to allergy vs tolerance. IgE-mediated food allergy is associated with production of allergen-specific IgE, low or no allergen-specific IgG1 or IgG4, as well as increased Th2 and low Treg cytokine responses to allergen, whereas non-allergic children demonstrate a Treg or Th1 predominant cytokine response or fail to respond to allergen. In addition, children with food allergy have fewer TGFβ+ lymphocytes in duodenal epithelium and lamina propria as well as reduced TGFβ expression in duodenal epithelium. Importantly, this reduced T regulatory activity in children with food allergy is present from the time of

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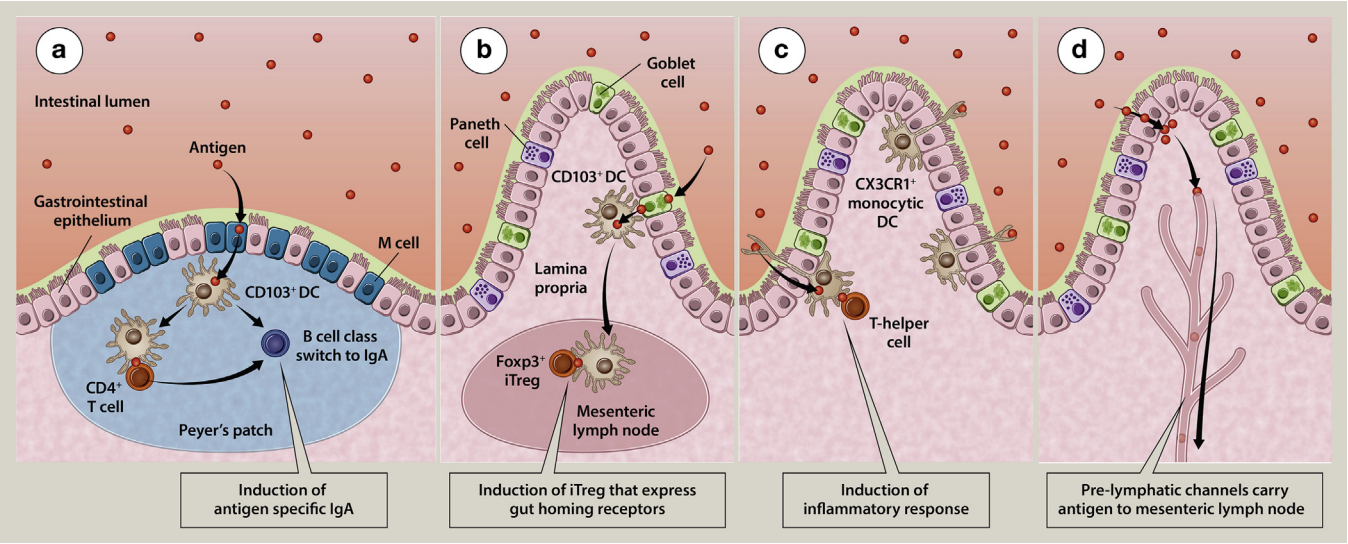

Figure 1 Major mechanisms of luminal antigen sampling. (Taken from Tang MLK, The physiological induction of tolerance to allergens. In: "Allergy, immunity and tolerance in early childhood: The first steps of the Atopic March". Ed: Sampson HA and Wahn U. Elsevier 2015.). (**a**). Transcytosis of antigen by M cells. M cells are specialized epithelial cells in the follicle-associated epithelium overlying Peyer's patches (PP) and isolated lymphoid follicles (ILF) that preferentially sample particulate antigens such as commensal bacteria from the small intestine, delivering these to CD103+ DC within PP and ILF. These promote IgA responses. (**b**). Antigen sampling by goblet cells promotes the induction of tolerogenic responses to soluble antigens. Goblet cell-associated passages (GAPs) allow the selective delivery of small soluble antigens (e.g. dietary proteins) across the epithelium to CD103+ DC in the underlying lamina propria. (**c**). CX3CR1+ DC within the lamina propria are capable of directly sampling luminal antigens by extending transepithelial dendrites across the epithelium. DC within the Peyer's patch are also capable of forming transepithelial dendrites that extend between M cells to capture pathogenic bacteria or particulate antigens. Transepithelial dendrite antigen sampling is primarily activated in response to pathogens and predominantly promotes protective inflammatory responses, suggesting that the principal function of CX3CR1+ DC is to initiate protective inflammatory responses before pathogens breach the epithelial barrier. (**d**). Paracellular leak around epithelial cells. In the healthy homeostatic state, paracellular leak of low molecular weight soluble antigens leads to transient collection of antigen just beneath the epithelium followed by rapid clearance through prelymphatic channels and lacteals to the draining mesenteric lymph nodes, where antigen processing by resident DC proceeds. In contrast to M cells and GAPs, paracellular leak preferentially allows passage of smaller soluble antigens (less than 10 kD in size), which are not efficiently captured by lamina propria DC. It is currently uncertain whether antigens sampled by this pathway lead to inflammatory or tolerogenic immune responses within the mesenteric lymph nodes. Intestinal inflammation is associated with transit of larger macromolecules such as proteins and carbohydrates.

birth, prior to the onset of disease. Conversely, resolution of IgE mediated food allergy is associated with reduction in allergen-specific IgE, reversion to Th1 dominant cytokine responses to allergen and increased numbers of circulating Treg. Nevertheless, Th2 cytokine production can be observed in both food allergic and tolerant subjects, although the intensity of Th2 cytokine production is highest in those with food allergy.

Searching for an effective treatment: desensitization vs tolerance

When evaluating the effectiveness of potential food allergy treatments, it is important to distinguish between the outcomes of 'desensitization' and 'tolerance'. Desensitization describes the ability to ingest a food without reaction while continuing on regular doses of that food (e.g. continuing oral immunotherapy). Successful desensitization in the absence of tolerance is mediated by changes in effector cells (mast cells, basophils), without modulation of underlying pathogenic immune mechanisms; thus, the individual remains allergic to the allergen. In contrast, tolerance is the ability to ingest a food without reaction even after discontinuation of oral immunotherapy for a period of weeks to months. Tolerance is believed to reflect sustained reprogramming of the immune response to allergen, involving regulatory T cells and/or allergen-specific anergy and clonal deletion. Desensitization can be determined clinically by performing a food challenge while a subject is still receiving oral immunotherapy or eating regular doses of a food, and tolerance is confirmed by performing a food challenge after oral immunotherapy or food intake has been stopped for a period of time. Currently, there is no consensus regarding the duration of secondary elimination required to demonstrate true long-lasting tolerance, although experts in the field recommend stopping food intake for 8–12 weeks before performing a food challenge to assess for tolerance.

Oral immunotherapy for treatment of food allergy

Oral immunotherapy (OIT) was first reported to successfully treat a child with egg anaphylaxis in 1908. Modern OIT regimens commonly comprise a rush phase, build-up phase and maintenance phase. During the rush phase, the dose is rapidly increased from micrograms to milligrams over several hours. In the build-up phase, doses are continued on a daily basis with dose increases performed periodically (usually every 2 weeks) for a number of months until the target maintenance dose is reached. The maintenance dose is then maintained on a daily basis for a number of years. As all food allergies can resolve spontaneously over time, it is important to include a control or placebo treatment when evaluating the efficacy or effectiveness of a treatment intervention.