Immunology of Asthma

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Outline

- Consensus characteristics
- Allergens:role in asthma
- Immune/inflammatory basis
- Genetic basis
- Non-atopic (intrinsic) asthma
- Viral infection exacerbation of asthma
- Immune targets for therapy

Asthma-consensus characteristics

- Chronic inflammatory disorder of airway
- Mast cell,eosinophil, T cell infiltration
- Inflammation promotes clinical symptoms (wheezing, etc.)
- Variable airflow obstruction
- Airway hyperresponsiveness

Allergens: role in asthma

- Allergen sensitization is linked to risk of asthma
  - Indoor allergens (house dust mites)
  - Outdoor seasonal fungus (*Alternaria*)
- Asthma severity correlates with allergen exposure
- Reduced allergen exposure improves asthma

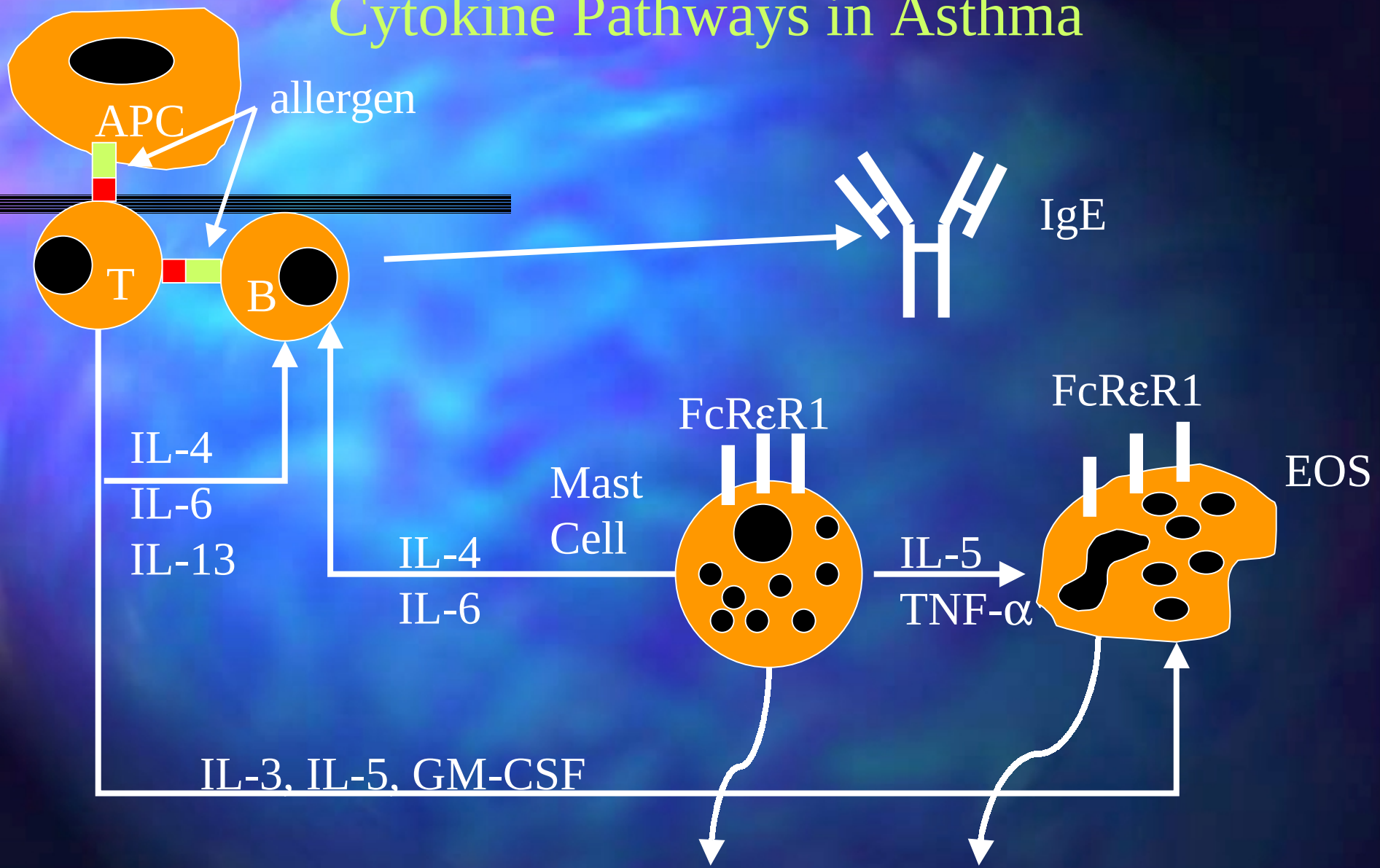
Allergens:role in asthma

- Antigen-specific IgE to aeroallergens develops at ~2-3 years old in predisposed individuals (Atopy: genetic predisposition to form IgE)
- Allergen-induced asthma peaks in second decade
- Sensitization to indoor and outdoor allergens should be evaluated in asthma patients

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

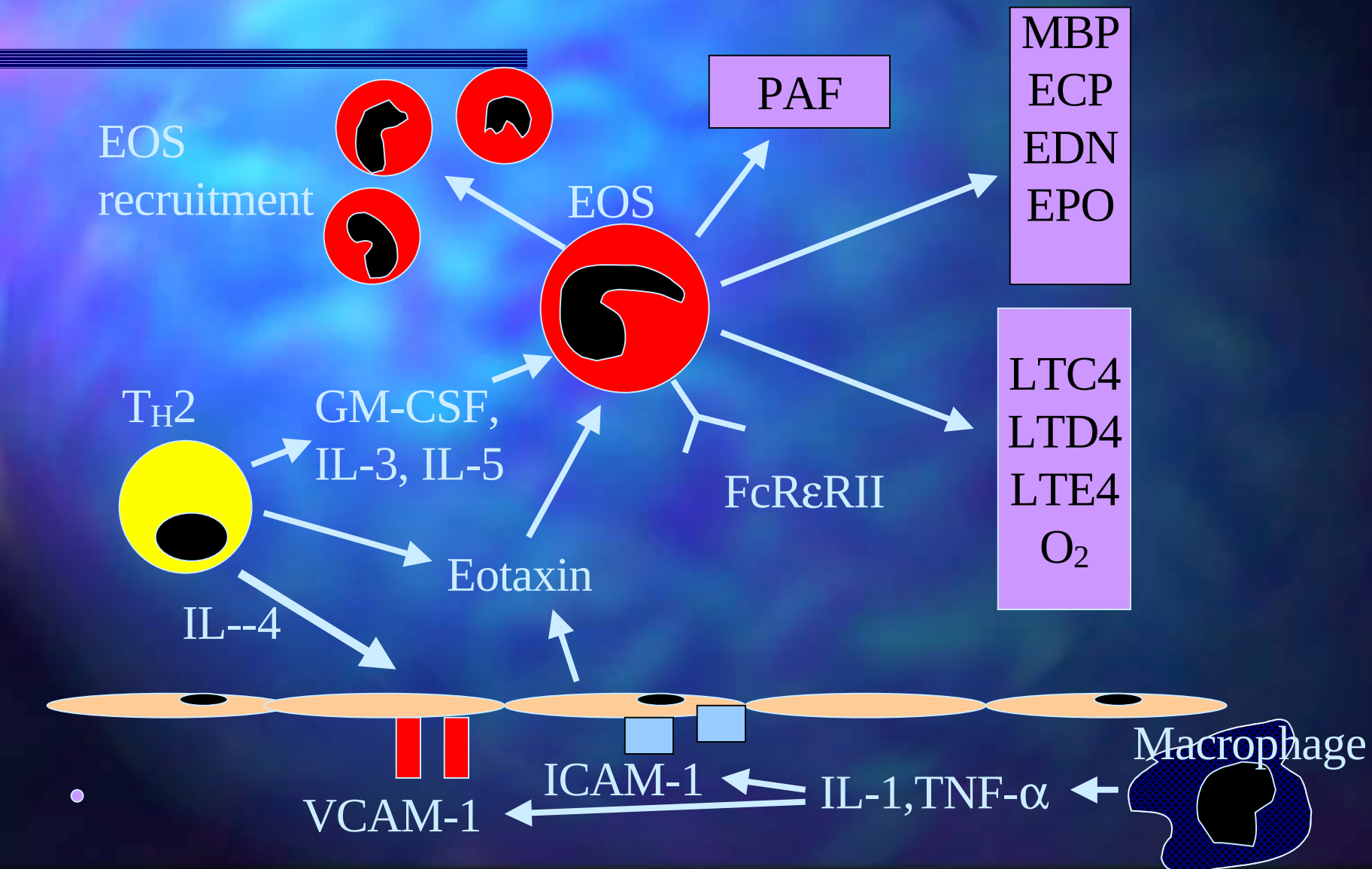


Cytokines and mediators of allergy/inflammation

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)

Role of Inflammation in Airway Hyperresponsiveness

- Principal mechanism defining **intensity** of bronchial hyperresponsiveness, but can be independent
- Relationship of inflammatory tissue changes and hyperresponsiveness is ill-defined
- Eosinophil cationic proteins and toxins damage epithelium and alter airway hyperactivity and cilial function

Multigenic Basis for Asthma

- Asthma related to inheritance of variants of multiple genes related to IgE synthesis and cytokine signalling by IL-4 and IL-13

Non-atopic (intrinsic) asthma (10-33%of asthmatics)

- Negative skin tests
- No clinical/family history of allergy
- Serum [IgE] is normal
- Older patients
- More severe

Intrinsic and Extrinsic Asthma share Immunopathology

- Infiltrating eos & Th2 secreting IL-4/IL-5
- CC chemokines and FcRε(+) cells
- IgE expression
  - Local IgE production (intrinsic)
  - Generalized IgE production (extrinsic/atopic)

Theories for Etiology of Intrinsic Asthma

- Autoallergy following viral respiratory infection
- Allergy to an unknown or undetected allergen

Viral infection exacerbation of asthma

- Major cause of asthma exacerbation
- Virus infection causes
  - Chemokine (RANTES, eotaxin) and adhesion molecule (ICAM-1) induction recruits eosinophils
  - Virus infection kills epithelial cells exposing airway nerve endings
  - Eosinophil proteins affect tone and reactivity

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
  - Cytokine modulators (Anti-IL-5, CCR3 antagonists)
  - Cell adhesion blockers (VLA-4 inhibitors)
  - Anti-inflammatory cytokines (IL-10)
- Drugs that inhibit allergen presentation
  - Anti-IgE (humanized antibody E25)
  - Anti-B7-2, anti-CD28, CTLA-4-Ig

Future Therapies for Allergic Inflammation

- Inhibitors of T_H2 lymphocytes
  - Interferon-gamma, IL-12
  - Transcription factor inhibitors
- General anti-inflammatory approaches
  - Novel corticosteroids
  - Phosphodiesterase inhibitors
  - MAP kinase inhibitors

Preventive Immunotherapy (T_H2 to T_H1 shift)

- Allergen gene immunization (DNA vaccines)
- Allergen peptide immunotherapy
- Antisense oligonucleotide gene therapy

References

- Lemanske,R.F.,Jr., and Busse, W.W. 1997. Asthma. JAMA 278:1855-1873.
- 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.
- Future Treatments in Allergic Disease, (Respiratory Care Treatment Update-Allergic Disease), http://www.medscape.com/Medscape/RespiratoryCare/TreatmentUpdate/2000/tu02/pnt-tu02.html