A sweet path toward tolerance in the gut

Gabriel A Rabinovich

Uncovering how the immune system of the mucosa surmounts allergic reactions may open new avenues to treat inflammatory conditions in the gut. New findings in mice now show that a C-type lectin receptor in dendritic cells (DCs) protects against food antigens that cause systemic anaphylaxis—promoting oral tolerance (pages aaa–bbb)^. PR1

To cope with microbial, environmental and food antigen challenges, mucosal surfaces are equipped with a unique system composed of a network of immune effector and regulatory cells and a portfolio of proinflammatory and anti-inflammatory mediators, such as cytokines, chemokines and cell surface receptors that tightly control the balance between responsiveness and tolerance[1]. Despite considerable progress toward defining the functions of single components of this network, there is still no integrated portrait of the mechanisms that regulate these 'immunological decisions'.

In this issue of *Nature Medicine*, Zhou *et al.*[2] describe in mice a 'sweet' path signaled by the glycan-binding receptor SIGN-R1 that conditions the mucosal immune system to reduce the anaphylactic response triggered by food allergens. A sugar-modified antigen activates C-type lectin receptor (CLR)-specific ICAM-3 grabbing non–integrin-related-1 (SIGNR1) expressed on DCs to release interleukin-10 (IL-10), which, in turn, induces the generation of T regulatory type 1 (Tr1) cells, resulting in tolerance to food allergies. These findings uncover a new way to induce oral tolerance with sugar-modified antigens.

SIGNR1 is a mouse homolog of human DC-SIGN that has specificity for mannose- and fucose-containing glycans and is expressed in marginal zone macrophages in the spleen and DCs in lymph nodes[3,4]. SIGNR1 has been implicated in the capture of microbial

polysaccharides[5] and influenza virus[6] and has emerged as a mediator of the anti-inflammatory activity of intravenous immunoglobulins in autoimmune diseases[7].

In the quest to understand the molecular basis of oral tolerance in mucosal tissues, Zhou *et al.*[2] now unveil a new function for SIGNR1 as a gatekeeper in mucosal immunity. By mimicking the highly mannosylated structures typical of pathogens[4], the authors used chemically modified bovine serum albumin (BSA) bearing 51 moles of mannosides (Man_{51}-BSA) to induce oral tolerance in mice[2]. Specific recognition of Man_{51}-BSA by SIGNR1 expressed by lamina propria DCs unleashed a cascade of tolerogenic events involving the secretion of IL-10, which promoted the generation of IL-10–producing FoxP3^{−} Tr1 cells (**Fig. 1**). In a mouse model of food allergy, the anti-inflammatory activity of Tr1 cells successfully prevented systemic anaphylaxis after challenge with nonmodified BSA, as evidenced by decreased histamine amounts, reduced vascular permeability and decreased immunoglobulin E responses.

This study adds SIGNR1 as a new piece of the 'tolerogenic puzzle' that links the structure of a food antigen to the activation of regulatory lamina propria DCs and to the differentiation of IL-10–producing Tr1 cells[2]. Through their ability to sense signals from the local environment and shape the course of an immune response, CD11c^{+}CD11b^{+} lamina propria DCs are central modulators in driving tolerance by capturing antigens in the intestine and migrating to mesenteric lymph nodes where they instruct the differentiation of regulatory T cells[8]. Recognition of mannosylated antigens by SIGNR1 on lamina propria DCs thus may be crucial in triggering IL-10 production. Although engagement of SIGNR1 on DCs led to phosphorylation of the mitogen-activated protein kinase c-Jun N-terminal kinase *in vitro*

and sustained expression of the chemokine receptor CCR7 to reach mesenteric lymph nodes[2], the precise signaling pathways underlying these processes need to be addressed.

Emerging evidence suggests that endogenous glycan-binding proteins may serve as signaling molecules that convey pathogen, tumor or environmental information into DC differentiation programs[9]. Similar to binding of SIGNR1, engagement of dectin-1, a CLR responsible for recognizing β-glucans on yeasts, instructs DCs to become tolerogenic[10], whereas the C-type macrophage galactose lectin endows DCs with T cell inhibitory capacity[11]. Moreover, in mouse models of autoimmune brain inflammation, targeting a central nervous system peptide to the CLR DEC205 on immature DCs confers tolerance *in vivo*[12]. Strikingly, in these models, delivery of mannosylated myelin-derived antigens suppressed autoimmune neuroinflammation, whereas unglycosylated peptides aggravated inflammatory disease[13], which further supports the conclusions of the work by Zhou *et al.*[2].

Together, these observations suggest that the natural function of CLRs may extend beyond their role as antigen uptake receptors, and they may serve as gatekeepers involved in immune tolerance and homeostasis. Yet this tolerogenic function is not limited to CLRs, as galectin-1, a member of a family of β-galactoside–binding proteins, can also fuel an immunoregulatory circuit mediated by IL-27–producing DCs and IL-10–secreting Tr1 cells, which facilitates recovery of chronic inflammatory diseases[14]. Distinct protein-glycan systems, therefore, may have evolved as 'on-and-off' switches that control the induction of tolerogenic versus inflammatory DCs, emphasizing the imperative need of deciphering the complex information encoded by the 'glycome'.

These findings have profound therapeutic implications. Food hypersensitivity, resulting

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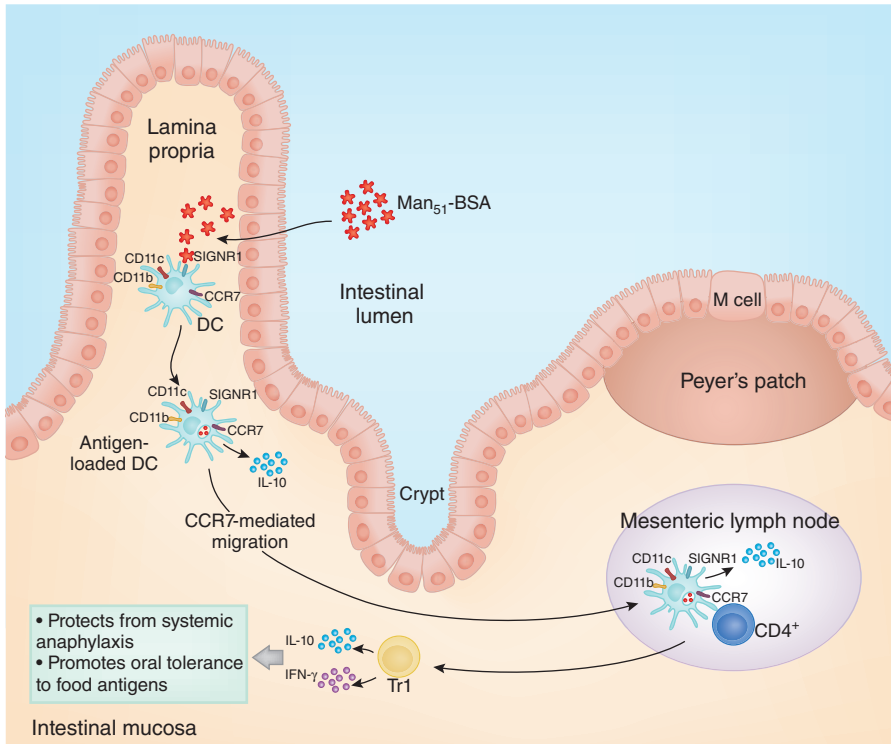e-mail: gabyrabi@dna.uba.ar or gabyrabi@gmail.com^

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Figure 1 The C-type lectin SIGNR1 amplifies tolerogenic circuits in mucosal immunity. Capture of Man$_{51}$-BSA by the C-type lectin SIGNR1 on lamina propria DCs unleashes a cascade of tolerogenic events involving secretion of IL-10, which leads to the generation of Tr1 cells in mesenteric lymph nodes. CCR7 expression may direct lamina propria DCs to mesenteric lymph nodes to encounter T cells. Upon differentiation, Tr1 cells secrete IL-10 and interferon-γ (IFN-γ) to prevent systemic anaphylaxis and promote oral tolerance in response to food allergens.

from impaired tolerogenic mechanisms in the gastrointestinal mucosa, is an increasingly common disorder affecting ~6% of children and ~4% of adults, with potentially life-threatening complications including systemic anaphylaxis[15]. Although the current standard of care involves dietary avoidance of the implicated allergen (for example, milk, eggs or peanuts), the increased understanding of regulatory mechanisms in mucosal tissues is shifting the focus of treatment and prevention toward inducing oral tolerance[15].

Here the authors propose a new therapeutic strategy based on the delivery of a sugar-modified antigen, Man$_{51}$-BSA, to prevent food anaphylaxis by activating local tolerogenic mechanisms[2]. These tolerogenic signals could rapidly spread to the systemic compartment, as splenocytes from Man$_{51}$-BSA–treated mice were able to prevent anaphylactic reactions when adoptively transferred to BSA-sensitized mice[2]. In contrast, interruption of SIGNR1-glycan interactions might provide adjuvant capacity to mucosal vaccines.

But there are still essential issues to be addressed before embracing this approach in clinical settings. Does the human homolog DC-SIGN play a similar tolerogenic part to mouse SIGNR1? If so, are the expression levels of mouse SIGNR1 and human DC-SIGN optimal so that they might activate this tolerogenic circuit during ongoing systemic anaphylaxis? Alternatively, can mannosylated antigens bind other glycoreceptors in mucosal tissues of allergic individuals in such a way so that it ^ could thwart the efficacy of this approach by switching tolerogenic to inflammatory circuits?

Although much remains to be learned, the study by Zhou *et al.*[2] provides a crucial step in our understanding of the molecular mechanisms of oral tolerance and the pivotal role of protein-glycan interactions in this circuit, offering a new therapeutic approach based on the administration of 'sweet' antigens to prevent or attenuate anaphylactic episodes.

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