Basic Science of Food Allergy and Food Oral Immunotherapy

From Tolerance to Treatment

Brian Modena, MD

Modena Health

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Learning Objectives

01

Define immune mechanisms of oral tolerance to food antigens.

02

Explain immunopathogenesis of IgE-mediated food allergy.

03

Identify contributing genetic and environmental factors in food allergy.

04

Describe how oral immunotherapy (OIT) induces immune modulation.

Breakdown in Tolerance Leading to Food Allergy

Loss of Treg function → skewed Th2 responses

Th2 cytokines Increases and Persists

IL-4 leading to IgE class switching

IL-5 leading to eosinophil activation

IL-13: Mucus production, epithelial dysfunction

Allergen-specific IgE binds to FcεRI receptors on mast cells and basophils → hypersensitivity reactions

Key Mechanism to Prevent Food Allergy

In a TGFβ and retinoic acid dependent mechanism, CD103+ dendritic cells (DCs) carry food antigens from the lamina propria to mesenteric lymph nodes where they interact with T-cells and promote the formation of forkhead box protein 3 (FOXP3) positive regulatory T (Treg) cells

Tregs migrate to the lamina propria and undergo expansion, the latter of which is dependent on the production of IL-10 by CX3CR1+ macrophages

Etiology of Food Allergy

Genetic factors

- FLG mutations (epithelial barrier defects)
- **HLA** polymorphisms
- IL4 mutations (increased production)

Developmental factors

- Maturation of gut
- Maturation of immune cells (e.g. dendritic cells)

Environmental factors

- Delayed introduction of allergenic foods (LEAP trial, Du Toit et al., NEJM 2015)
- Antibiotic use, early-life dysbiosis

Immune factors

- Reduced Treg numbers/function, impaired microbial signals
- Tendency for T2 Inflammatory Pathway ‘

Genome Wide Association Studies – Attempts to Discover the Genetic Roots of Food Allergy

Marenholz et al, (Nat Communications 8, 1056 (2017)) including 497 cases vs. 2387k controls, discovered five loci at genome-wide significance:

1. Clade B serpin (SERPINB) gene cluster at 18q21.3, *SERPINB7/B2*
2. Cytokine gene cluster at 5q31.1, *IL4/KIF3A*
3. **Filaggrin gene (*FLG*)**
4. *C11orf30/LRRC32* locus
5. **Human leukocyte antigen (HLA) region**

Age-related Immunological Plasticity Occurs Early in Life

Food allergy starts early in life, typically before the **age of 6 months**, and by function, has an increased ability to change in response to external factors.

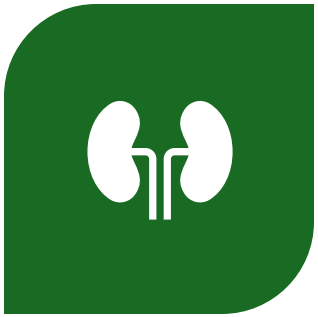
Allergy responses in infants are weak: low T-cell receptor affinity, unstable Gata-3 transcription factor expression and low IL-4 production.

Ripening / persistence / increase in the T2 inflammatory response (IL4, 5, 13) seen in the first years prevents tolerance / SU.*

- *Increasing and/or high levels of IgE early life correlate with food allergy persistence.
- ***Expansion of the IgE epitopes** during first few years of life associates with food allergy persistence.
- Peanut-sensitized children who consumed peanut and remained tolerant did not show epitope spreading.

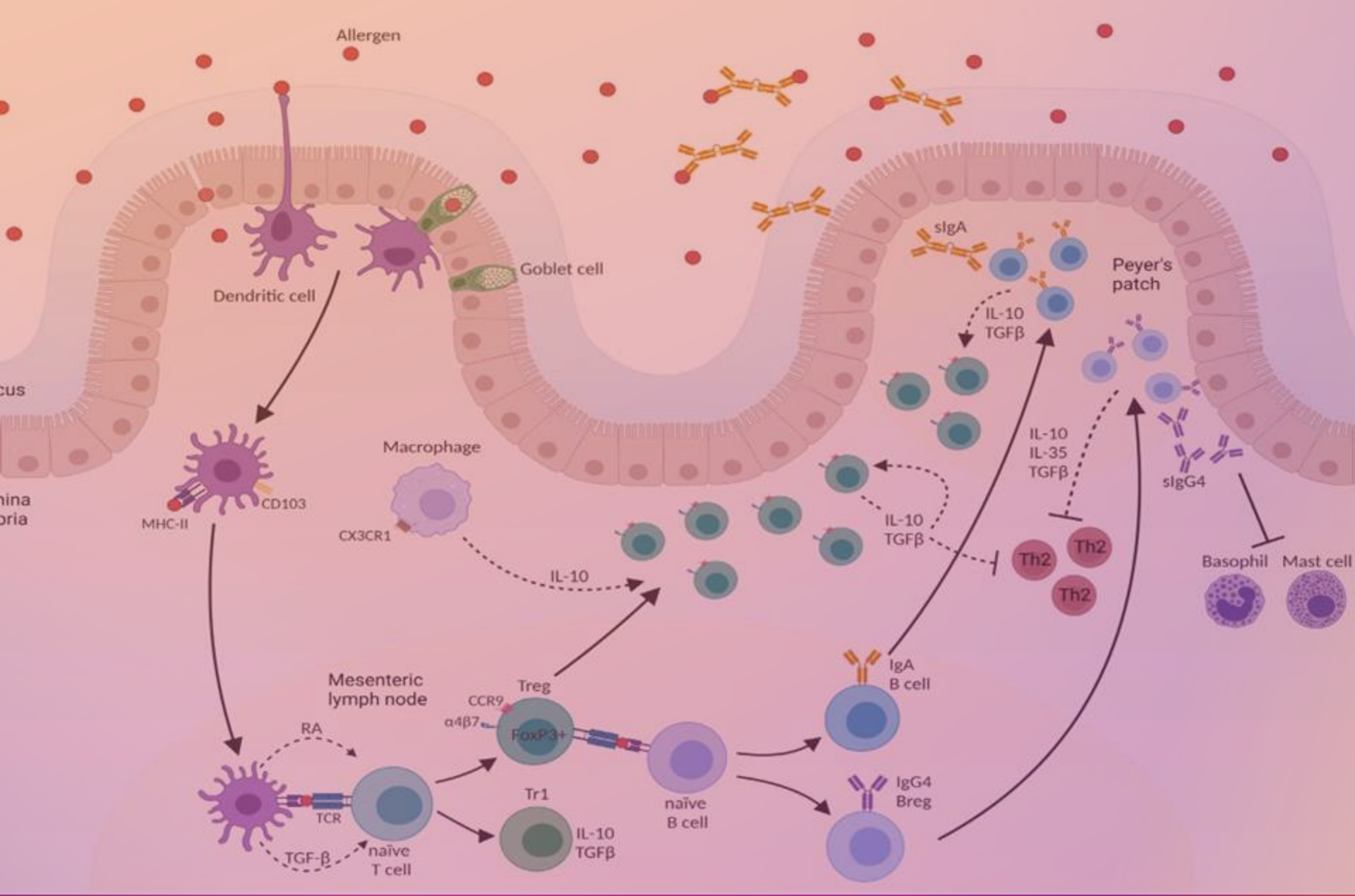
Mucosal Immune System

THE GUT-ASSOCIATED LYMPHOID TISSUE (GALT) IN THE INTESTINAL MUCOSA CONTAINS A HIGH CONCENTRATION OF IMMUNE CELLS, INCLUDING APCS, T CELLS, AND B CELLS.



THESE CELLS WORK TOGETHER TO LIMIT INFLAMMATORY RESPONSES TO FOOD ANTIGENS AND COMMENSAL BACTERIA, MAINTAINING A STATE OF TOLERANCE.

THE GUT MICROBIOTA PLAYS A ROLE IN REGULATING THE IMMUNE SYSTEM AND PROMOTING TOLERANCE.



Barten et al., Oral immunotherapy as a curative treatment for food-allergic preschool children: Current evidence and potential underlying Mechanisms. Pediatr Allergy Immunol. 2023)

Gastrointestinal Maturation and Increase Risk of Food Allergy Development in Infants

In summary, exposure of the intestinal epithelium and intestinal mucosal immune system to higher levels of intact protein, i.e. **increased epithelial antigen passage** is the major, overarching theme for the increased susceptibility of infants and young children to FA.

Why?

- Infants and young children have lower gastric acid secretion
- Gastric emptying is faster until age 3 years
- Chymotrypsin and carboxypeptidase activity is lowest in newborns and increases w/ age.
- Overall, protein digestion is considerably lower compared to adults

Why Do Pediatric Transplant Patients Show a Higher Incidence of Food Allery

Evidence from studies, such as those in pediatric transplant patients, shows a higher incidence of food allergies in children on calcineurin inhibitors compared to the general population, likely because:

- **Disruption of Gut Barrier Function**: Calcineurin inhibitors can impair the intestinal epithelial barrier, increasing gut permeability ("leaky gut
- **Altered Immune Regulation**: Disrupt the balance between Th1 and Th2 immune pathways, favoring Th2 responses
- **Gut Microbiota Dysbiosis**: Calcineurin inhibitors can alter the gut microbiome, reducing microbial diversity or beneficial bacteria that promote immune tolerance.
- **Immune Development in Childhood**: Children's immune systems are still maturing, making them more susceptible to environmental influences like immunosuppressive drugs.

Gastrointestinal Maturation and Increase Risk of Food Allergy Development in Infants

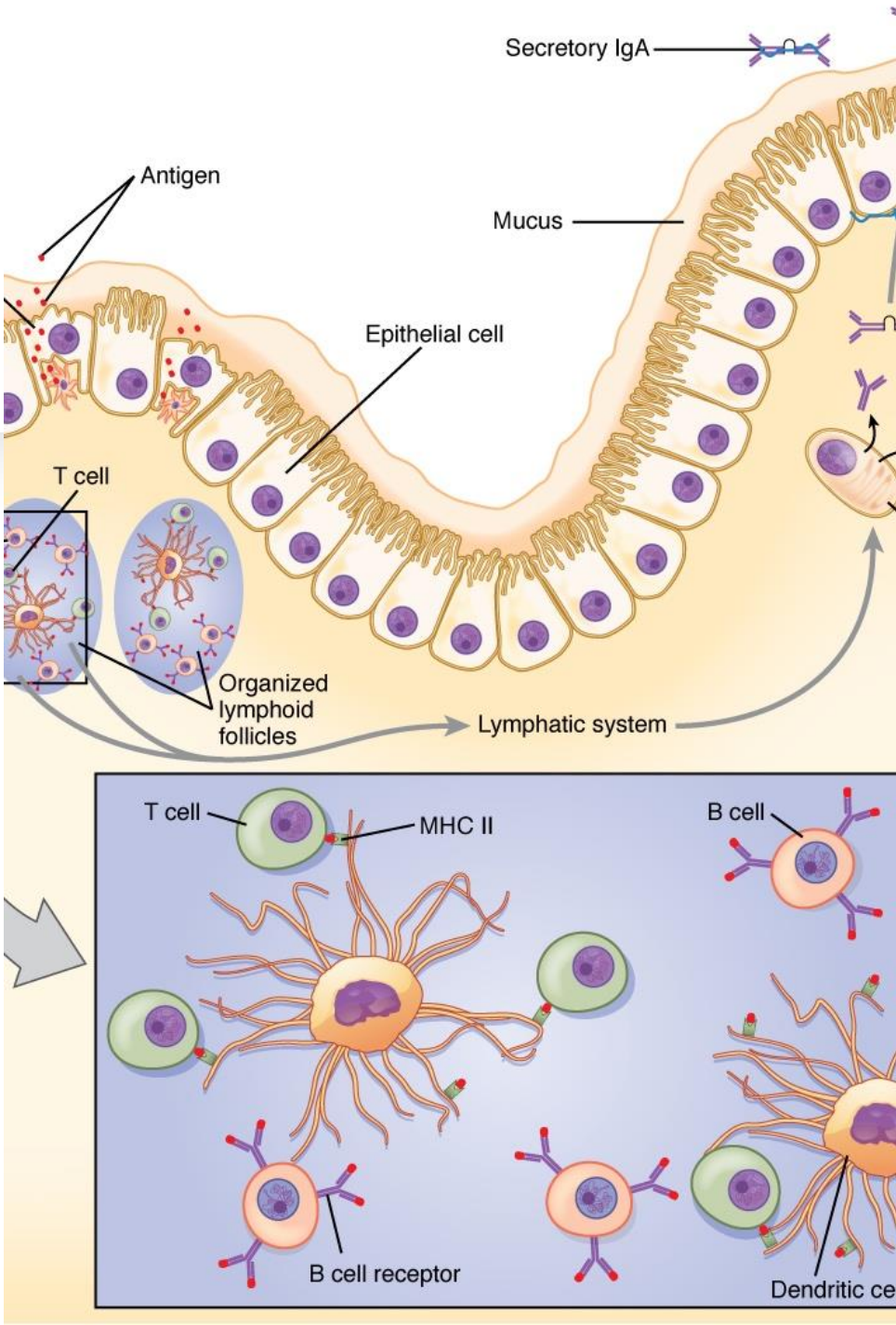
- In summary, infants have **increased epithelial antigen passage (is the theory).**
- **Why? (cont'd)**
- Due to high endocytic capacity of immature intestinal epithelial cells, enhanced macromolecular transfer takes place.*
- Increased exposure of the intestinal mucosal immune system
- Loss of endocytic capacity occurs with epithelial maturation and 'gut closure,' which may occur as early as 22 weeks after birth.

- *May also explain a mechanism of OIT to induce permanent tolerance.

- Barten et al., Oral immunotherapy as a curative treatment for food-allergic preschool children: Current evidence and potential underlying Mechanisms. Pediatr Allergy Immunol. 2023)

Quick Summary of Antigen Sampling in the Gut

- Specialized epithelial cells (M cells, goblet cells) and CX3CR1+ macrophages transfer antigens to lamina propria dendritic cells.
- **CD103+ dendritic cells** process antigens and migrate to mesenteric lymph nodes (MLNs) (Mucida et al., Science 2007), presenting them to T cells.
- Tolerogenic DCs induce Treg differentiation from naive CD4+ T cells, typically guided by the inflammatory milieu, presence of TGF-beta and retinoic acid.
- Tregs (Foxp3+) play a crucial role in suppressing activation of other T cells, most importantly, Th2 cells.



Maturation of the Dendritic Cells (DCs)

- Several populations of DCs inhabit the subepithelial regions (monocyte-derived, conventional, plasmacytoid) and are instrumental in determining immune responses.
- In summary, in the early immune system of neonates, DCs are lower in numbers and costimulatory receptors (CD80, CD86, and CD40) are decreased, ability to induce Type 1 inflammatory responses is lower in monocyte DCs.
- Fetal DCs do secrete higher levels of regulatory cytokines (e.g. IL-10) promoting Tregs, but depends on CD103+ DCs.

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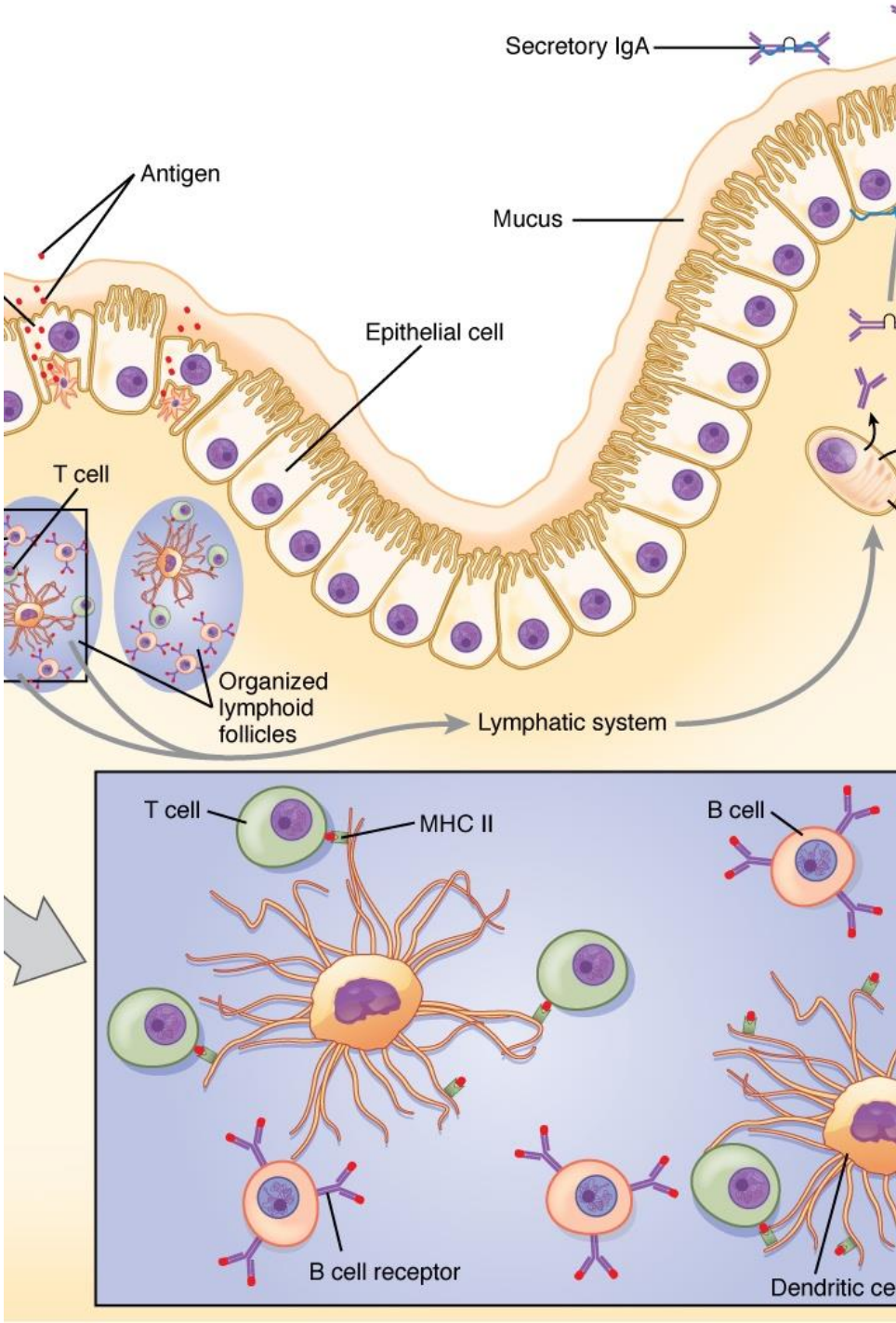

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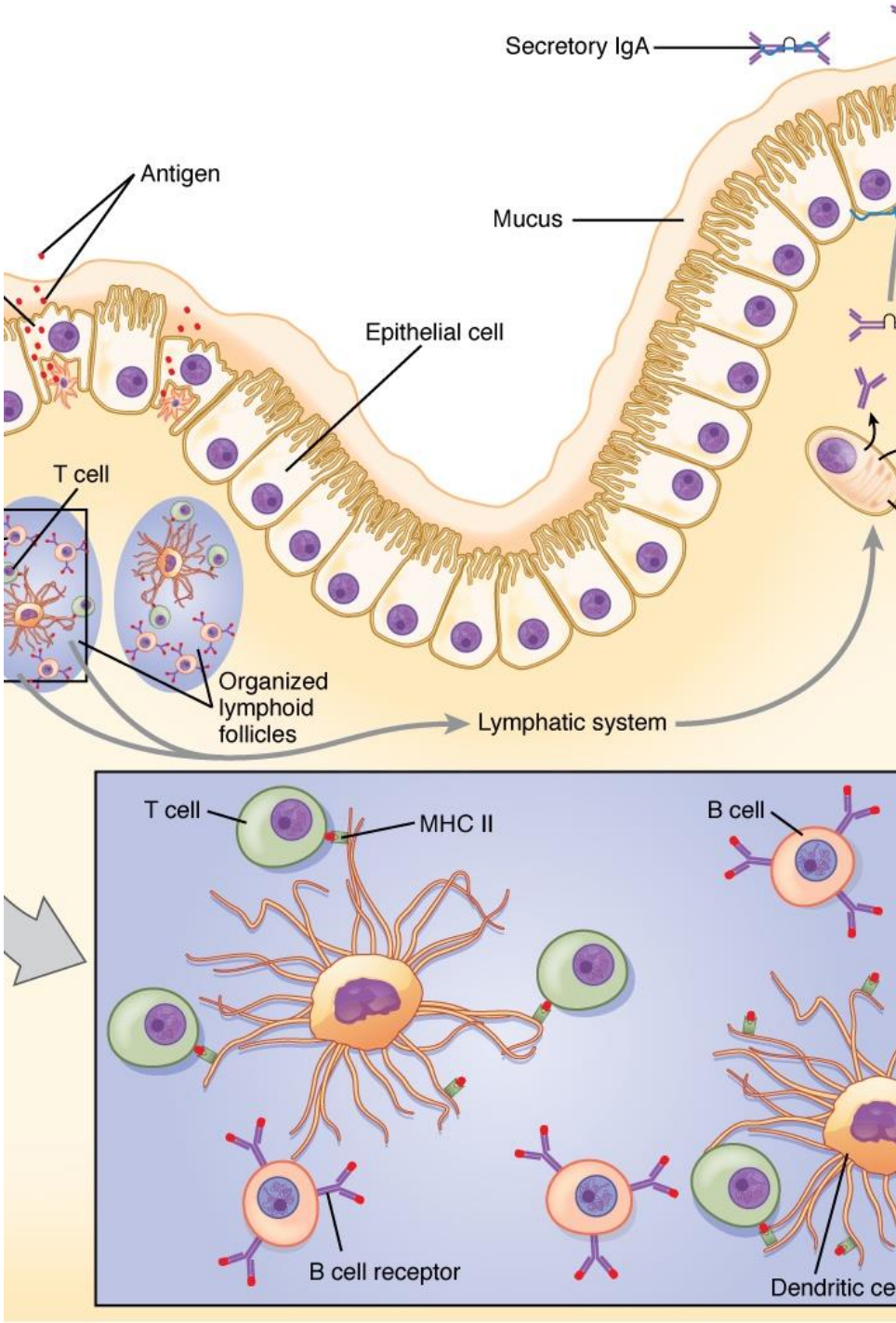


Maturation of the T cells

- In summary, absolute #'s of naïve T cells strongly increases after birth peaking at 4 week, and are higher in pediatric tissues, including the intestines.
- These naïve T cells are skewed to T2 high immunity (generated during pregnancy to tolerate maternal alloantigens), but at the same time CD4+ naïve T cells are predisposed to differentiate in Tregs.
- **Tregs are key to immune tolerance**.
- Neonatal Tregs preferentially migrate to the gut > skin.

Maturation of B cells

- B-cells are responsible for IgE, but also play an important role in in tolerance as IgG- and IgA-producing regulatory B cells.
- Isotype switching to produce IgG and IgA is limited during the first 6 months of life.
- Affinity maturation is blunted in the first 2 years after birth.
- Transition from transitional and naïve B cells early in children to more memory B-cell populations gradually increase.

What are Treg and Bregs & Why Are They Important?

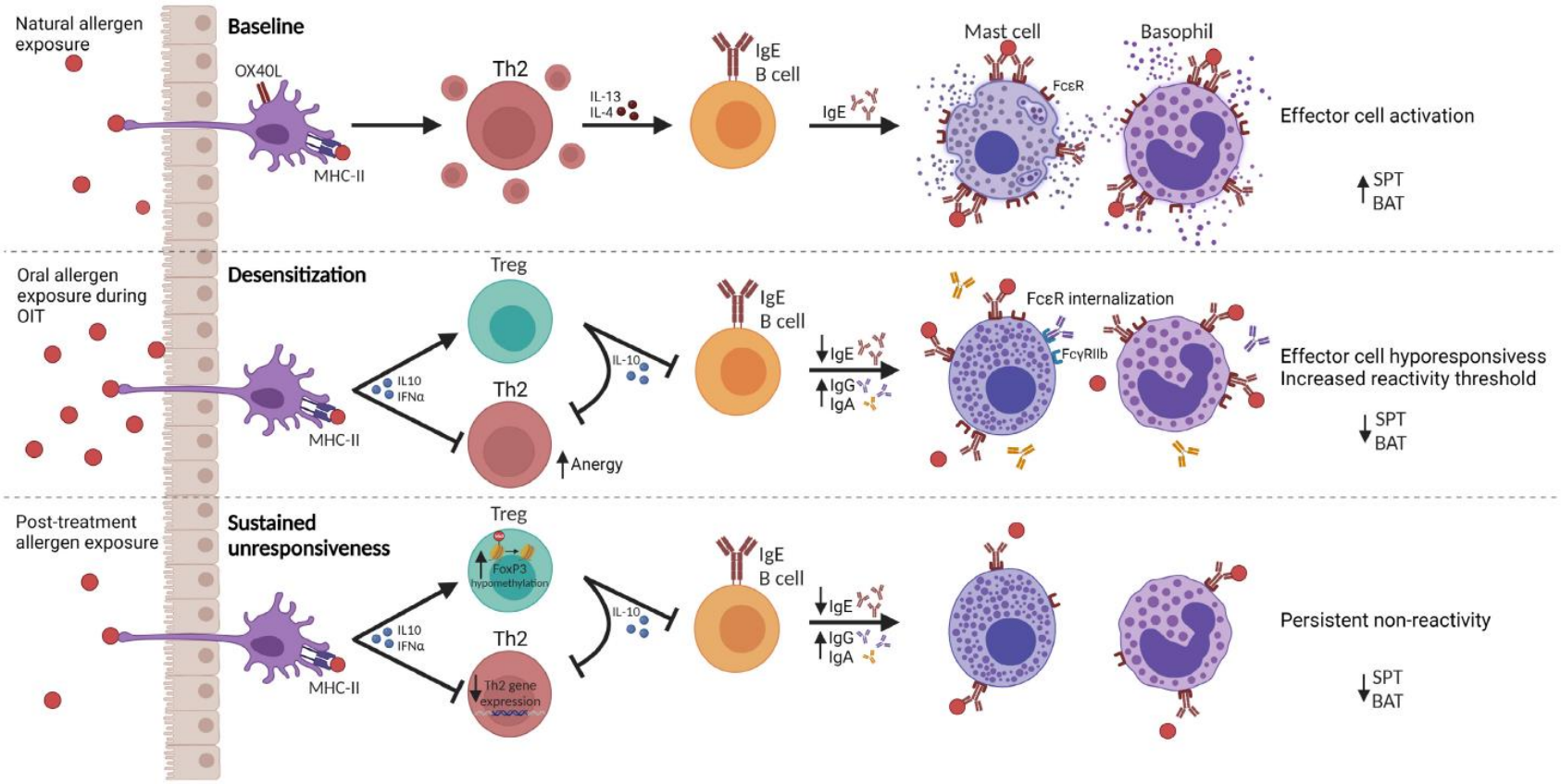
Induced Tregs (iTregs) arise in mesenteric lymph nodes with help of:

- TGF-β (transforming growth factor-beta)
- Retinoic acid (vitamin A derivative)
- IL-10 (immune-regulatory cytokine)

Tregs express Foxp3, CTLA-4, and produce IL-10/TGF-β to suppress effector T cells (Josefowicz et al., Immunity 2012).

Bregs (CD5+) can suppress IgE-mediated allergic responses by production of IL-10, TGF-beta.

- - Contribute to production of IgG4 antibodies, blocking allergic reactions.



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What are the Theories of How OIT Shapes in the Early Immune System:

INDUCTION OF HYPORESPONSIVENESS OF TH2 EFFECTOR CELLS

INCREASED PRODUCTION OF IL-10 BY DCS, AND EFFECTS ON T EFFECTOR CELLS: DECREASING T2 RESPONSES AND INDUCING TREGS.

INDUCTION OF FOXP3+ TREGS WITH ENHANCED RESPONSES OCCURS THROUGH OIT-INDUCED EPIGENETIC CHANGES, WHICH DON'T APPEAR TO BE AGE LIMITED.

Observed Occurrences with Oral Immunotherapy

Controlled exposure to increasing doses of allergen results in the following immunologic outcomes:

- Reduced allergen-specific Th2 cytokines
- Induction of allergen-specific Tregs (Syed et al., JACI 2014)
- Increased allergen-specific IgG4 (blocking antibody) (Savilahti et al., JACI 2010)
- Decreased mast cell/basophil reactivity (Bedoret et al., JACI 2012)
- Outcome: Desensitization → increased reaction threshold
- In some cases: sustained unresponsiveness (SU)
- Under normal conditions, it is thought that repeat exposure to low doses of antigen promote the development of Tregs (Chehade M, Mayer L. J Allergy Clin Immunol. 2005)
- In contrast, exposure to large amounts of antigen leads to T-cell anergy or FAS-mediated clonal deletion, both of which result in the secretion of TGF-β. (Chen et al,Nature. 1995;376(6536):177–80.)

Additional Possible Components of Immune Alterations with OIT

- sIgA produced by plasma cells in the lamina propria, which neutralizes food antigens in the lumen (Brandtzaeg, Ann N Y Acad Sci 2012)
- Improvement in tight junctions and mucin layer to maintain epithelial barrier.
- Commensal microbiota:, which produce SCFAs like butyrate → epigenetic induction of Tregs (Furusawa et al., Nature 2013)
- **Decreased basophil reactivity**

Basophil Changes that Occur with OIT

- Decreased basophil reactivity, which does not appear to be restricted to the food antigen used in OIT.
- OIT induces an overall state of **basophil hyporesponsiveness** or anergy, which does not appear to depend on sIgE levels.
- Plasma from subjects post-peanut OIT was able to suppress basophil activation by pre-OIT sera through IgG4 binding to FcγRIIb, the inhibitory receptor to which IgG4 binds with high affinity.
- Persistence of decreased SPT and basophil activation tests is associated with SU.

Barshow et al., Clin Exp Allergy. 2021 April ; 51(4): 527–535. doi:10.1111/cea.13824.

Immunologic Shifts During OIT

Pre-OIT (Allergy) vs Post-OIT (Desensitized):

Th2 cells: High → Reduced

Tregs: Low → Increased Foxp3+, IL-10+ Tregs

IgE: High → Slight decrease

IgG4: Low → Increased

Mast cell and Basophil activity: High → Decreased

References

1. Pabst & Mowat, Nat Rev Immunol. 2012
2. Mucida et al., Science. 2007
3. Furusawa et al., Nature. 2013
4. Josefowicz et al., Immunity. 2012
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