GENETIC ROLE IN ASTHMA DEVELOPMENT

PRESENTED BY

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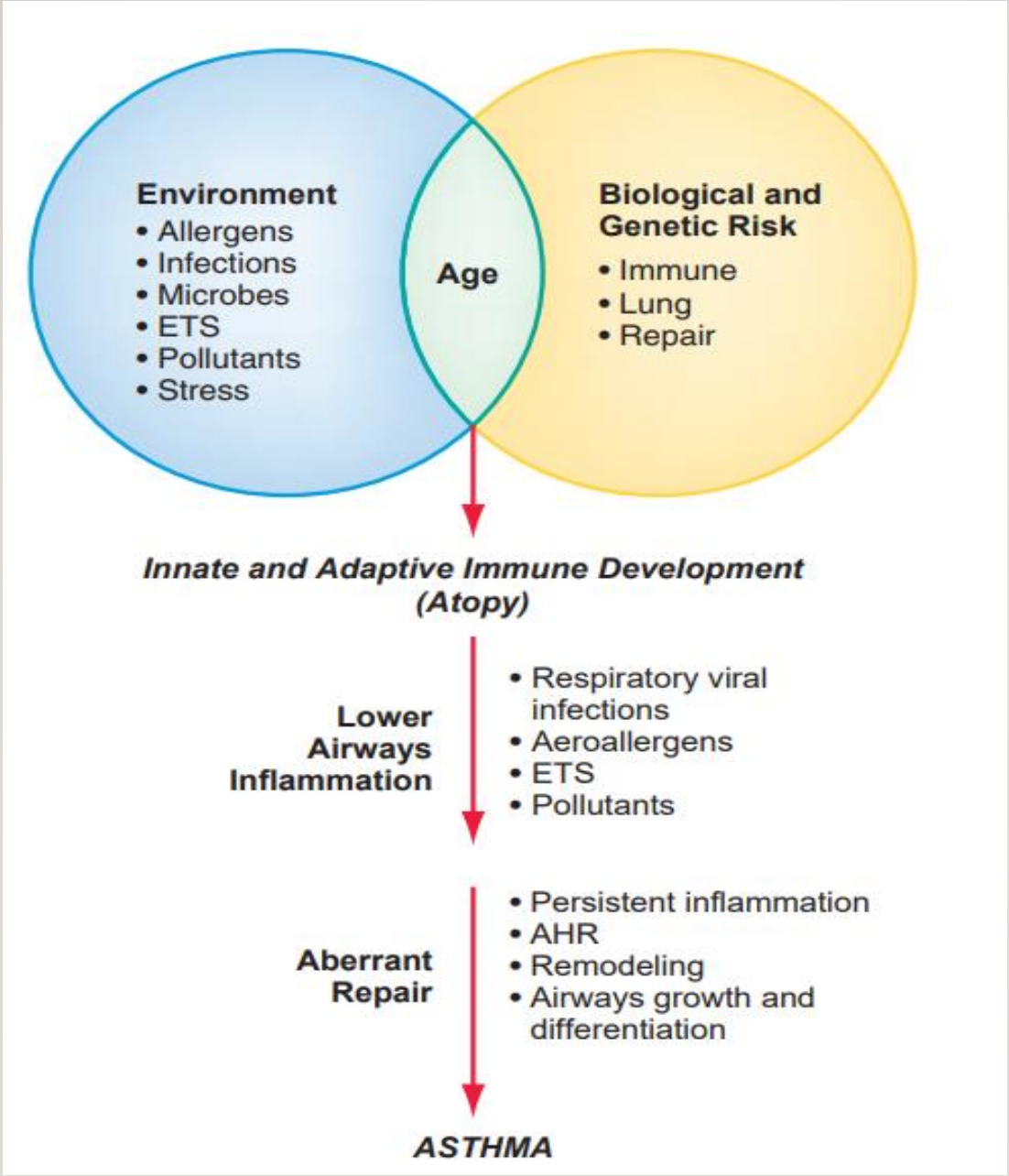
INTRODUCTION

- Asthma is a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction.
- Although the cause of childhood asthma has not been determined, a combination of environmental exposures and inherent biologic and genetic susceptibilities has been implicated


Environment
• Allergens
• Infections
• Microbes
• ETS
• Pollutants
• Stress
Age
Biological and Genetic Risk
• Immune
• Lung
• Repair
Innate and Adaptive Immune Development (Atopy)
Lower Airways Inflammation
• Respiratory viral infections
• Aeroallergens
• ETS
• Pollutants
Aberrant Repair
• Persistent inflammation
• AHR
• Remodeling
• Airways growth and differentiation
ASTHMA

INTRODUCTION

- A combination of environmental and genetic factors in early life shape how the immune system develops and responds to ubiquitous environmental exposures.
- In the susceptible host, immune responses to common airways exposures (e.g., respiratory viruses, allergens, tobacco smoke, air pollutants) can stimulate prolonged, pathogenic inflammation and aberrant repair of injured airways tissues

INTRODUCTION

- Lung dysfunction (AHR, reduced airflow) and airway remodeling develop.
- These pathogenic processes in the growing lung during early life adversely affect airways growth and differentiation, leading to altered airways at mature ages.
- Once asthma has developed, ongoing inflammatory exposures appear to worsen it, driving disease persistence and increasing the risk of severe exacerbations.

EPIDEMIOLOGY

- Asthma is a common chronic disease, causing considerable morbidity.
- In 2011, >10 million children (14% of U.S. children) had ever been diagnosed with asthma, with 70% of this group reporting current asthma.
- Male gender and living in poverty are demographic risk factors for having childhood asthma in the United States.
- About 15% of boys vs 13% of girls have had asthma; and 18% of all children living in poor families (income

EPIDEMIOLOGY

- Childhood asthma is among the most common causes of childhood emergency department visits, hospitalizations, and missed school days.
- In the United States in 2006, childhood asthma accounted for 593,000 emergency department (ED) visits, 155,000 hospitalizations, and 167 deaths.
- A disparity in asthma outcomes links high rates of asthma hospitalization and death with poverty, ethnic minorities, and urban living.

EPIDEMIOLOGY

- In the past 2 decades, black children have had 2-7 times more ED visits, hospitalizations, and deaths as a result of asthma than nonblack children.
- Although current asthma prevalence is higher in black than in nonblack U.S.

EPIDEMIOLOGY

- Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in our management and pharmacopeia to treat asthma.
- Although childhood asthma may have plateaued in the United States after 2008, numerous studies conducted in other countries have reported an increase in asthma prevalence of approximately 50% per decade.

EPIDEMIOLOGY

- Asthma prevalence correlated well with reported allergic rhinoconjunctivitis and atopic eczema prevalence.
- Childhood asthma seems more prevalent in modern metropolitan locales and more affluent nations, and is strongly linked with other allergic conditions.
- In contrast, children living in rural areas of developing countries and farming communities with domestic animals are less likely to experience asthma and allergy.

EPIDEMIOLOGY

- Approximately 80% of all asthmatic patients report disease onset prior to 6 yr of age.
- Early childhood risk factors for persistent asthma have been identified and have been described as major (parent asthma, eczema, inhalant allergen sensitization) and minor (allergic rhinitis, wheezing apart from colds, ≥4% peripheral blood eosinophils, food allergen sensitization) risk factors.

GENE-ENVIRONMENT INTERACTIONS

- Environmental factors modify genetic risk:
- Allergen
- Pollutants
- Viral infections (CDHR3 genetic polymorphisms regulating responses to respiratory virus infection)

ENVIRONMENT

- Recurrent wheezing episodes in early childhood are associated with common respiratory viruses, especially rhinoviruses, respiratory syncytial virus (RSV), influenza virus, adenovirus, parainfluenza virus, and human metapneumovirus.
- This association implies that host features affecting immunologic host defense, inflammation, and the extent of airways injury from ubiquitous viral pathogens underlie susceptibility to recurrent wheezing in early childhood.

ENVIRONMENT

- Environmental tobacco smoke and common air pollutants can aggravate airways inflammation and increase asthma severity.
- Cold, dry air, hyperventilation from physical play or exercise, and strong odors can trigger bronchoconstriction.
- Living in rural or farming communities may be a protective environmental factor.

ROLE OF GENETICS IN ASTHMA

- Genetic factors contribute to asthma susceptibility, severity, and treatment response.
- To date, more than 100 genetic loci have been linked to asthma, although relatively few have consistently been linked to asthma in different study cohorts.
- Consistent loci include genetic variants that underlie susceptibility to common exposures such as respiratory viruses and air pollutants.

FIVE BROAD GROUPS IDENTIFIED AS CONTRIBUTING TO ASTHMA

- Genes that can directly modulate the response to environmental exposures.
- Genes that maintain the integrity of the epithelial barrier at the mucosal surface (FLG).
- Immune responses can be regulated by genes.
- Genes involved in determining the tissue response to chronic inflammation (e.g., airway remodeling) (ADAM33. GSDMB .SMAD3)
- Some disease-modifying genes.

GENES THAT CAN DIRECTLY MODULATE THE RESPONSE TO ENVIRONMENTAL EXPOSURES

- Genes CD14 and TLR4
- IL33 is an alarmin that is released from airway epithelial cells in response to rhinovirus
- CDHR3, a receptor found on airway epithelial cells that can influence rhinovirus infection and disease exacerbation.
- glutathione S transferase [GST]), which modulate the effect of exposures involving

GENES INVOLVED CHRONIC INFLAMMATION (AIRWAY REMODELING)

- ADAM33
- GSDMB
- SMAD3

MAJOR ASTHMA-ASSOCIATED GENES

- Genome-wide association studies (GWAS) identified multiple risk loci.
- IL33: Involved in airway inflammation
- ORMDL3: Regulates sphingolipid metabolism
- GSDMB: Associated with airway remodeling

MAJOR ASTHMA-ASSOCIATED GENES

- ORMDL3 has been linked to calcium homeostasis in airway smooth muscle cells leading to airway hyperresponsiveness.
- Recently it has been shown that GSDMB is elevated in the airway epithelium in asthma
- SMAD3, an intracellular signaling protein that is activated by the profibrotic cytokine transforming growth factor-β (TGF-β)

EARLY DEVELOPMENT AND ASTHMA SUSCEPTIBILITY

- ADAM33 was identified as an asthma-susceptibility gene
- A polymorphism in ADAM33 is associated with early-life measures of lung function
- The positionally cloned asthma gene ADAM33 has been associated with accelerated lung function decline in patients with asthma.

MAJOR ASTHMA-ASSOCIATED GENES

- More recently several previously described asthma genes have also been shown to associate with disease exacerbation, suggesting a modification role also
- GSDMB
- IL33(IL13 is a strong candidate gene)
- RAD50
- IL1RL1
- novel gene CDHR3

GENETIC PATHWAYS IN ASTHMA

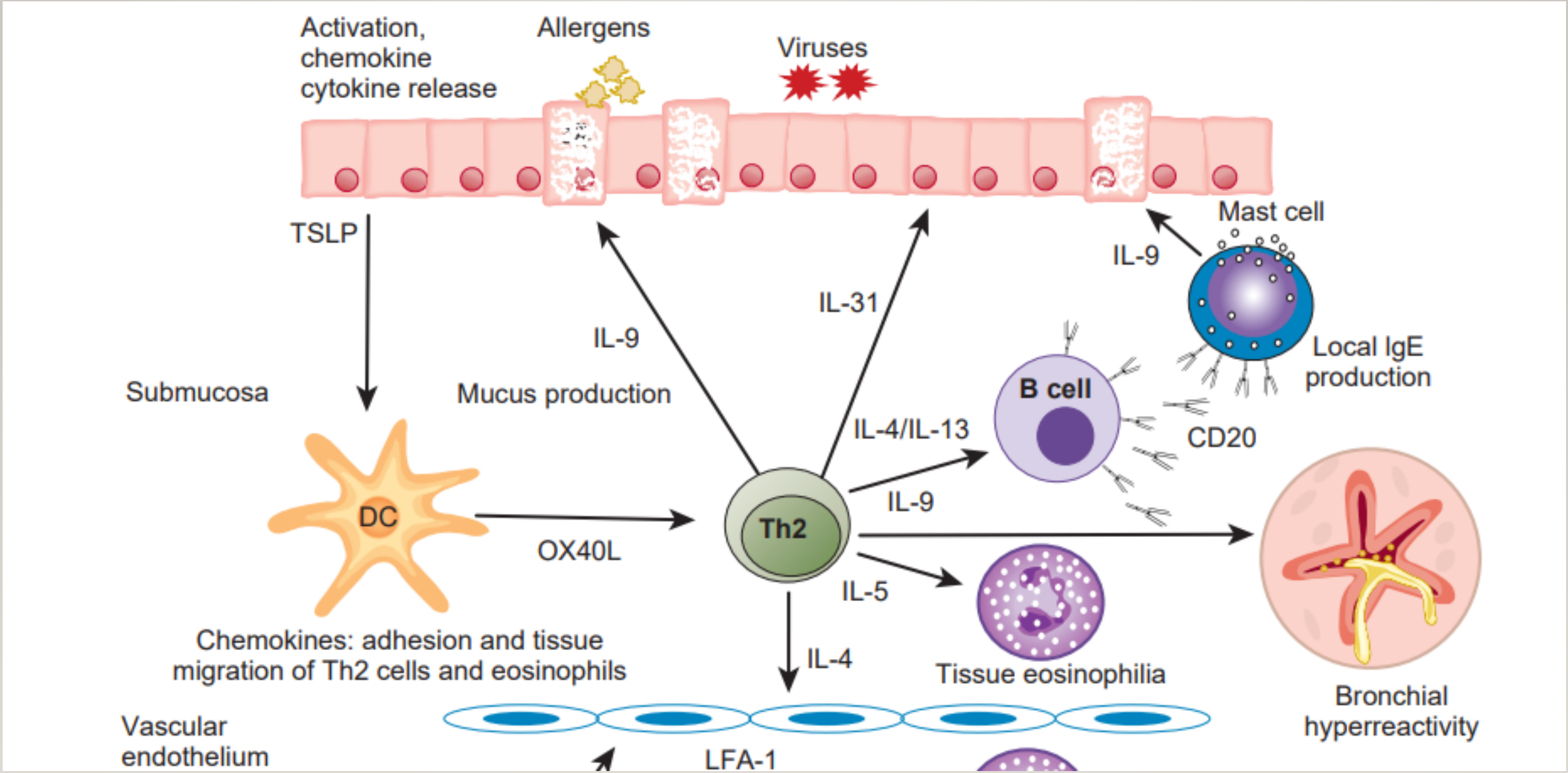
- Immune response regulation
- Genetic Markers for Asthma Risk
  - SNPs in IL4, IL5, and IL13 genes.
- Epithelial barrier function

ASTHMATIC INFLAMMATION

- Epithelial cell activation with production of proinflammatory cytokines and chemokines induces inflammation and contributes to a T-helper cell type 2 (Th2) response with tumor necrosis factor (TNF)-α, interleukin (IL)-13, thymic stromal lymphopoietin (TSLP), IL-25, IL-31, and IL-33.
- Migration of inflammatory cells to asthmatic tissues is regulated by chemokines.

ASTHMATIC INFLAMMATION

- Th2 and eosinophil migration are induced by eotaxin, monocyte-derived chemokine (MDC), and activation-regulated chemokine (TARC).
- Epithelial apoptosis and shedding is observed, mainly mediated by interferon (IFN)-γ and TNF-α.
- The adaptive Th2 response includes the production of IL-4, IL-5, IL-9, and IL-13.


Activation,
chemokine
cytokine release
Allergens
Viruses
TSLP
Submucosa
IL-9
Mucus production
IL-31
Mast cell
IL-9
Local IgE
production
B cell
CD20
IL-4/IL-13
IL-9
DC
OX40L
Th2
IL-5
IL-4
Chemokines: adhesion and tissue
migration of Th2 cells and eosinophils
Tissue eosinophilia
Bronchial
hyperreactivity
Vascular
endothelium
LFA-1

PHARMACOGENETICS OF ASTHMA

- Genetic variations influence drug response.
- β2-Adrenergic Receptor (ADRB2) Gene
  - Variants affect bronchodilator response. β2-adrenergic receptor polymorphism responses to leukotriene receptor antagonists or leukotriene synthesis inhibitors.
- Glucocorticoid Response Genes
  - FCER2: Predicts response to inhaled corticosteroids

BENEFITS OF GENETIC STUDIES OF ALLERGIC DISEASES

- To understand the heritable component of diseases or traits
- Explication of disease pathogenesis by identification of genes and molecular pathways, generating novel pharmacologic targets
- Identification of environmental-genetic interactions and prevention of disease through environmental modification
- Determination of the likelihood of a therapeutic response or adverse response (i.e., pharmacogenetics) as the basis for individualized treatment plans.

THANK YOU FOR YOUR ATTENTION

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