

2nd Edition

GLOBAL ATLAS OF ASTHMA



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MAST CELLS IN ASTHMA

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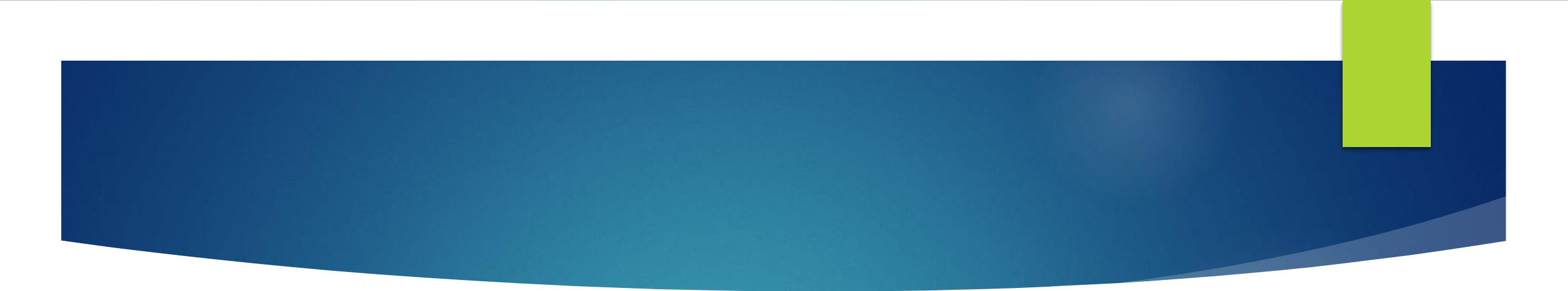
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- ▶ **More than** 90% of asthma in children and 50% in adults is classified as **allergic asthma**.
 - ▶ **Mast cells** (MCs) are involved in the pathogenesis of **both allergic and nonallergic asthma**.
 - ▶ **Mast cells** are the effector cells of immediate type hypersensitivity reactions and contribute to upper and lower airway inflammation and symptoms in allergic patients.
 - ▶ They are **derived from hematopoietic progenitors** from the yolk sac in embryo and from the bone marrow in children and adults and mature under the influence of SCF/KIT.

- ▶ **Their function in innate immune system** include first line defense against pathogens, neutralization of toxins, as well as recruitment of other immune cells.
- ▶ Based on their location and protease content, **at least 2 pools of mast cells** are observed: **connective tissue mast cells** (CTMC) carrying tryptase, chymase, CPA3 and cathepsin G and **mucosal mast cells** (MMC) carrying primarily tryptase in their granules.
- ▶ **Both types** are found in the human lung.
- ▶ **In healthy individuals** they reside in lamina propria and around blood vessels, while **in asthma** MCs infiltrate airway smooth muscle, epithelium and mucosal glands.

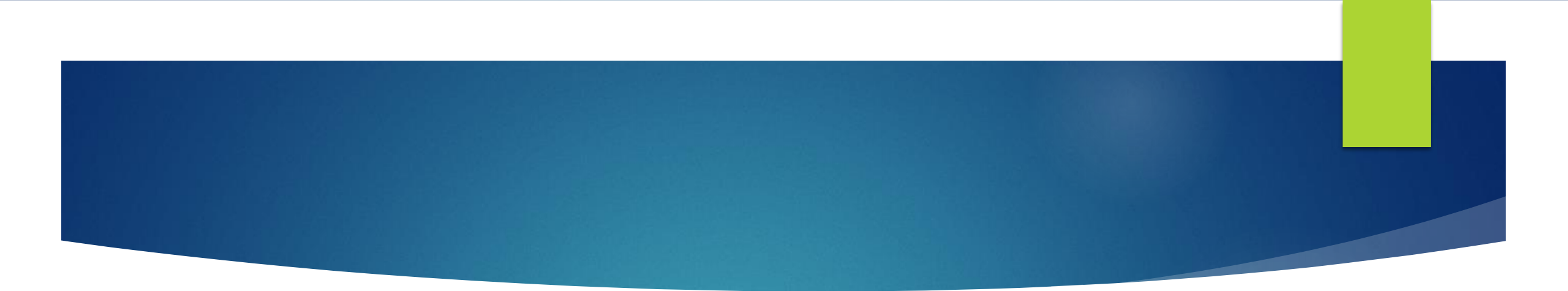
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- ▶ **Mast cells release a variety of mediators** (Table 1) through IgE or non- IgE dependent triggers (Table 2) which contribute to ***inflammation and pathogenesis of asthma***.
 - ▶ **Interestingly**, **alveolar mast cells** have low IgE receptor expression, which is *upregulated in allergic asthma*.
 - ▶ **The biologic effects of mast cell mediators** include bronchial smooth muscle contraction, mucus production, airway remodeling and recruitment of other inflammatory cells.

TABLE 1**Effect of selected mast cell mediators in the asthmatic inflammation**

Mediator	Effect in asthma
Histamine	Bronchoconstriction, vascular permeability, chemotaxis, mucus secretion
PGD2	Bronchoconstriction, chemotaxis
CysLTs	Bronchoconstriction, mucus production, vascular permeability
LTB4	Chemotaxis
PAF	Bronchoconstriction, vascular permeability
Tryptase	Possibly fibrosis and tissue remodeling
Chymase	Extracellular matrix degradation and turnover
IL4	Tissue remodeling, Th2 cytokine production
IL5	Eosinophil migration
IL6	Enhances Ig production, mucus secretion, ASM contractility
IL33	Inflammatory cytokine production
IL13	Mucus production, ASM contractility
TNF	Th2 cytokine production, adhesion of inflammatory cells, ASM contractility
TSLP	Th2 cytokine induction
TGFβ1	Airway fibrosis
VEGF	Angiogenesis
FGF2	Fibrosis

TABLE 2**Selected triggers of mast cell activation**

Trigger	Receptor
IgE	FcεRI and FcεRII
IgG	FcγRI
Complement C3a and C5a	C3aR, C5aR
Cationic peptides	MRGPRX2
Stem cell factor	KIT
Microbial components, PAMPs	TLRs
Endogenous peptides	SPR, MRGPRX2
Epithelial-derived cytokines (TSLP, IL-33)	TSLP receptor, ST2
Purines (adenosine, ATP)	P2X, P2Y, adenosine receptors

KEY MESSAGES

- Mast cells play critical pathogenetic roles in both allergic and non-allergic asthma
- Mast cell density in bronchial biopsies correlate with asthma severity
- Mast cell mediators contribute to inflammation, airway hyperreactivity, mucus secretion and airway remodeling
- Novel interventions targeting mast cells, mast cells mediators, or their activation pathways should be explored for future asthma therapies