2ες αλλεργιολογικές εξελίξεις 2008

Mast cell:

a hinge between innate and adaptive immunity

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***Ciona intestinalis*,**
an urochordate regarded as an ancestor of vertebrates
some 550 million years ago,
contains cells that closely resemble
mammalian connective tissue-type mast cells

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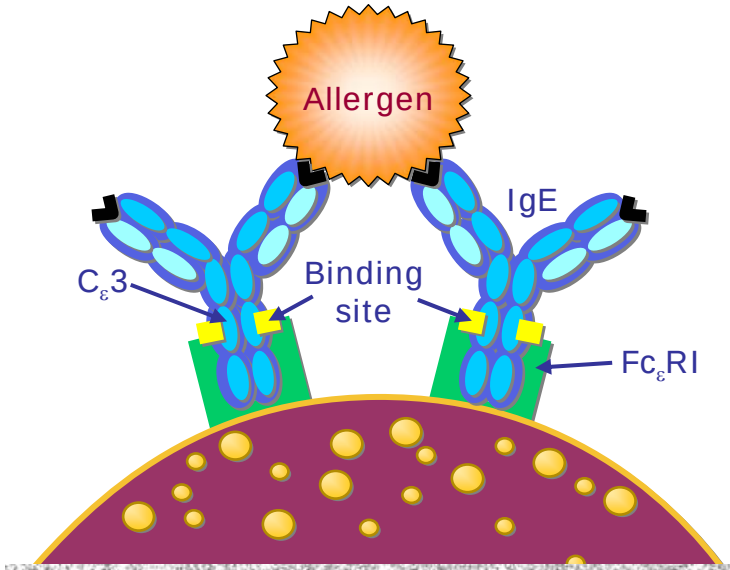


Mast cell:

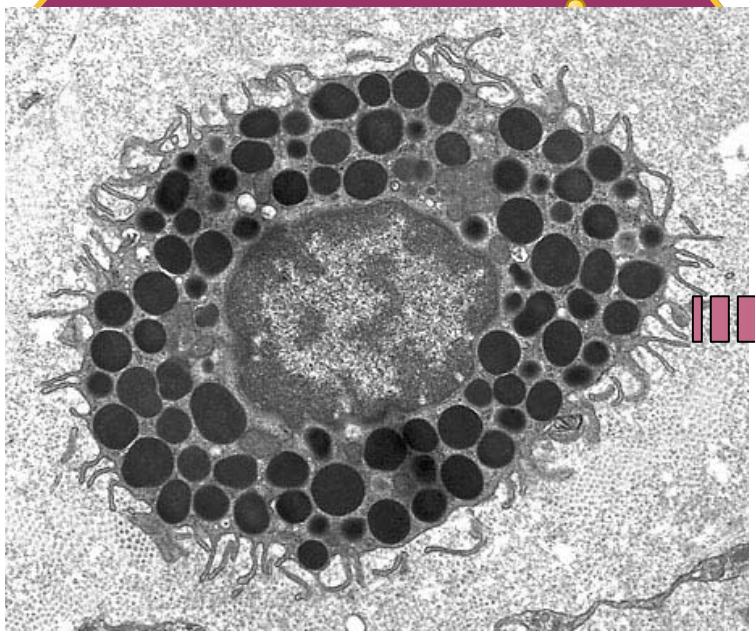
the integral effector cell

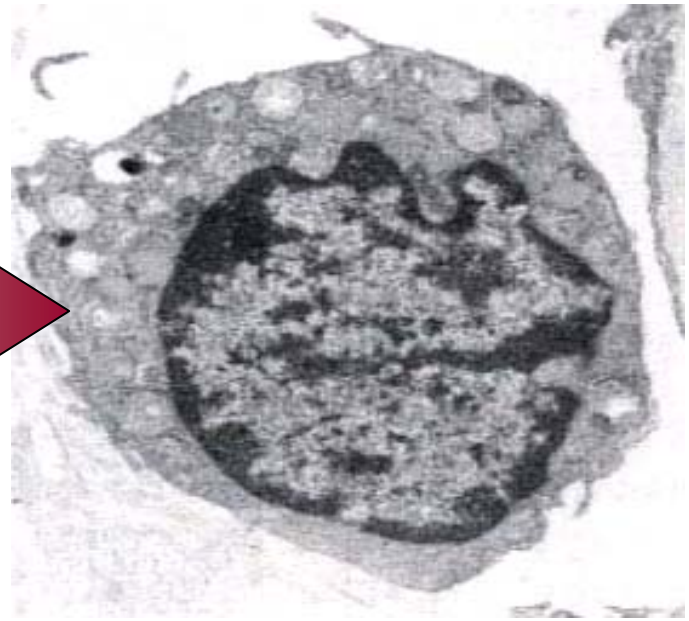
in IgE-associated disorders

almost exclusively known

for having a detrimental

role for the host





Most mast-cell data derive solely from experiments in mice or rats, species that never suffer from allergic and most other mast-cell-associated human diseases

Laboratory tools to study mast cells

Tool	Human	Murine
Transformed mast-cell lines	• Leukaemia-derived human mast-cell lines (HMC-1, LAD-1 and LAD-2)	• Rat basophilic leukaemia cells • Other murine cell lines (IL-3 dependent and IL-3 independent)
Primary cultures of mast cells from progenitor cells	• Cord-blood-derived mast cells • Peripheral-blood-derived mast cells	• Mouse bone-marrow-derived mast cells • Others (such as fetal skin-derived mast cells, fetal liver-derived mast cells and spleen-derived mast cells)
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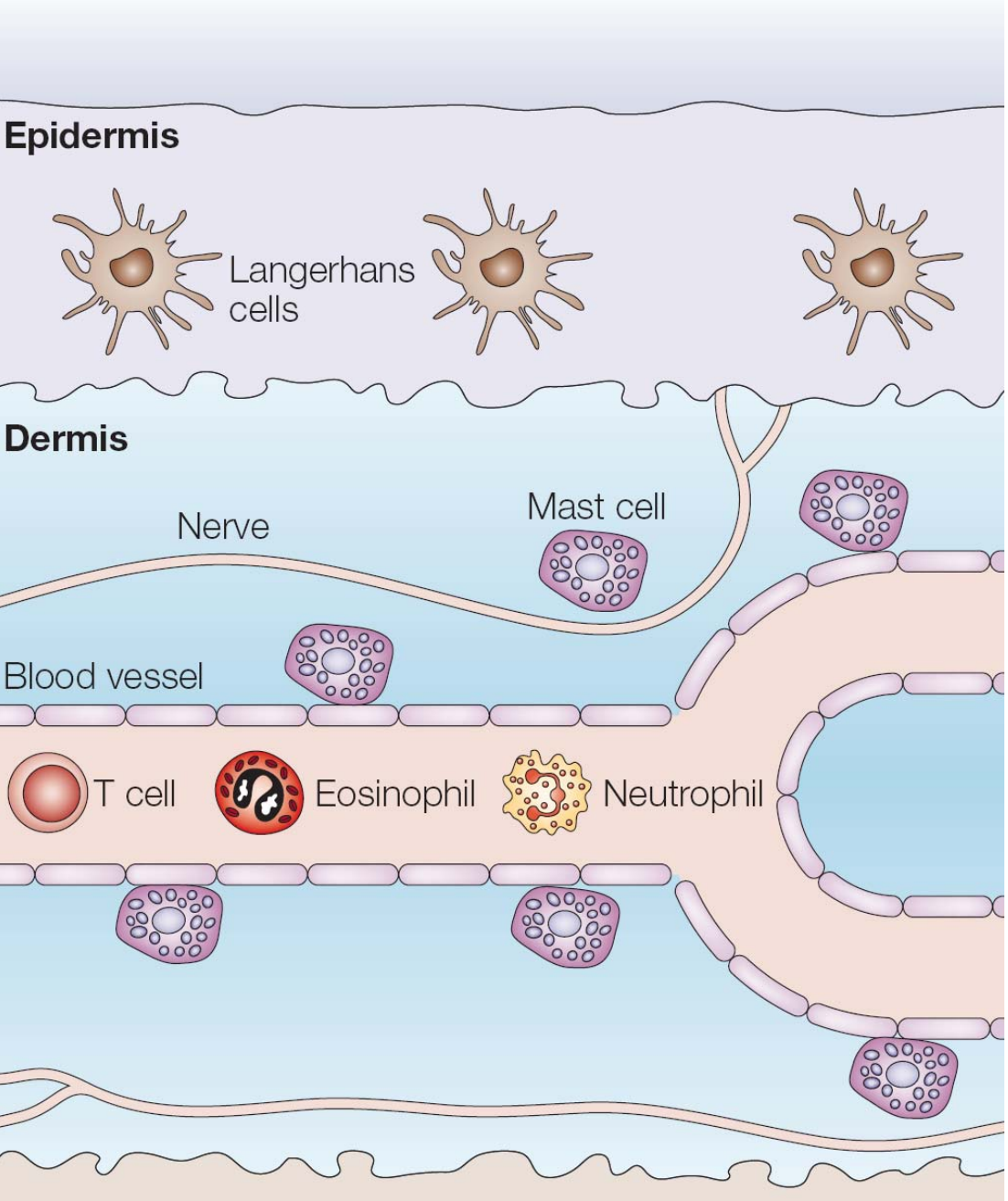
Primary cultures of tissue mast cells	• Human skin mast cells, human mucosal mast cells (lung/intestine) • Human mast cells of other origin (heart, uterus and kidney)	• Peritoneal mast cells • Isolated mucosal or skin mast cells are more difficult to obtain (small amounts of tissue and low mast-cell densities)
In vivo examination of mast cells	• Histology (Carnoy fixation, trypan blue staining) • Immunohistochemistry (anti-tryptase staining) • Mast-cell mediator measurement (tryptase or methyl-histamine in urine)	• Mast-cell-deficient mice and rats ($Kit^{W/W-v}$, $Kit^{W-f/W-f}$ and $Kit^{W-sh/W-sh}$ mice, and $Kit^{W-s/W-s}$ rats)

Bischoff SC. *Nat Rev Immunol* 2007;7:93

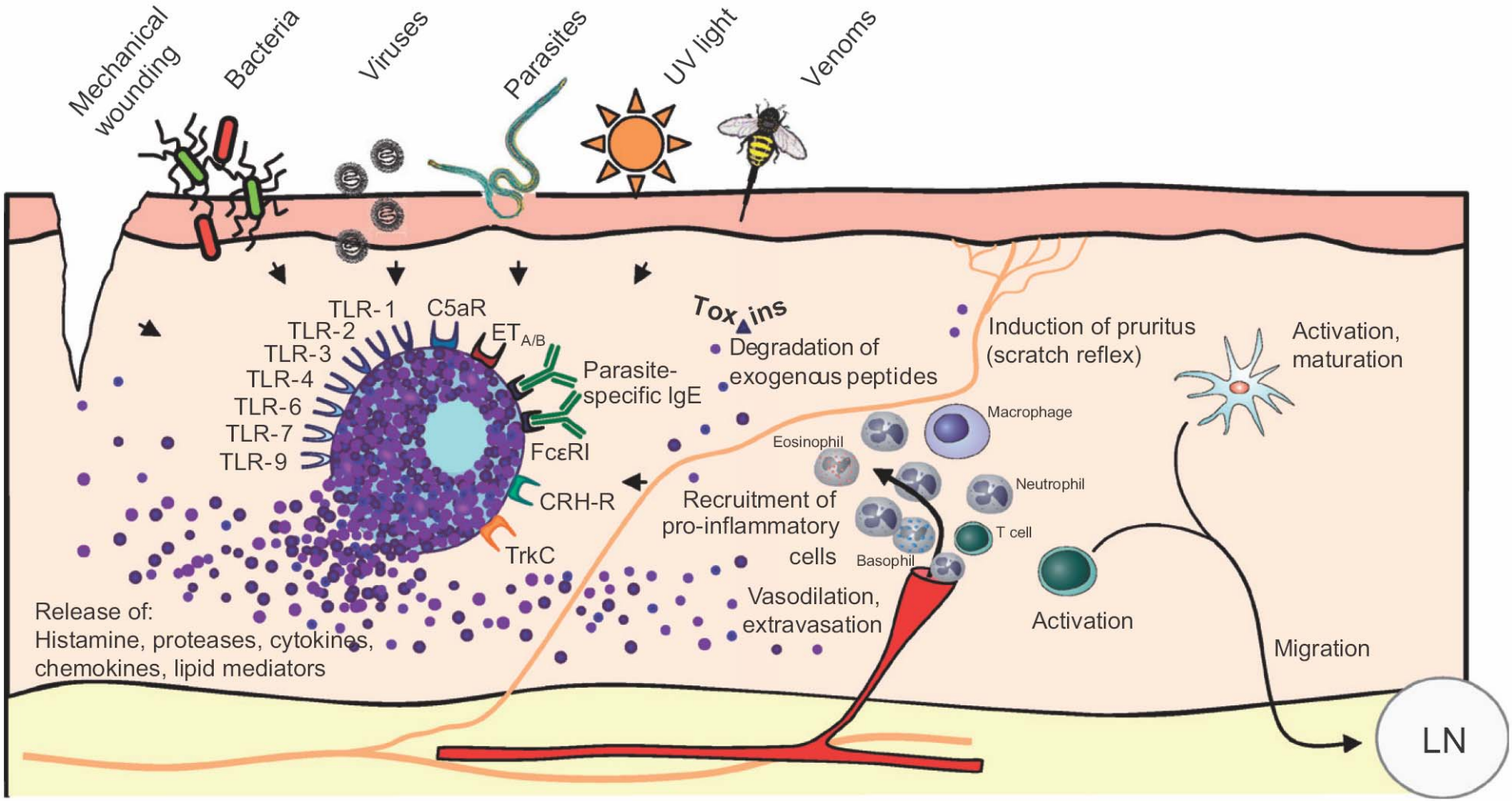


Mast cells are strategically located very near sites where the body comes in contact with the external environment, which is a prime location for the initiation and modulation of innate immune responses

How mast cells sense danger

Receptor class	Examples of receptors
Direct receptors for pathogen products	
Toll-like receptors	TLR1 TLR2 TLR3 TLR4 TLR6 TLR9
Mannosylated receptors	CD48
Indirect receptors for products of immune responses to pathogens	
Fc receptors	FcεRI FcγRI, FcγRII and FcγRIII
Complement receptors	CR2, CR4 and CR5 C5aR and C3aR
Protease-activated receptors	PAR2
Cytokine receptors	IL-1R and IFN-γR IL-10R and IL-12R
Chemokine receptors	CCR3, CCR5 and CXCR4

How mast cells sense danger

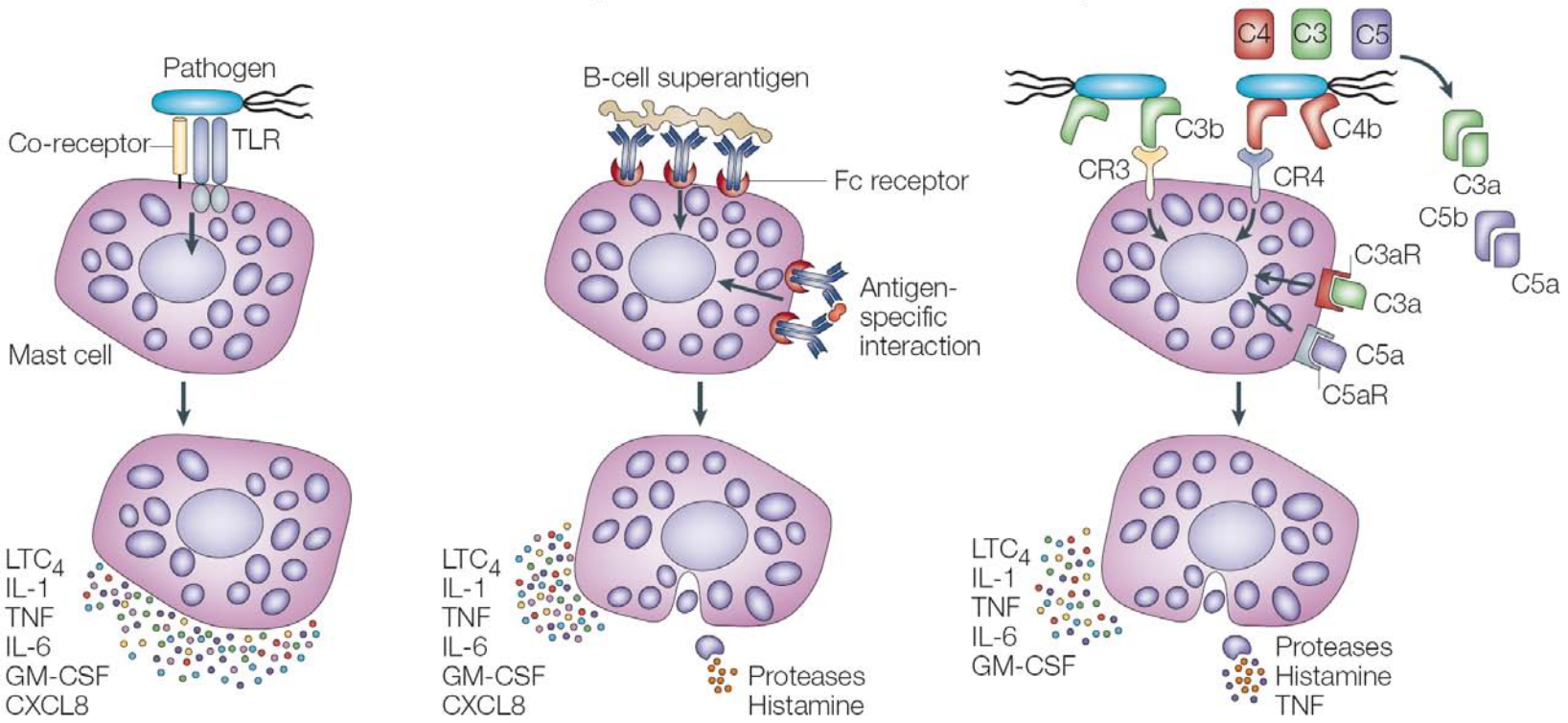


IgE-independent activation of mast cells

Direct interactions

FcR-mediated activation

CR-mediated activation



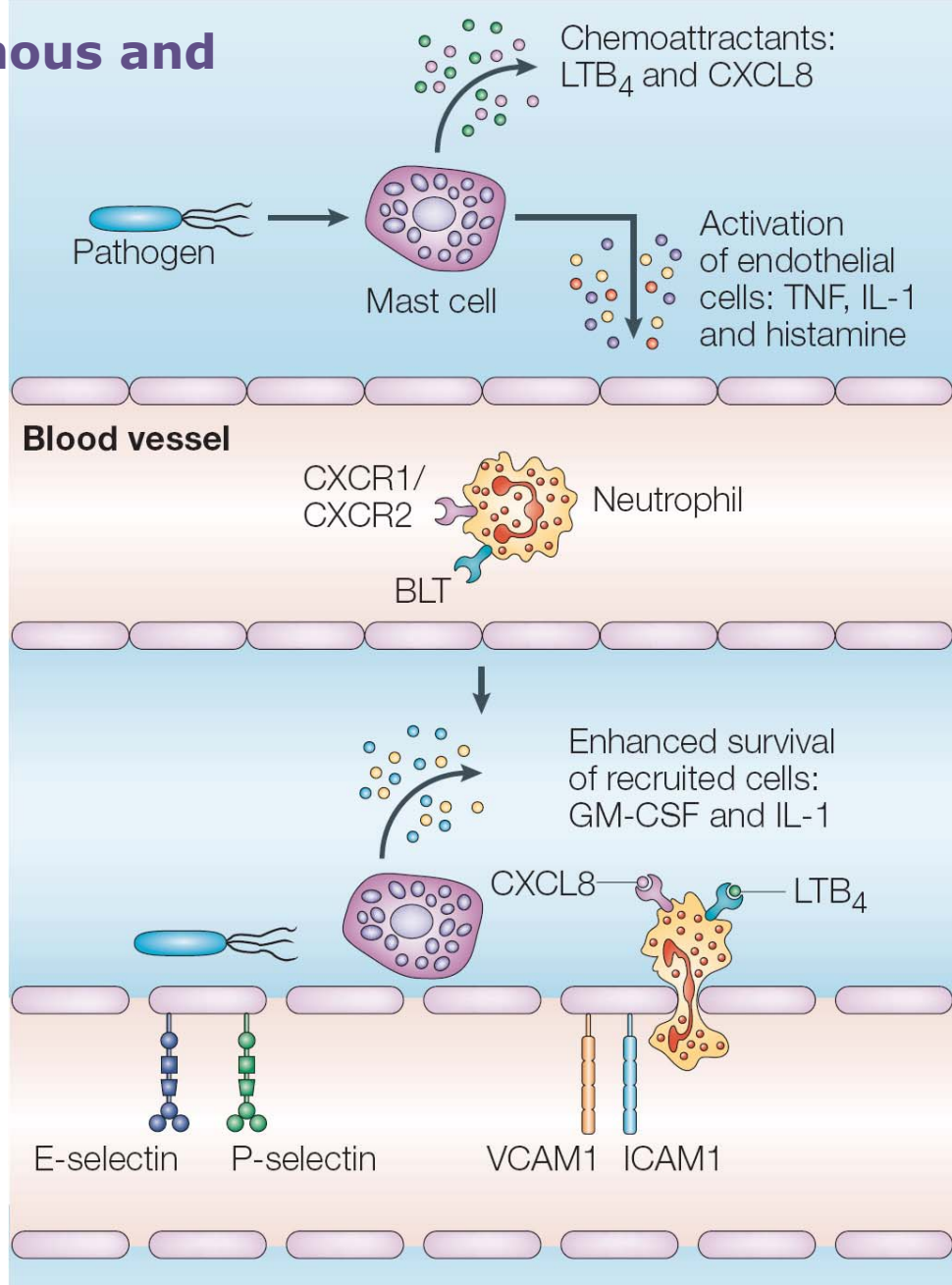
- A variety of substances (bacterial toxins, defensins, sarafotoxins, etc.) activate MCs without a need for specific receptors.

Different stimuli induce discrete cytokine production by MCs

Stimulus	Pathway	Effects		
		Histamine release	Degranulation	Cytokine production
High antigen dose	Lyn/Syk all MAPKs	+	+	IL-13, IL-10, IFN-γ, TNF-α
Low antigen dose	Fyn p38	–	–	IL-2, IL-4, IL-6, MIP, MCP
H_2O_2	Fyn p38		+	IL-4, IL-5, IL-6
LPS	Via TLR4 all MAPKs	–	–	IL-5, IL-10, IL-13, IL-6, TNF-α
Peptidoglican	Via TRL2	+	–	IL-5, IL-10, IL-13
AgNO3	ERK1, ERK2	+	+	–
Micobacterium tuberculosis	Via CD48 protein Giα	+	+	IL-6, TNF-α

Frossi B et al. *J Leuk Biol* 2004;75:579

1. **Enhance resistance to endogenous and exogenous toxins**
2. **Phagocytose and kill bacteria**
3. **Induce local inflammation**

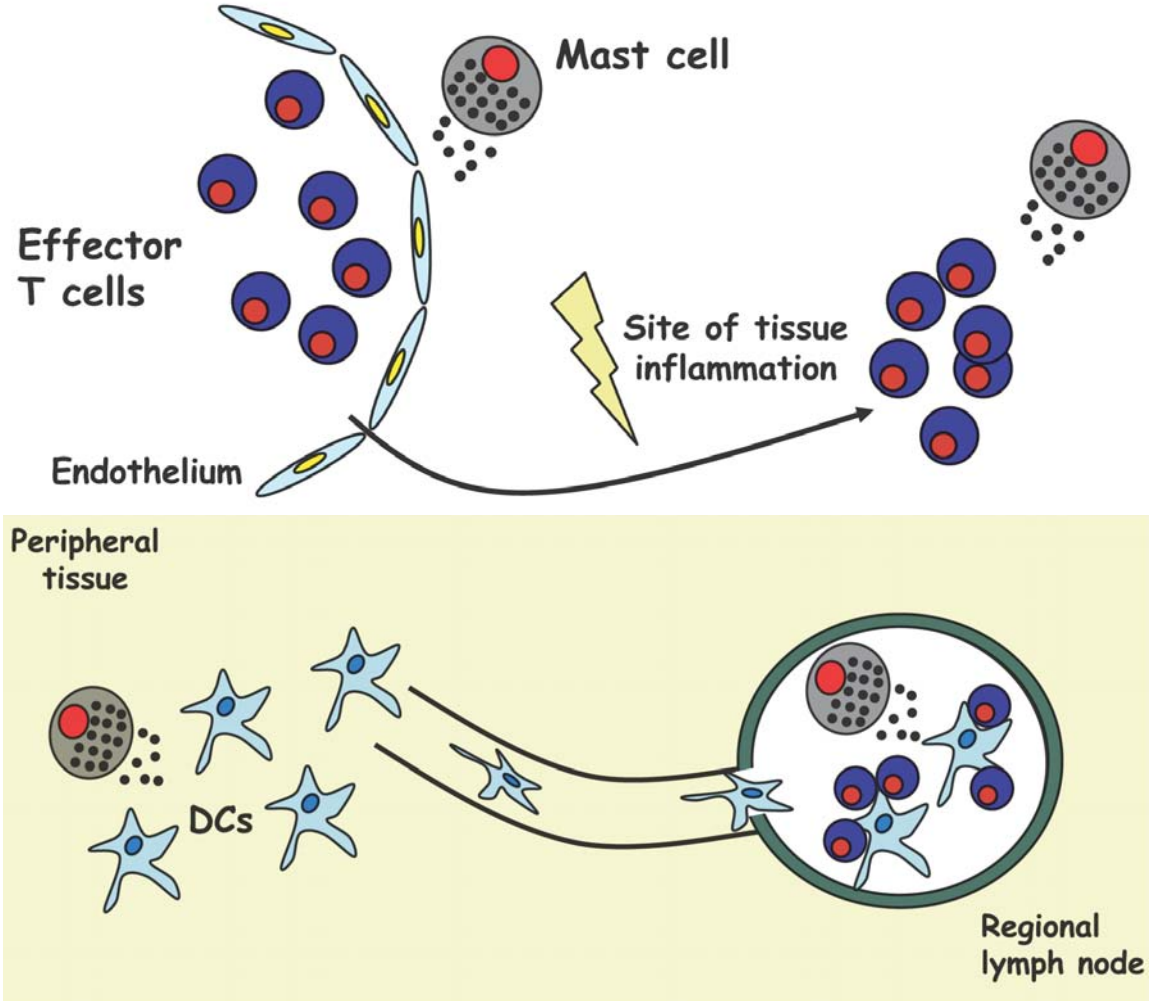


Mast cells enhance

immune effector-cell recruitment

By rapidly inducing innate reactions and local inflammation

MCs are setting the stage on which cells of the adaptive immunity are primed



MC-derived factors regulating trafficking

For T cells:

- CCL2 (MCP-1)
- CCL3 (MIP-1α)
- CCL4 (MIP-1β)
- CCL5 (RANTES)
- CCL20 (MIP-3α)
- CXCL1 (KC)
- CXCL10 (IP-10)
- histamine
- LTB_4
- LTC_4
- TNFα
- IL-1β
- IL-6
- IL-16
- lymphotactin

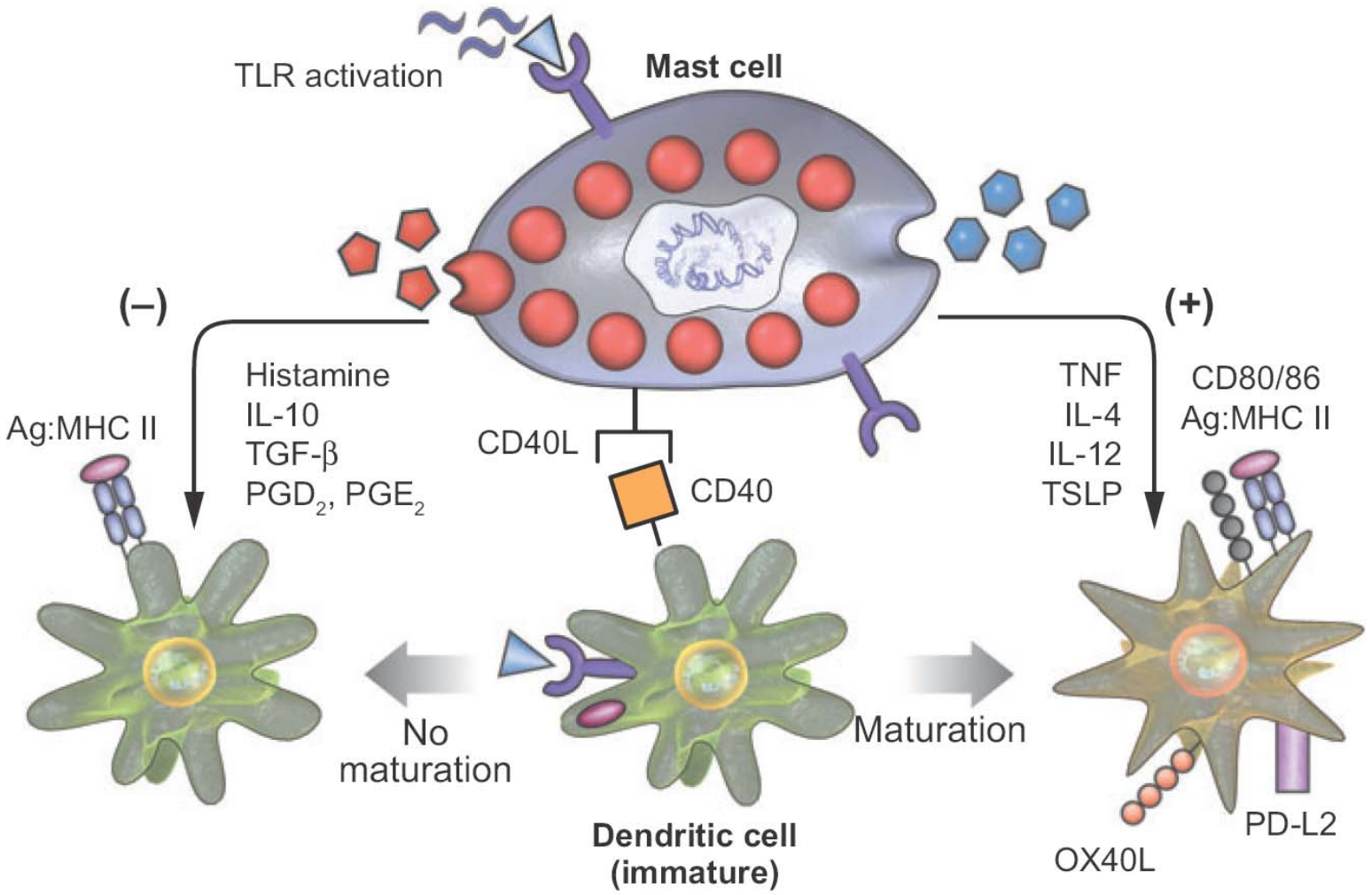
For Dendritic cells:

- TNFα
- PGE2
- CCL5
- IL-1α
- IL-1β
- IL-16
- IL-18

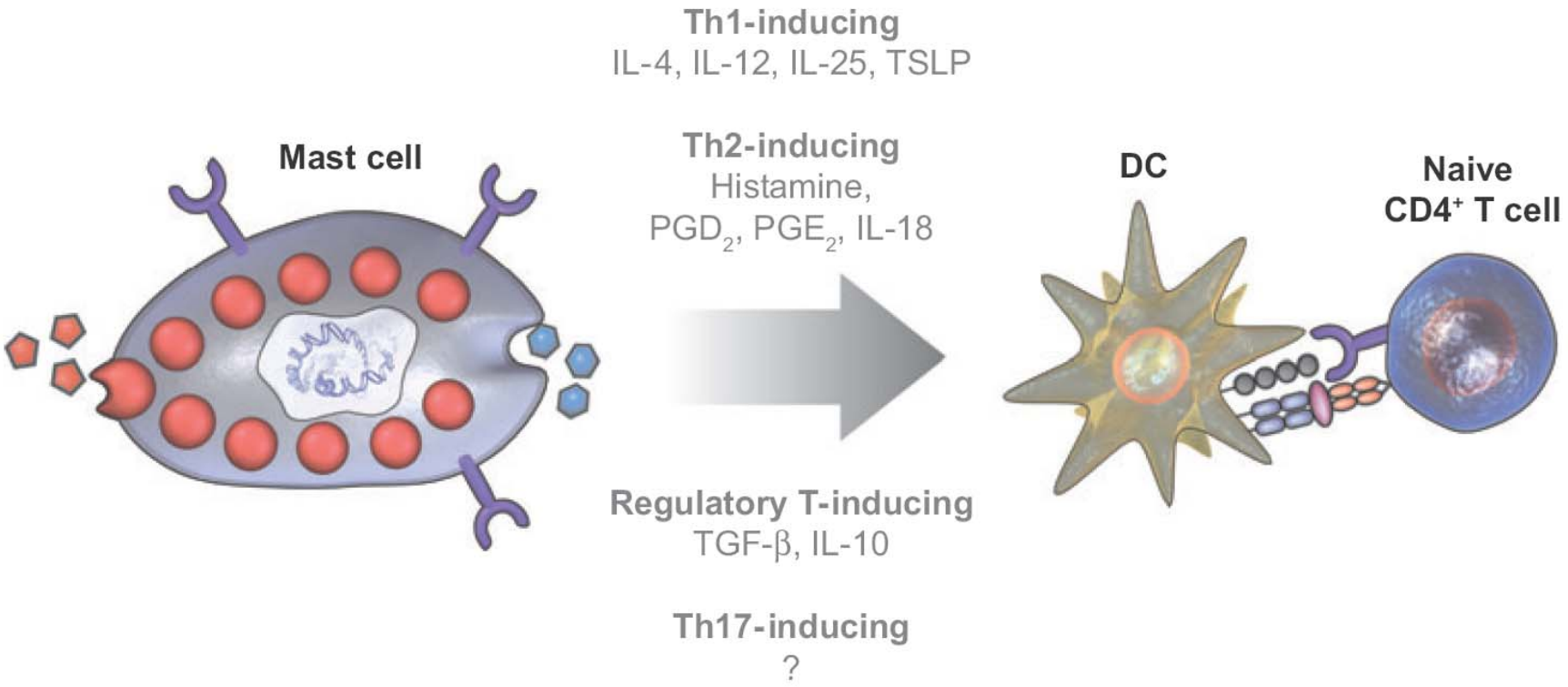
Mast cells are necessary for inducing local LN hypertrophy following infection

MC-derived factor	*Effect on DCs*
Histamine	↓ IL-12 – Promotes Th2 skewing of T cells
Leukotrienes	Enhances migration – ↑ IL-10 and ↓ IL-12
Prostaglandins	PGD_2: ↓ IL-12 and promotes Th2 skewing – PGE_2: ↑ IL-10 Essential for migration ↑ production of Th2-attracting chemokines Inhibits maturation of DC during infection
IL-4	↓ IL-10 leading to ↑ IL-12 – ↓ PGE production
TNF	Enhances DC migration – Produces tolerogenic DC that induce Tregs
TGF-β	Promotes DC generation of $CD4^+CD25^+$ Tregs ↑ expression of chemokine receptors – Essential for generation of LCs
TSLP	Promotes inflammatory Th2-skewing of T cells by ex vivo human DC
Serotonin	Differentiates DC with ↓ stimulatory capacity but ↑ cytokine production
Heparin	Differentiates $CD1a^+$ DC

Mast cell influence on DC responses



Direct (Ag-independent) MC–T cell interactions



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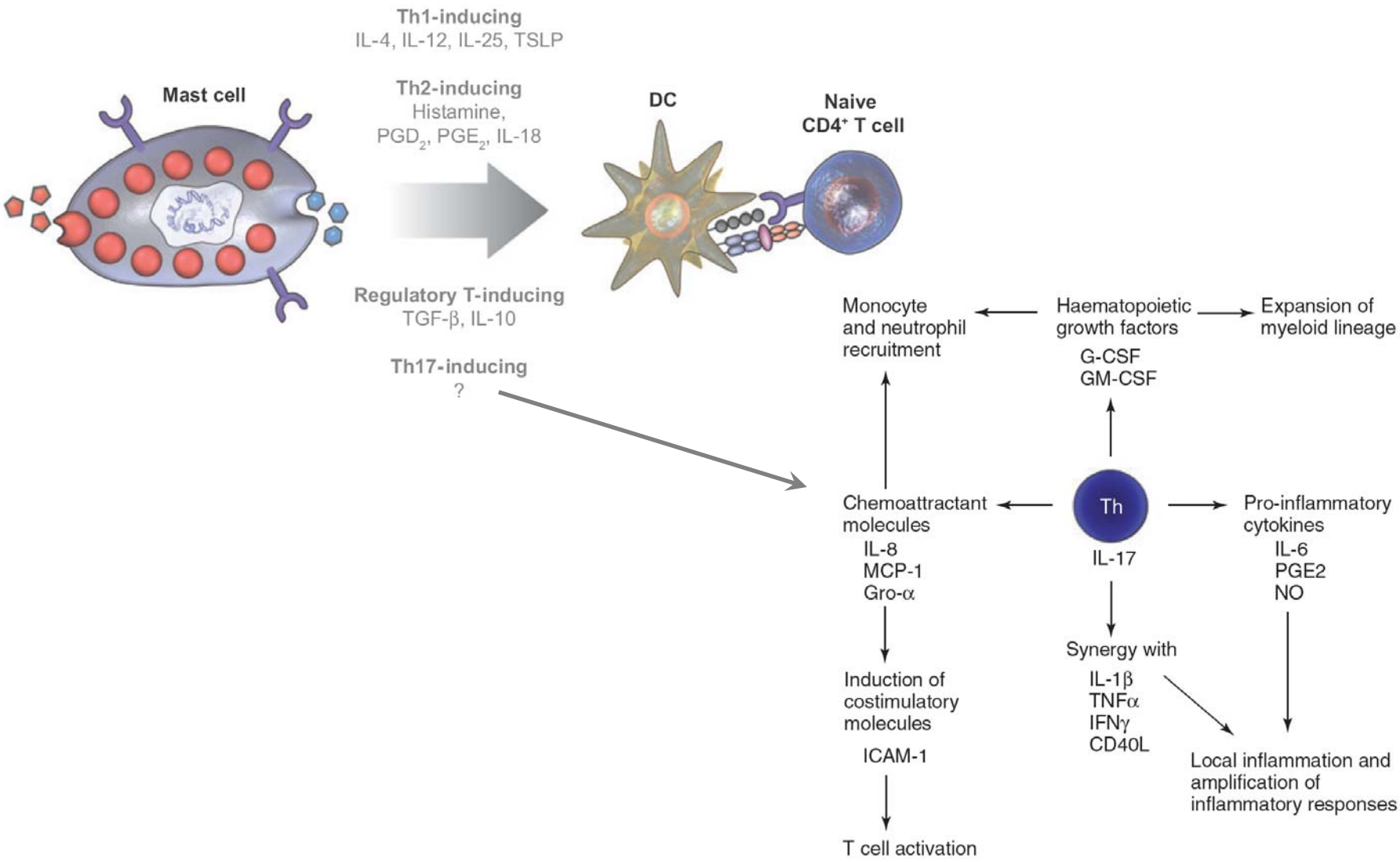
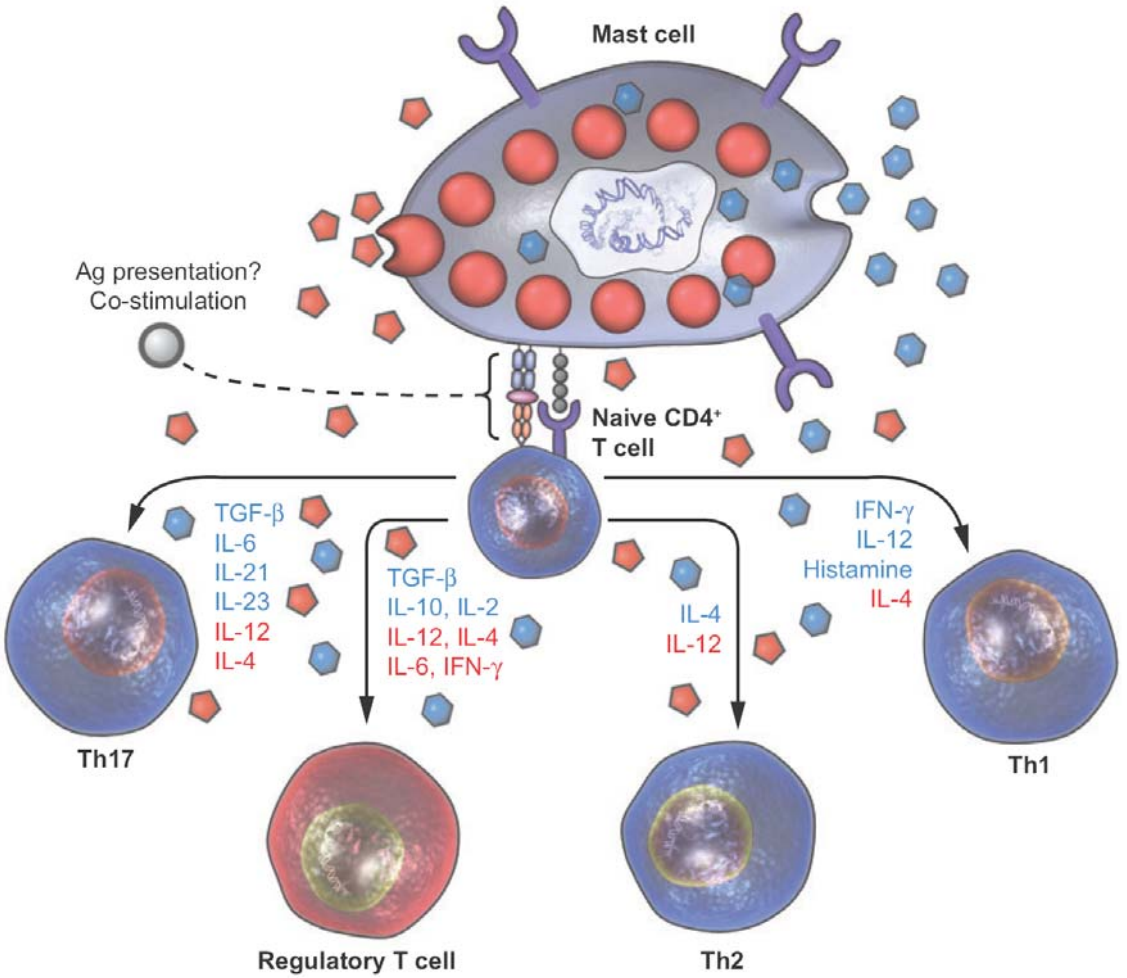
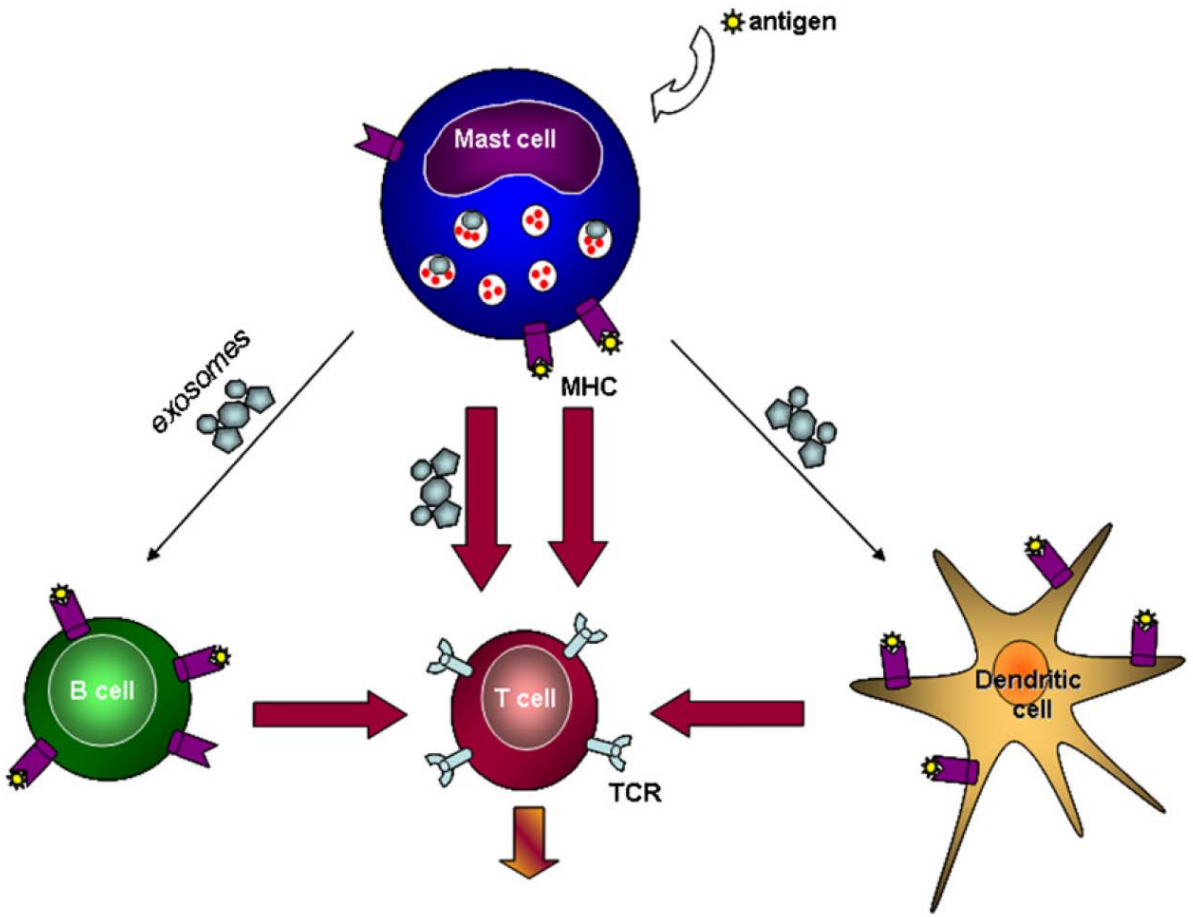


Some mast cell lines express MHC molecules and have antigen-presenting capability



Ag-dependent, MC-mediated induction of T cell responses



Ag-dependent, MC-mediated induction of T cell responses

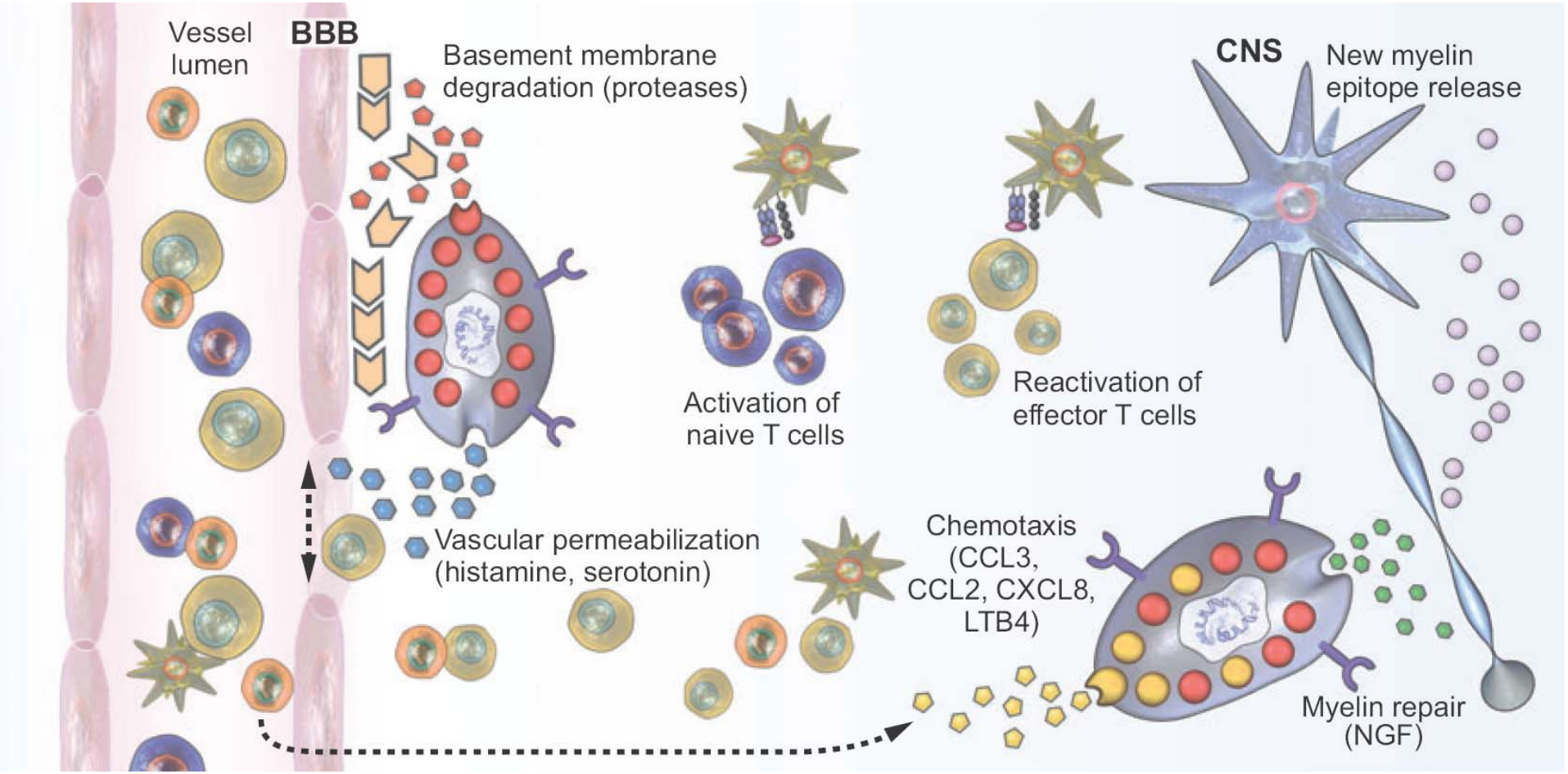
- Some mast cell lines express MHC molecules and have have antigen-presenting capability
- **Mast cells could provide direct costimulation to T cells via their expression of CD80, CD86, CD153, ICOSL, 41BB, CD40L and OX40L**
- **Mast cells enhance T cell proliferation and expression of activation markers through elaboration of cytokines such as IL-2, IL-4, IL-7, and IL-15**

Frandji P et al. *J Immunol* 1993;151:6318

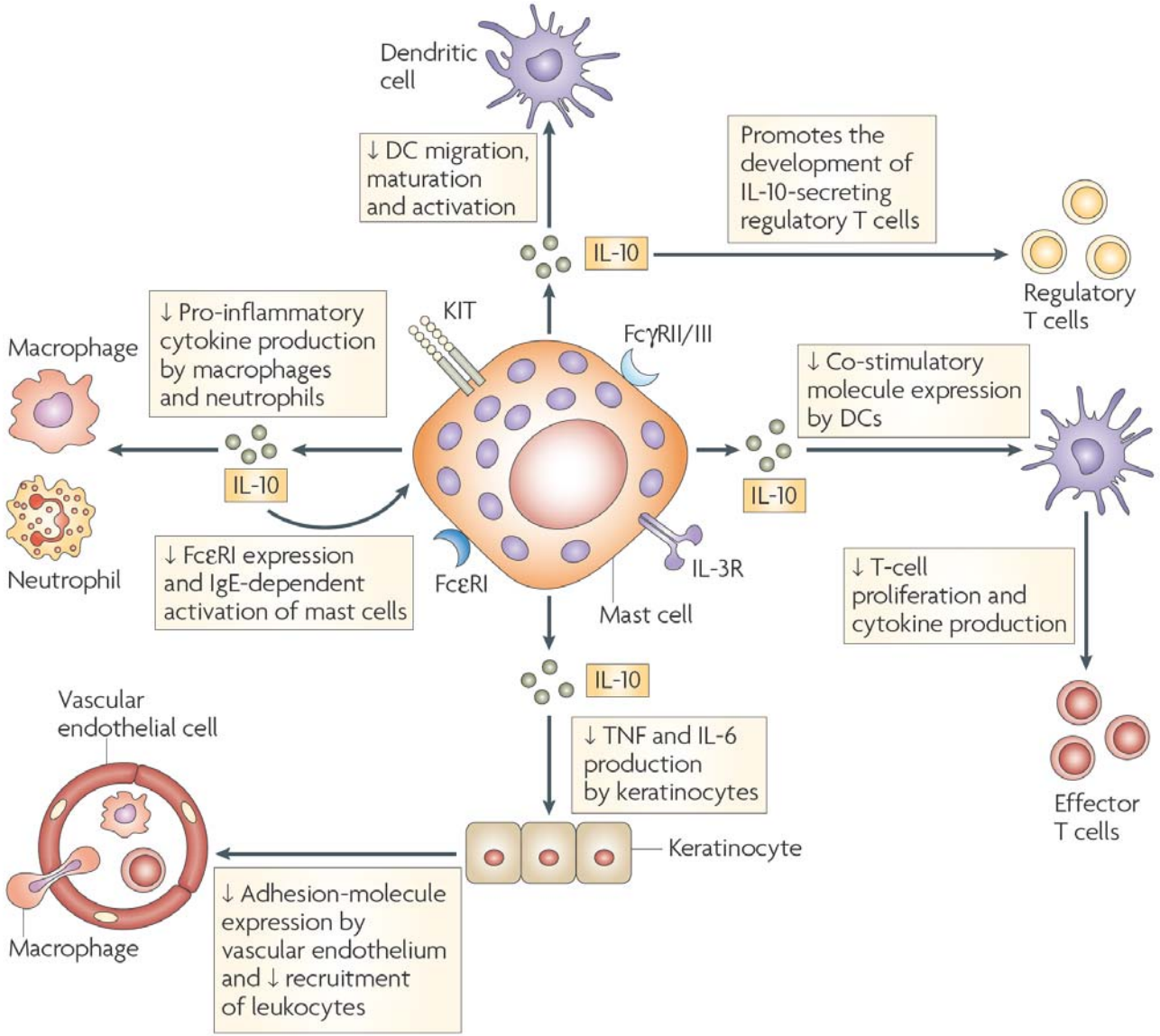
Fox CC et al. *Cell Immunol* 1994;158:253

Nakae S et al. *J Immunol* 2006;176:2238

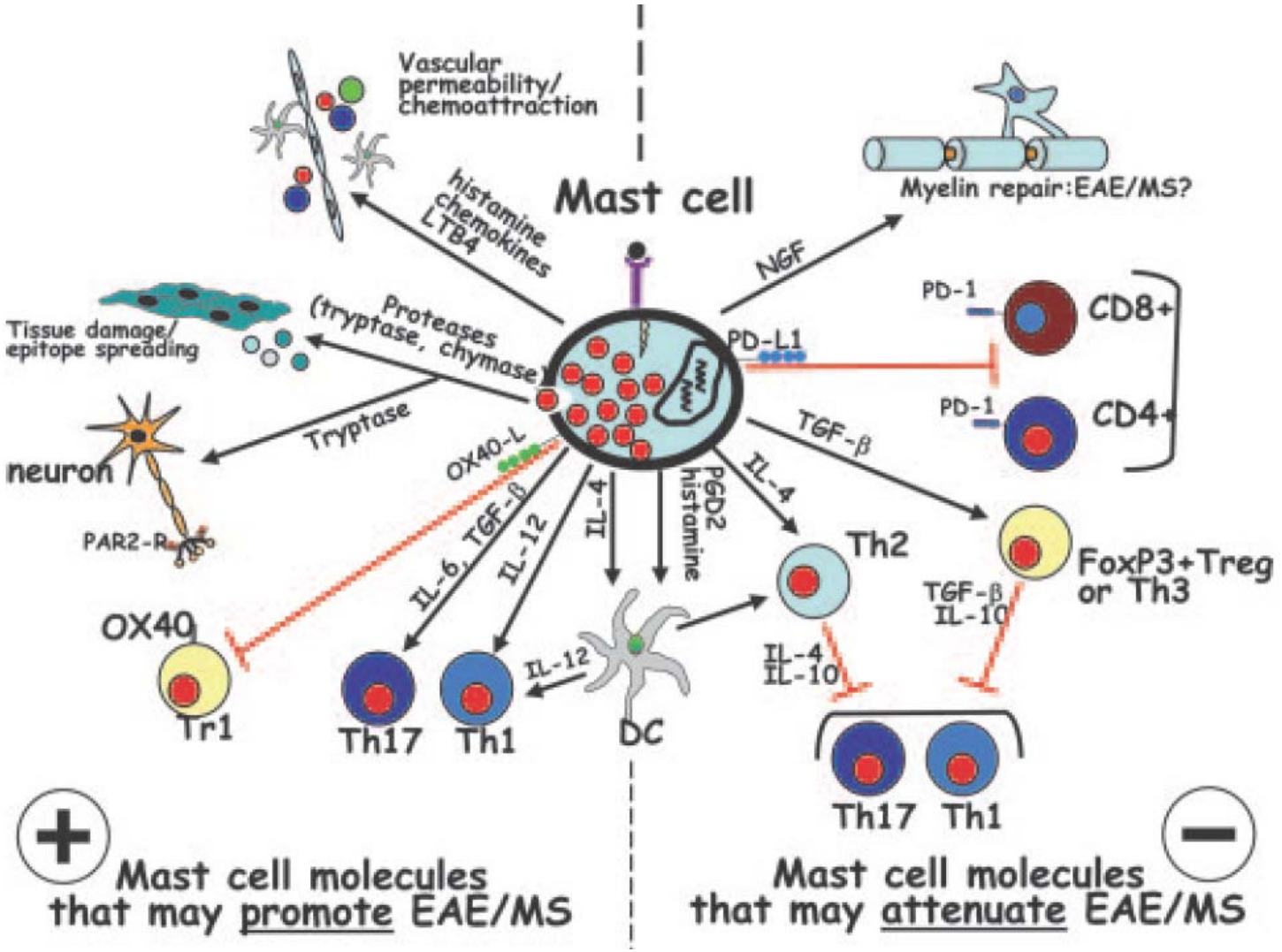
Mast cell proteases can promote epitope spreading



MC-mediated immunosuppression



The multitasking mast cell



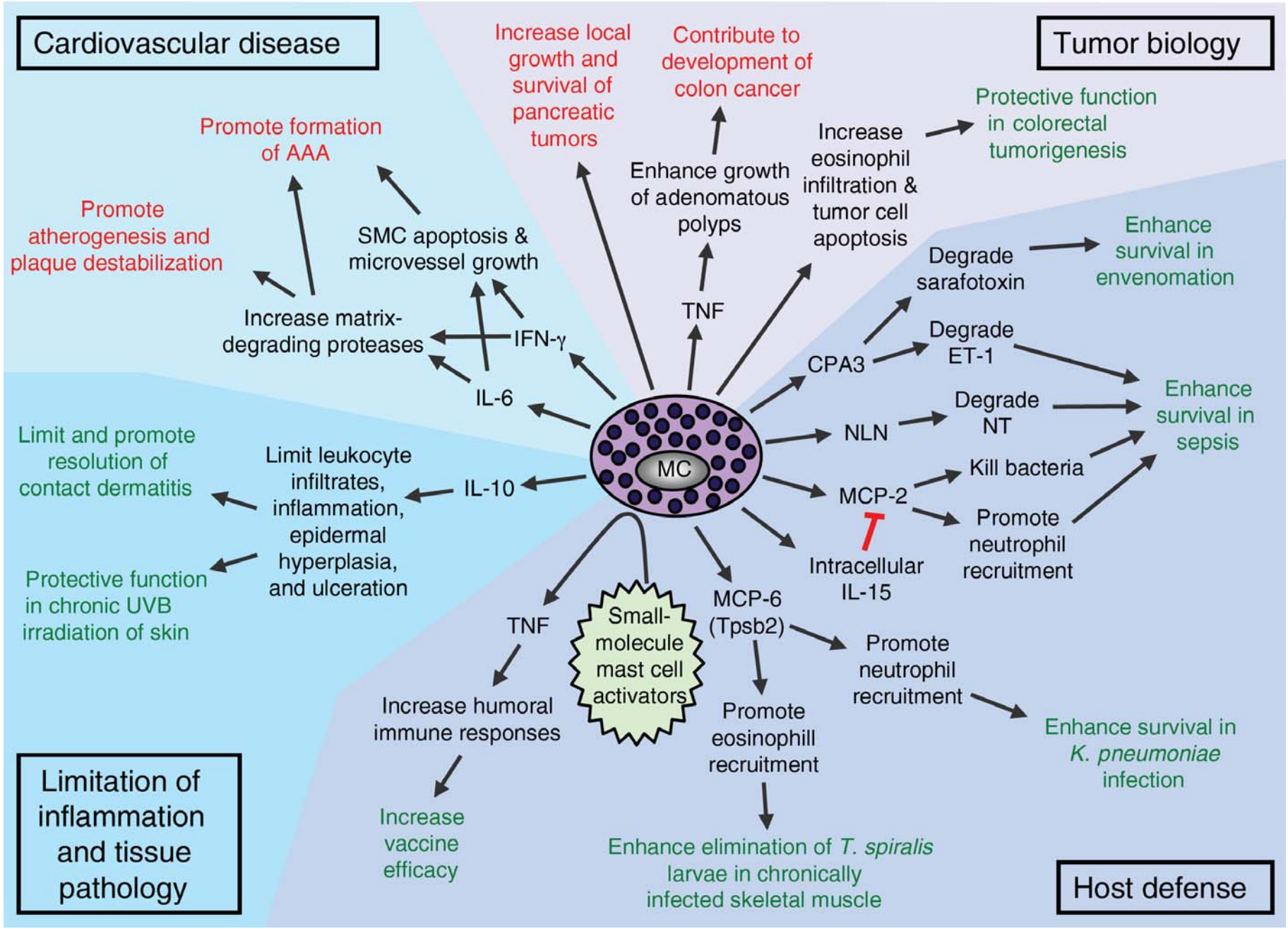
Mast cells are tuneable

a. **The anatomic sites of specific mast cell populations confer a unique tissue-specific phenotype.**

b. **Related to the distinct locations of mast cells are the unique subsets of target cells in different tissues adding to response variability.**

c. **It is the convergence of multiple agonists that dictates the final response of a single mast cell.**

d. **Genetically determined variability in mast cell numbers and responses may confer strikingly distinct response outcomes.**


Cardiovascular disease
Tumor biology
Limitation of inflammation and tissue pathology
Host defense
Promote formation of AAA
Promote atherogenesis and plaque destabilization
SMC apoptosis & microvessel growth
Increase matrix-degrading proteases
IFN-γ
IL-6
Increase local growth and survival of pancreatic tumors
Contribute to development of colon cancer
Enhance growth of adenomatous polyps
TNF
Increase eosinophil infiltration & tumor cell apoptosis
Protective function in colorectal tumorigenesis
Degrade sarafotoxin
Enhance survival in envenomation
CPA3
Degrade ET-1
Degrade NT
NLN
Enhance survival in sepsis
MC
Kill bacteria
MCP-2
Promote neutrophil recruitment
Intracellular IL-15
Limit and promote resolution of contact dermatitis
Limit leukocyte infiltrates, inflammation, epidermal hyperplasia, and ulceration
IL-10
Protective function in chronic UVB irradiation of skin
TNF
Small-molecule mast cell activators
MCP-6 (Tpsb2)
Promote neutrophil recruitment
Enhance survival in K. pneumoniae infection
Increase humoral immune responses
Promote eosinophill recruitment
Increase vaccine efficacy
Enhance elimination of T. spiralis larvae in chronically infected skeletal muscle

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Thank you for your attention