Immunology of Asthma

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Outline

- Consensus characteristics/incidence data
- Immune/inflammatory basis
- Etiology/Genetic basis
- Hygiene Hypothesis
- Future therapies

Asthma-consensus characteristics

- Chronic inflammatory disorder of airway
- Variable, reversible airflow obstruction
- Persistent airway hyperreactivity
- Airway remodeling

Asthma-incidence

- 20 million Americans have physician-diagnosed asthma
- 500,000 hospitalizations, and nearly 5000 deaths each year in the U.S.
- Disproportionately high in inner city children

Asthma-incidence (continued)

- African Americans hospitalized for asthma 3X more than other Americans
- African Americans and Hispanic Americans in inner cities 2-6X more likely to die from asthma
- prevalence of asthma has increased by more than 80% in all age and ethnic groups over the past two decades

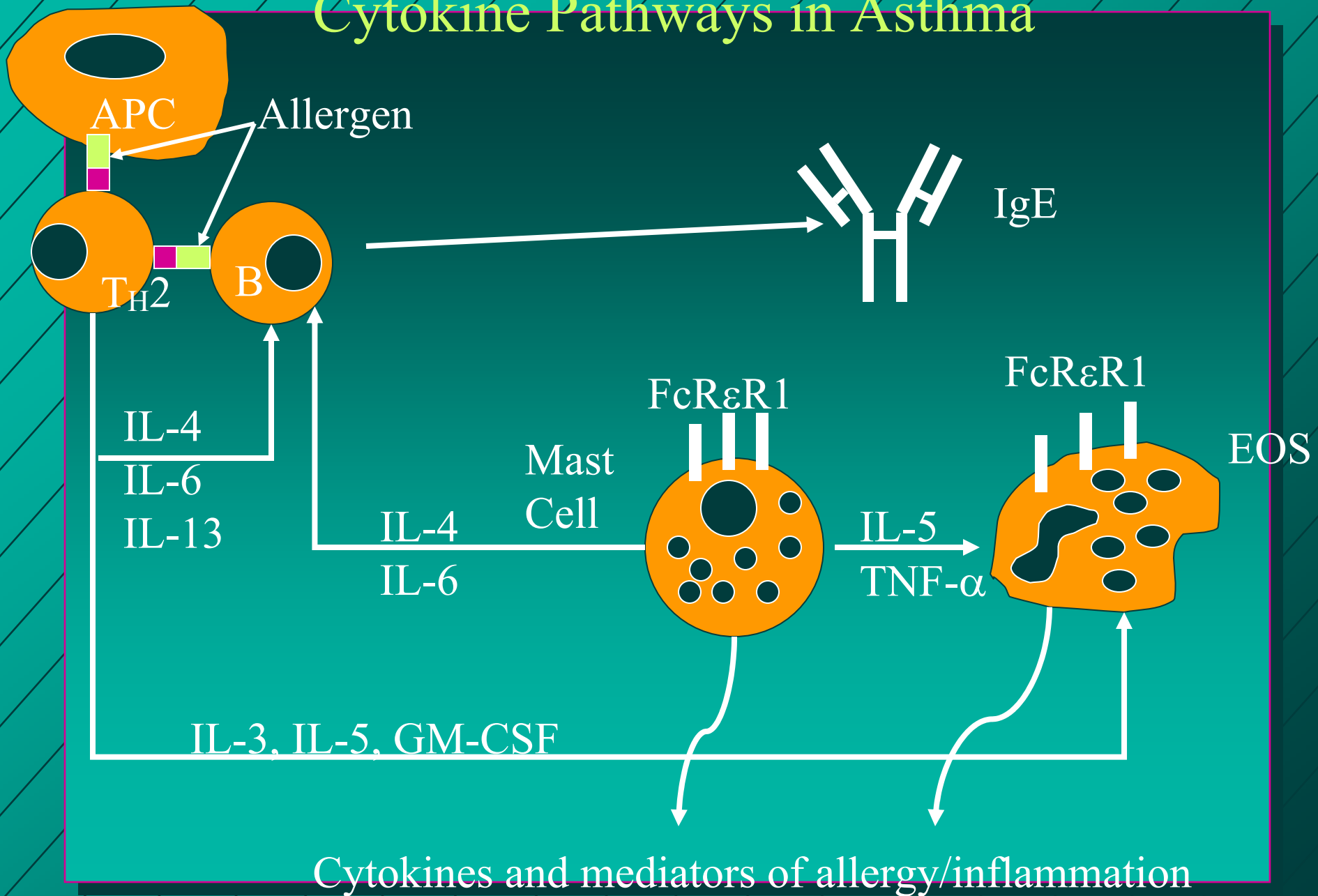
Acquired Immunity in Asthma

- Atopy(inherited propensity to produce IgE) is associated with AHR,asthma incidence,persistence, and severity
- Exposure to and sensitization to allergens correlates with risk for and severity of asthma
- Atopy is due to disequilibrium of cell mediated immunity (Th-1) vs. humoral responses (Th-2)
- Th-2 derived IL-4 and IL-13 promote IgE responses, AHR, eosinophilia, and airway mucus secretion

Review of Type I (IgE) Hypersensitivity

- Sensitization
  - IgE production
  - Mast cell Fc receptors (FcRε) bind IgE
- Allergen triggers mast cell degranulation
  - Acute phase bronchospasm, edema
  - Late phase inflammation
- Chronic Tcell/eosinophil infiltrate

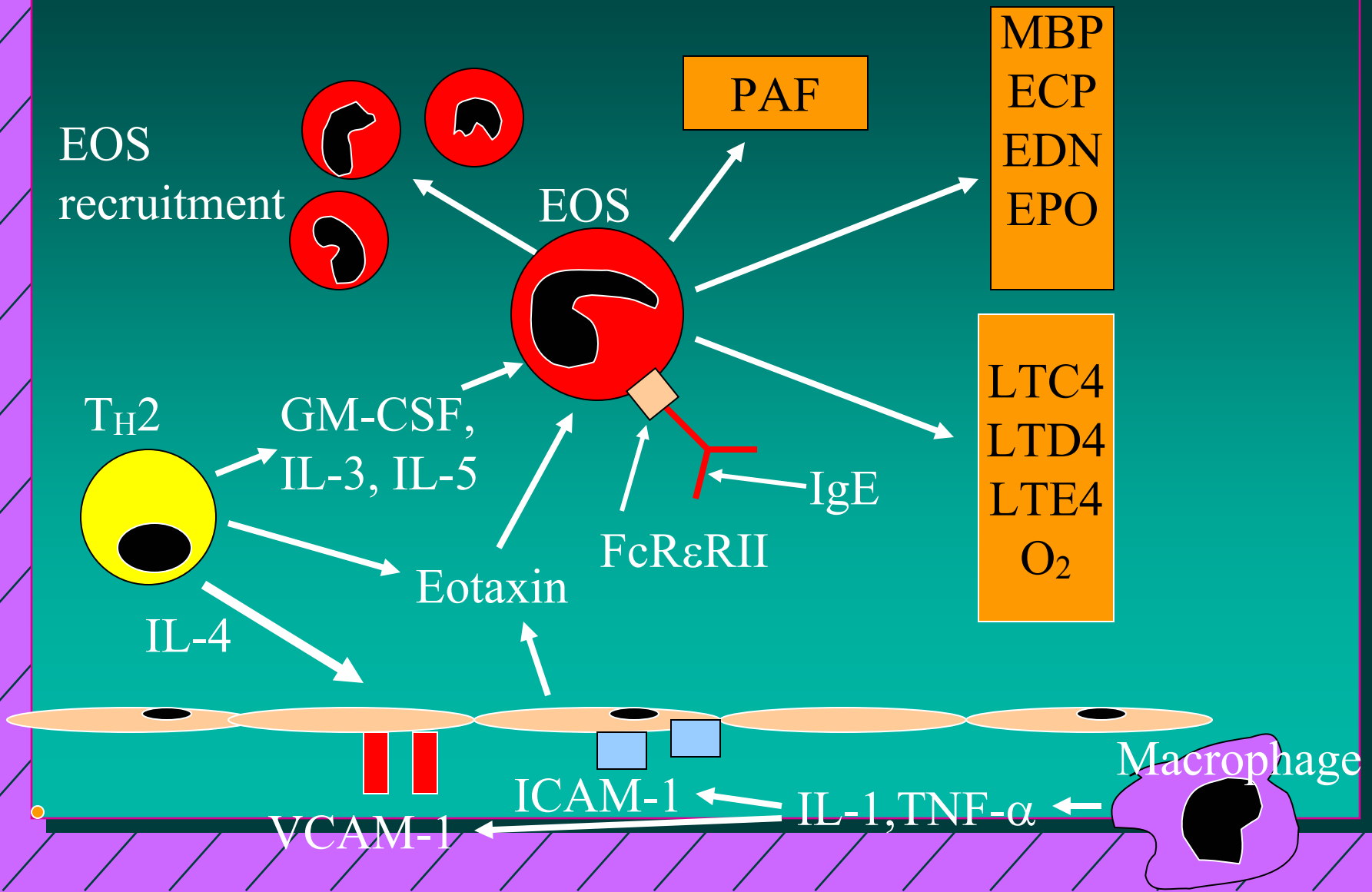
Cytokine Pathways in Asthma



T cell/mast cell/eosinophil cytokine cascade

- Leukocyte cytokines activate resident respiratory cells to release other cytokines
- Cytokines promote
  - More inflammation
  - Endothelial and epithelial cell changes
  - Tissue injury and repair (remodeling)
  - Angiogenesis and fibrosis

Eosinophil Recruitment in Asthma

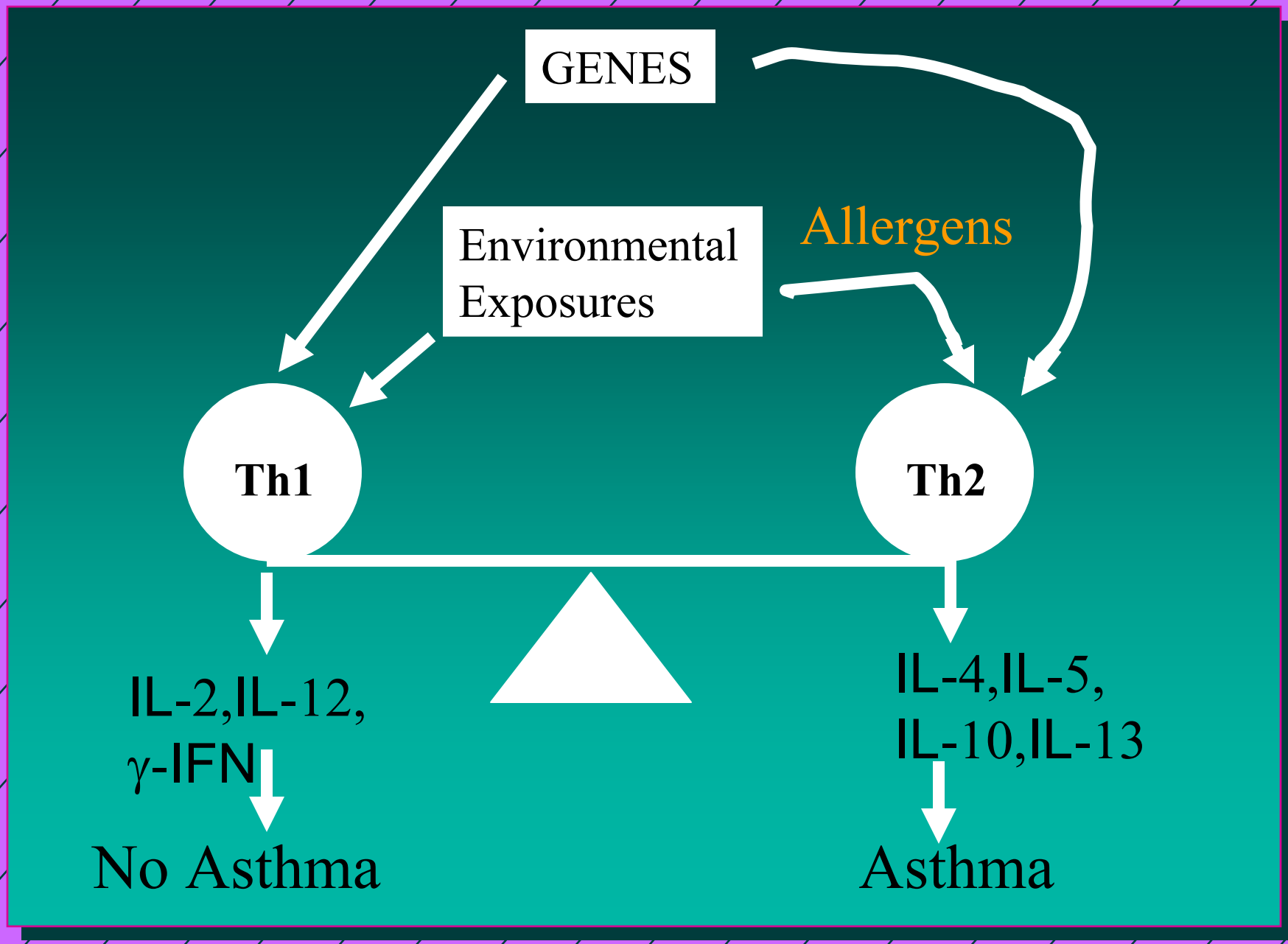


Mediators of Airflow Obstruction

- Bronchoconstriction (histamine, PAF, PGD2,LTC4,LTD4)
- Edema (as above plus bradykinin)
- Increased mucus secretion (cysteinyl leukotrienes)
- Airway remodeling (toxic eosinophil proteins, TNF-alpha)

Etiology of atopic asthma

- Imbalance of Th-1 vs. Th-2 immune responses caused by
  - Genetics
  - Uterine environment
  - Maternal and infant diet
  - Respiratory infections
  - Environmental exposures to allergens, tobacco smoke


GENES
Environmental Exposures
Allergens
Th1
Th2
IL-2,IL-12,
γ-IFN
No Asthma
IL-4,IL-5,
IL-10,IL-13
Asthma

Multigenic basis for asthma

- Cytokine genes (IL-4,5,6,9,12,13,etc.)
- Receptor genes (β2- adrenergic, glucocorticoid, IL4R)
- Enzymes (glutathione-s-transferase, NOS, LTA4 hydrolase)
- Other (HLA, selectins)

Hygiene Hypothesis

- Hygiene hypothesis: Lack of intense infections in industrialized countries owing to improved hygiene, vaccination, and use of antibiotics may alter the human immune system such that it responds inappropriately to innocuous substances. (increased allergy/asthma)

Hygiene hypothesis (continued)

- rationale: bacterial and viral infection during early life polarize immune reponse to Th1, counterbalancing proallergic Th2 responses. Reduced overall microbial burden results in weak Th1 and unrestrained Th2 response.
- Contradictions: increasing TH1 dependent autoimmunity. Th2 skewed helminth infection are not associated with allergy

Revised Hygiene Hypothesis-3

- Robust anti-inflammatory regulatory network (IL-10) is induced by **persistent** immune challenge (whether persistent Th1 or TH2). **Frequent antigenic challenge from an array of pathogens is needed for a balanced development of the immune system and prevention of allergic and inflammatory diseases.**

Hygiene Hypothesis- role of normal flora

- Composition of gut microflora can modulate DC maturation and effects on Th1/TH2/TH3 differentiation. Some normal flora (lactobacilli = **probiotics**) suppress IL-12 stimulation by other flora.

Development of Mucosal defenses in neonatal period

- **variable period of poorly developed functions**
  - Mucosal barrier function
  - Immunoregulatory network
- **Development dependent upon**
  - Establishment of normal flora
  - Timing and dose of initial dietary antigens

Oral Tolerance

- The most frequent outcome of an oral encounter with soluble food antigens and commensal flora is the induction of a state of specific immunological unresponsiveness --oral tolerance
- Mucosal exposure to living and multiplying pathogens leads to local and systemic priming of immune responses

Mechanisms of Oral Tolerance

- Suppressor T cells (CD4 **Th3** , **Tr-1**, intraepithelial **CD8 T** or γδ**T** cells) producing immunosuppressive **TGF-β**, **IL-10**
  - nonspecific "bystander" suppression can occur
- T cell anergy, T cell deletion
  - (high dose antigen)

Current anti-inflammatory therapies for Asthma

- Glucocorticoids (most potent agents available for allergic asthma) suppress multiple inflammatory genes
- Mediator antagonists
  - Histamine antagonists
  - Leukotriene receptor/lipoxygenase inhibitors

Future Therapies for Allergic Inflammation

- Inhibitors of eosinophilic inflammation
- Drugs that inhibit antigen presentation
- Inhibitors of Th2 lymphocytes
- General anti-inflammatory approaches
- Preventive immunotherapy (Th2 to Th1 shift)

References

- Maddox,L. and D.A.Schwartz. 2002. The pathophysiology of asthma. Annu. Rev. Med. 53:477-498.
- Lemanske,R.F.,Jr. 2000. Inflammatory events in asthma:An expanding question. J. Allergy Clin. Immunol. 105:S633-S636.
- Humbert M. et al. 1999. The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences. Immunology Today 20:528-533.
- Barnes,P.J. 2000. New directions in allergic diseases: Mechanisms-based anti-inflammatory therapies. J. Allergy Clin. Immunol. 106:5-16.