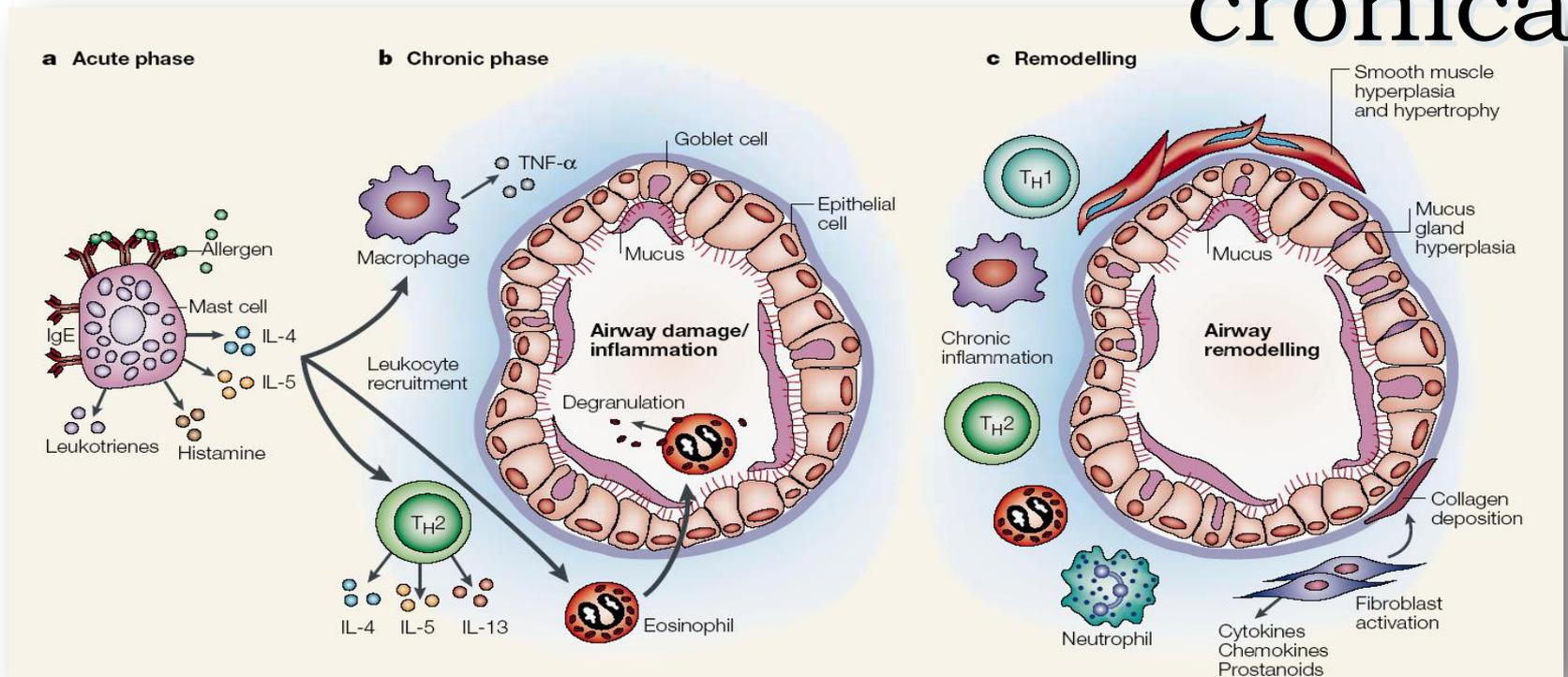


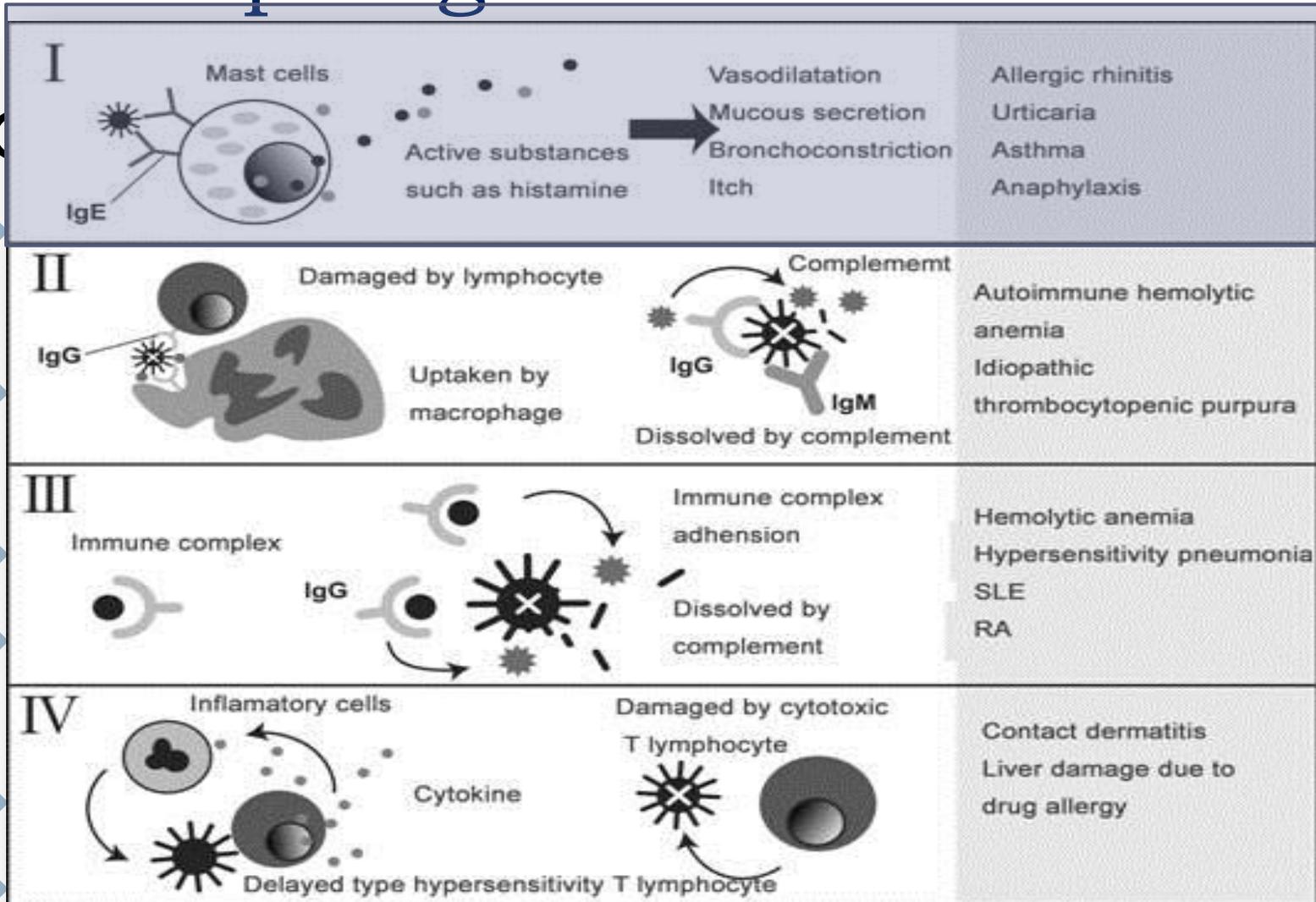
# Hipersensibilidad Tipo I inmediata: Inmunopatogenia del asma crónica



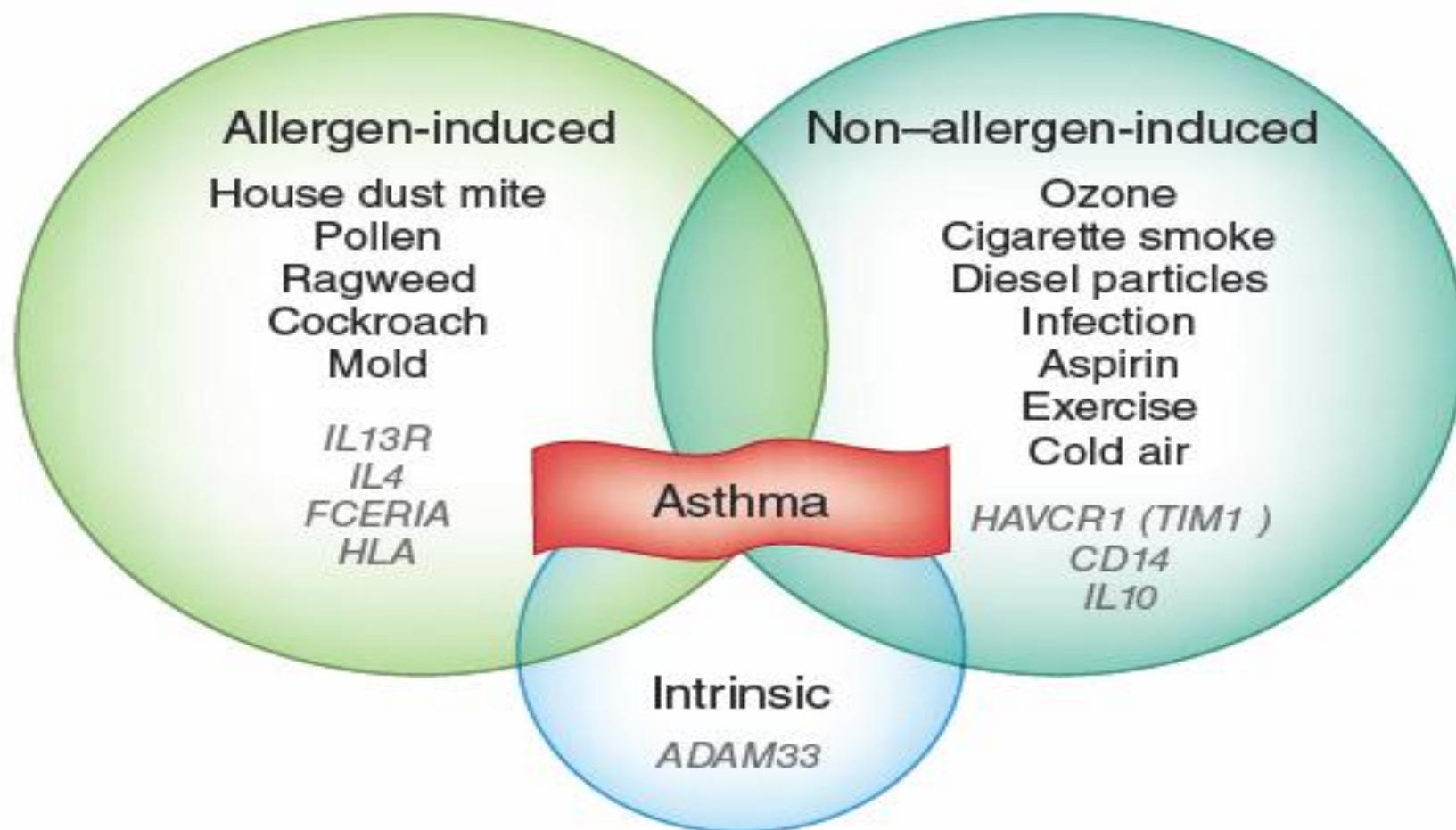
Siham Salmen Halabi

Instituto de Inmunología Clínica 2015

# Inmunopatogenia del asma crónica

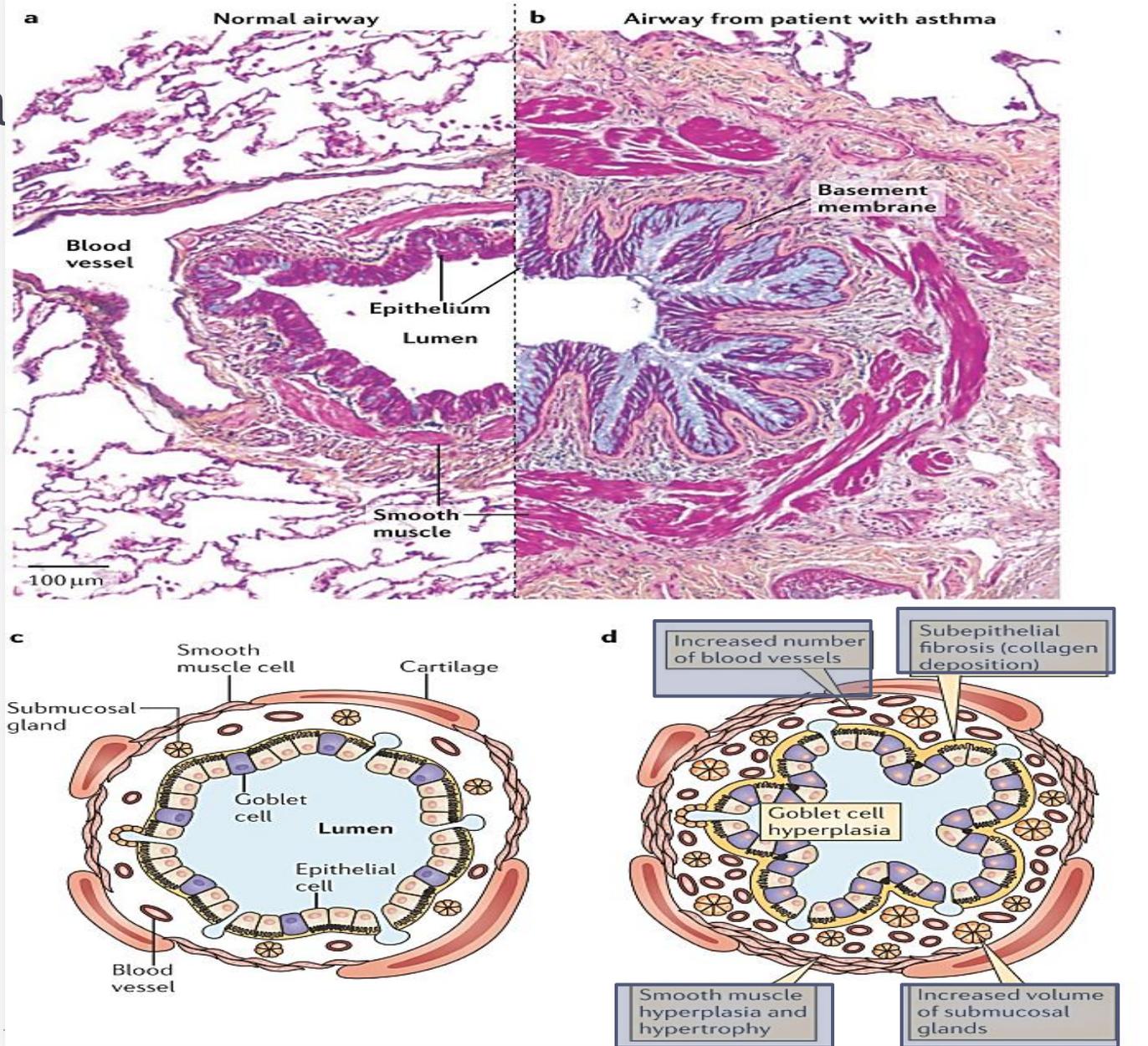


# HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma

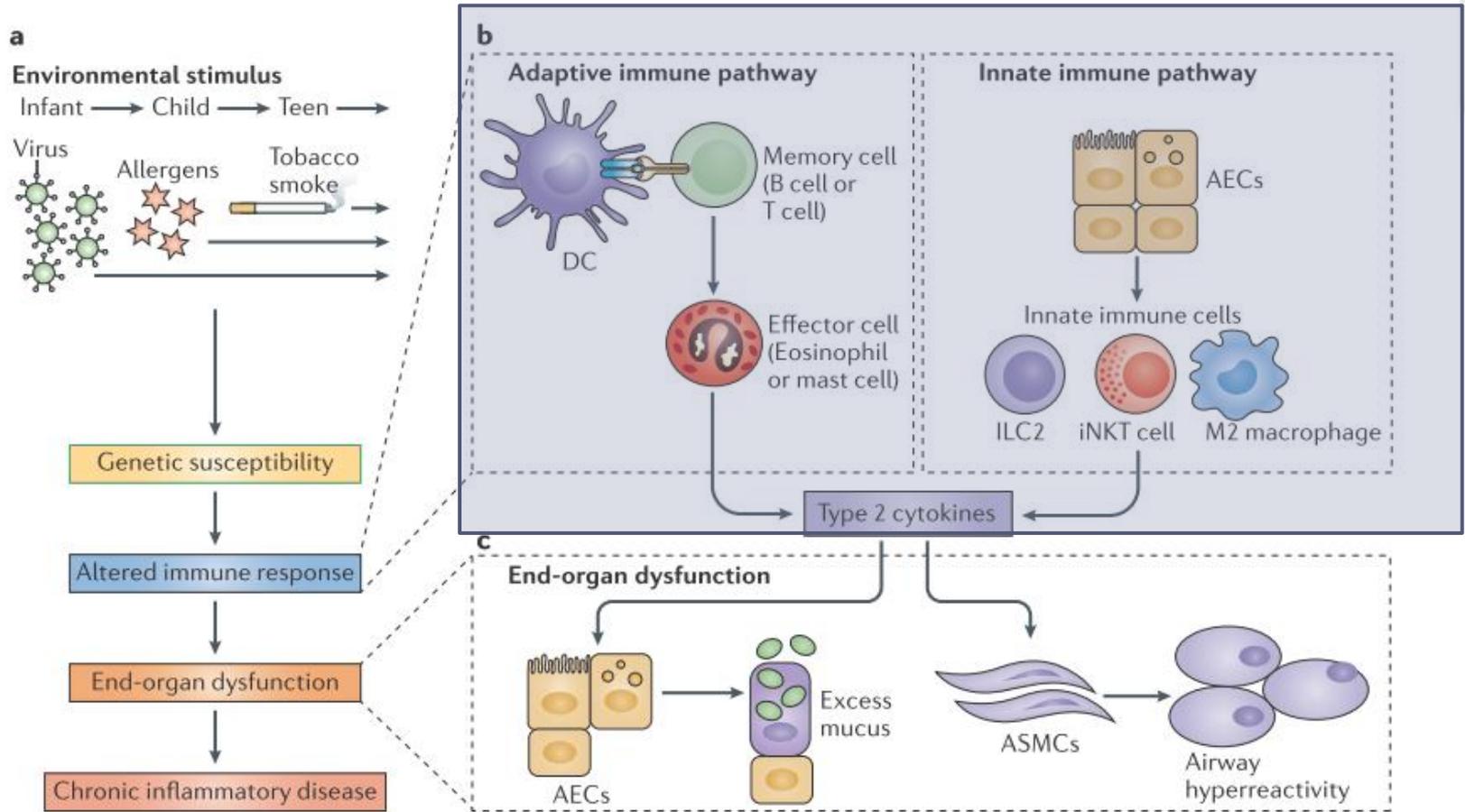


Es la enfermedad respiratoria crónica mas frecuente (10% adultos y 20% niños ): 300 millones de personas en el mundo

# Cambios a nivel de la mucosa bronquial Asma crónica

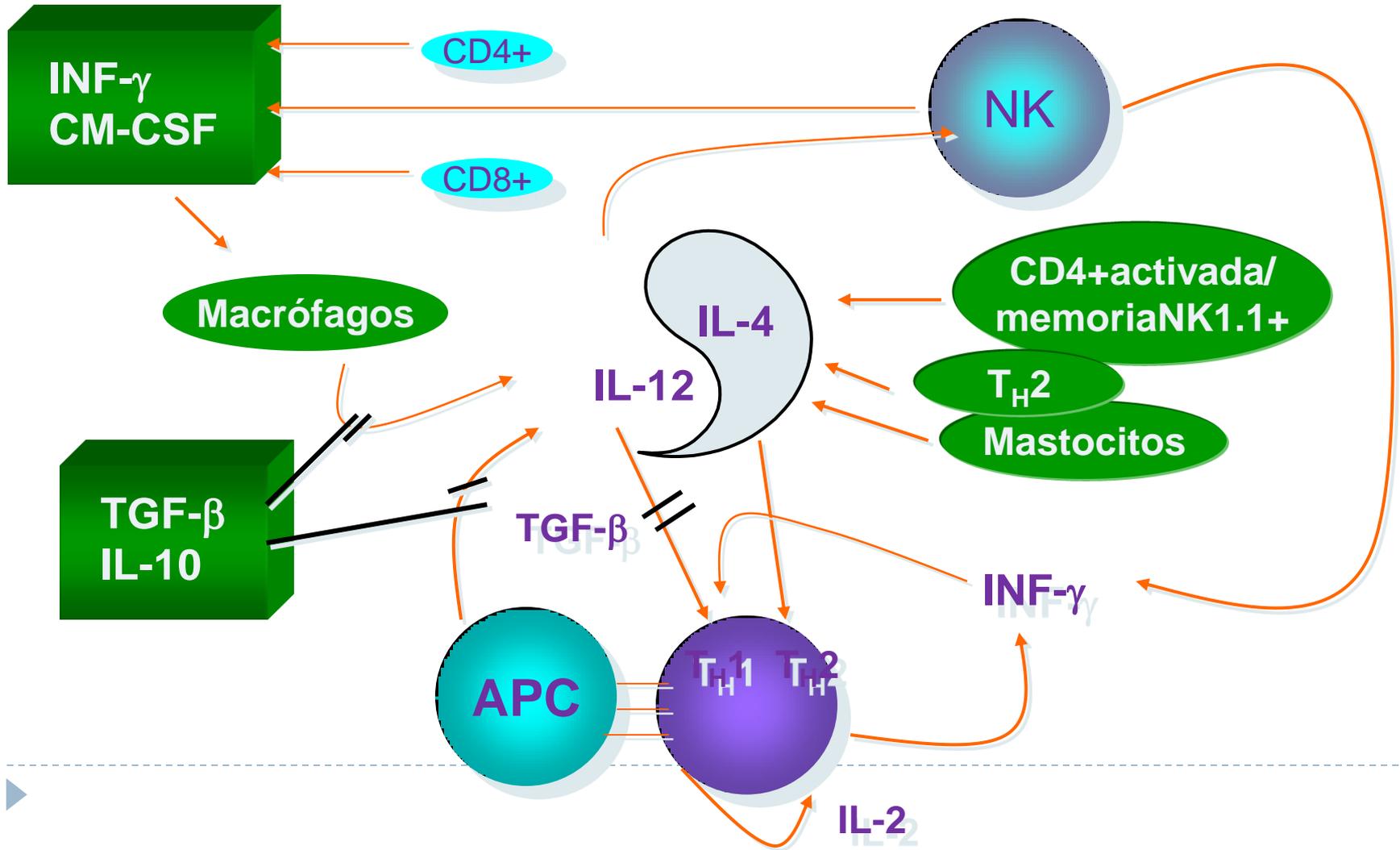


# HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma



# Polarización de la respuesta

## $T_H1/T_H2$



# HIPERSENSIBILIDAD INMEDIATA:

## Inmunopatogenia del asma Genes involucrados en la atopía

Región	Genes candidatos	Función	Fenotipo
5q31.1-q33	IL3, IL4, IL5, IL9, IL13, CSF2	IgE, incremento de la expresión de IL en los eosinófilos, basófilos, mastocitos y funciones de la IgE (respuesta TH2)	Niveles de IgE, asma, BHRB
6p21.3	ADRB2	Receptor acoplado a proteína G	Niveles de IgE, HRB, asma
	GRL	Modulación de RI	Desconocido
11q13	HLAD TNFA FCERIB	Presentación antigénica Mediadores de la RI Traducción de señal en basófilos, mastocitos y células dendríticas	IgE e IgG específica Asma Atopia, asma,
12q14.3-q24.1	FGF3	Promueve la proliferación celular Inhibe la actividad de la IL-4 Produce IL4	Atopia
14q11.2-13	IFN $\gamma$ SCF, NFKB STAT6	Aumenta la transcripción de IL4 y genes HLAD Factor transcripcional regulado por IL	Asma, atopía, Niveles de IgE " "
	TCRA, TCRD NFKB-I C5 y C5R	Interacción con complejos MHC-péptidos Activa genes moduladores de la RI	IgE específica
9q34y 19.13.3		Incrementa IL-12	Desconocido Ausencia favorece Th2

Polimorfismo en **CTLA-4** se asocia con incremento en IgE y rinitis alérgica

Polimorfismos en **IL-4 e IL-4R** asociado con asma

Polimorfismo en **PRR**, asociado con asma y sensibilización a los alérgenos

**Table 1** The functions of miRNAs in allergic diseases

miRNA	Disease	Function	Targets
miR-126	Asthma	Silencing reduced allergic inflammation in an HDM-induced mouse model of asthma [33] and reduced eosinophilia in the mouse model of chronic airway inflammation [34]	?
miR-221	Asthma	Upregulated in OVA-induced mouse models of asthma, ENREF_136 silencing reduces allergic inflammation [37]	Spred-2
miR-145	Asthma	Silencing reduced allergic inflammation in an HDM-induced mouse model of asthma [35]	?
miR-106a	Asthma	Silencing reduced allergic inflammation in an HDM-induced mouse model of asthma [36]	IL-10
let-7a	Asthma	Overexpression reduced allergic inflammation in an OVA-induced mouse model of asthma [48] Intravenous administration of LNA inhibitors impeded AHR in a mouse model of asthma [46]	IL-13
miR-21	Asthma, allergic rhinitis, contact dermatitis, EoE	Overexpressed in lung-specific IL-13 expressing transgenic mice with induced allergic airway inflammation [41] Overexpression reduced TLR2 agonist-induced lung inflammation in mice [43] Increased levels of Th1 cytokines and reduced eosinophilia in an OVA-induced mouse model of asthma in miR-21-deficient mice [42] Antenatal IgE production and development of allergic rhinitis [44] Upregulated in contact dermatitis lesional skin [47] Upregulated in EoE esophageal tissue [45•]	IL-12p35
miR-146a	Asthma?	Overexpressed in splenic CD4+ T lymphocytes [31] Reduced expression in CD8+ and CD4+ cells in patients under oral corticosteroid treatment [101] Reduces cytokine-induced apoptosis in human bronchial epithelial cells [59]	?
miR-375	EoE	Positive regulator of TSLP in human primary lung epithelial cells [52] Expression is modulated by IL-13 [46] Downregulated in EoE esophageal tissue [45•]	?
miR-133a	Asthma	Downregulation in mouse bronchial smooth muscle cells augmented airway contraction and hyperresponsiveness [61]	RhoA
miR-1	Asthma	Downregulated by VEGF in the lung endothelium, intranasal administration of miR-1 inhibited inflammatory responses to OVA, HDM and IL-13 overexpression Mpl [60]	Mpl
miR-155	Atopic dermatitis, asthma	Influences development of AD by downregulation of CTLA-4-negative regulator of T-cell activation [63] Is required for Th2-mediated eosinophilic inflammation in the OVA-induced mouse model of asthma [32•] miR-155-deficient mice spontaneously developed asthma-like inflammation in the lung and had increased levels of IL-4 and IL-5 in T cells [26]	CTLA-4 PU.1 c-Maf
miR-125b	CRS with nasal polyps	Upregulated in CRS with nasal polyps, influenced IFN- $\alpha/\beta$ production [68]	4E-BP1
miR-150	ACD	Nanovesicles containing miR-150 induced antigen-specific tolerance in ACD model in mice [84•]	

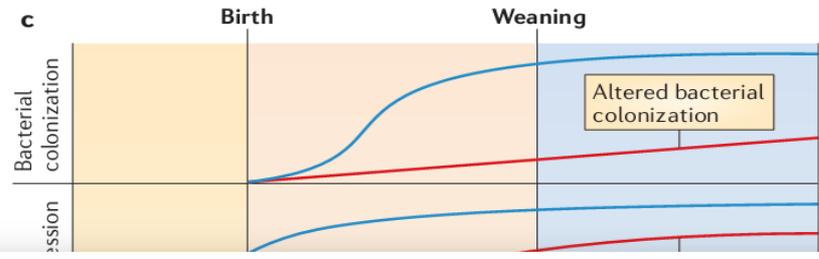
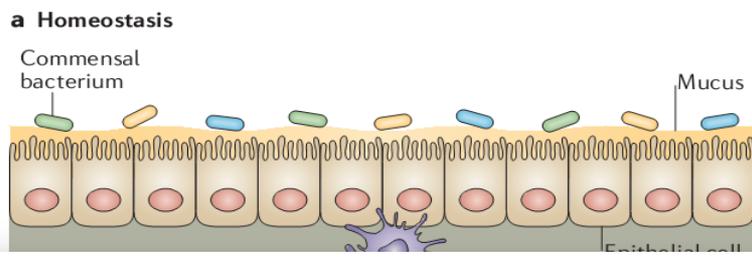
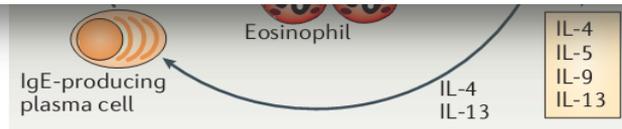


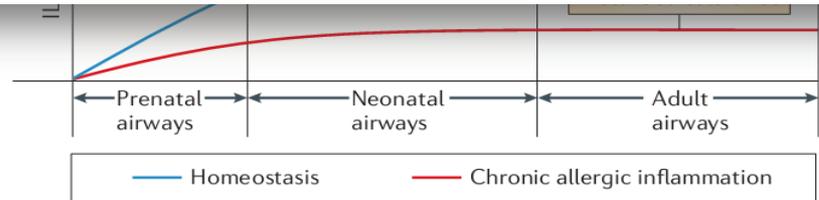
Table 1 | **Microorganisms affect the development of experimental and clinical asthma**

Source and route of microbial exposure	Examples of bacteria	Effect on asthma
Environmental microorganisms	<ul style="list-style-type: none"> <li>• <i>Acinetobacter lwoffii</i></li> <li>• <i>Eurotium</i> spp.</li> <li>• <i>Penicillium</i> spp.</li> </ul>	<ul style="list-style-type: none"> <li>• Transgenerational protection from experimental asthma</li> <li>• Asthma-protected children are exposed to a high level of bacteria and fungi/spores<sup>103,146</sup></li> </ul>
Respiratory microbiota	<ul style="list-style-type: none"> <li>• Proteobacteria</li> <li>• <i>Bacteroides</i> spp.</li> </ul>	<ul style="list-style-type: none"> <li>• Altered microbial colonization pattern of the respiratory mucosa in asthmatics and patients with COPD<sup>9</sup></li> </ul>
Intestinal microbiota	<ul style="list-style-type: none"> <li>• Lactobacillae</li> <li>• Bifidobacteriae</li> <li>• <i>Bacteroides</i> spp.</li> <li>• <i>Clostridium</i> spp.</li> </ul>	<ul style="list-style-type: none"> <li>• Altered quantitative distribution pattern of certain culturable microbial strains in young asthmatic patients<sup>121-125</sup></li> <li>• Depletion of gut microbiota exacerbates experimental asthma<sup>127</sup></li> </ul>
Urogenital microbiota	<ul style="list-style-type: none"> <li>• Vaginal microorganisms</li> </ul>	<ul style="list-style-type: none"> <li>• Indirect evidence from a model of Caesarean section; cause-effect relationship needs to be established<sup>129-131</sup></li> </ul>

COPD, chronic obstructive pulmonary disease.



NATURE REVIEWS | IMMUNOLOGY VOLUME 12 | JANUARY 2012



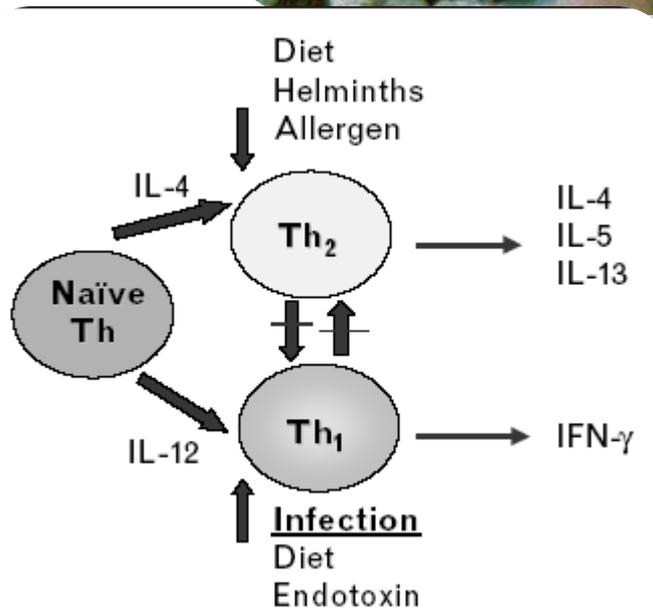
# HIPERSENSIBILIDAD INMEDIATA:

## Inmunopatogenia del asma Alergenos

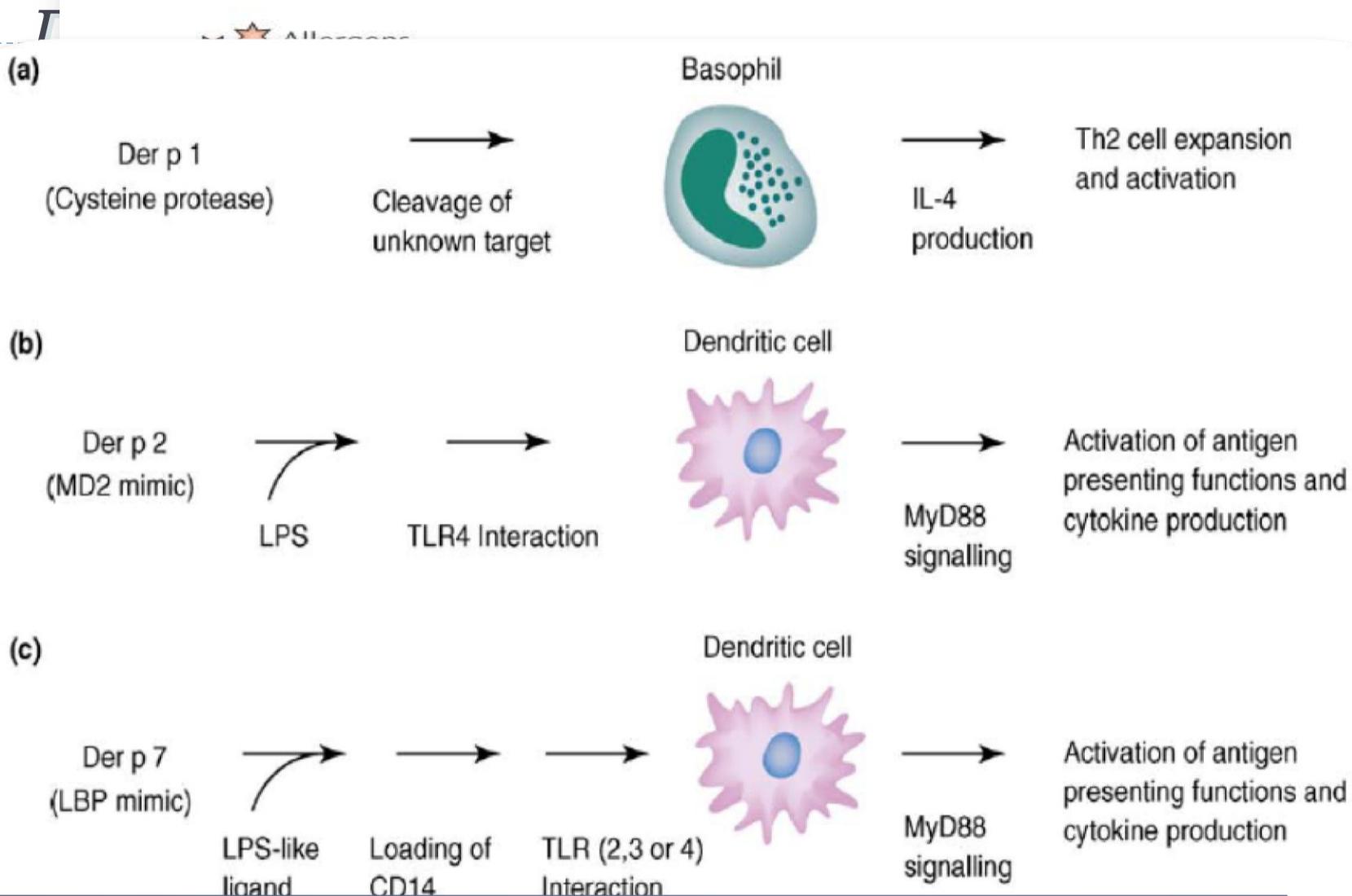
- ▶ Acaros (Derp I y 2)
  - ▶ Proteasas, quitinas
- ▶ Cucarachas (Bla g 2)
  - ▶ Quitinas
- ▶ Hongos saprófitos
  - ▶ Quitinas
- ▶ glicanos, endotoxina

TLR4 y sensibilización Th2

TLR2/MD88



# Immunopatogenia del asma:



TLR4, es activado por antígenos de los acaros, asociado con polarización Th2???,  
Derp2 es homólogo a MD2

# Polarización de la respuesta inmune: Inmunopatogenia del asma

Table 1 | Allergens that depend on proteolytic activity for affecting the DC-epithelial-cell interaction

Allergen	Enzyme	Mode of action	Effect	References
House-dust mite	Der p 1 Der p 9	Cleavage of tight-junction molecules (occludin, claudin)	Increase in epithelium permeability	11
		Activation of PAR2	Epithelial-cell activation, induction of GM-CSF production	17
	Cleavage of complement components (C5, C3)	Recruitment of innate immune cells	128	
	DC activation	T <sub>H</sub> 2-cell polarization	13	
	Cleavage of DC-SIGN and DC-SIGN-R	Failure to induce IL-10?	58	
	Cleavage of CD40	Failure to induce IL-12	59	
Aspergillus fumigatus and Aspergillus oryzae	Asp f5 Asp f6 Asp f11	Production of CCL17 and CCL22 by DCs	Recruitment of T <sub>H</sub> 2 cells	14
		Cleavage of CD25	T-cell activation	129
		Cleavage of CD23	Stimulation of IgE production by B cells	130
		Cleavage of tight-junction molecules	Increase in epithelium permeability	29
		Induction of IL-25	Promotion of T <sub>H</sub> 2-cell responses	81
Ragweed pollen Birch pollen	Amb a Bet v	Induction of chemokines	Recruitment of T <sub>H</sub> 2 cells and eosinophils	10,57
		Activation of unknown PAR	Epithelial-cell activation?	57
		Cleavage of tight-junction molecules	Increase in epithelium permeability	30
Cockroach allergens	Bla g	Cleavage of tight-junction molecules	Increase in epithelium permeability	31
		Activation of PAR2	Epithelial-cell activation	131

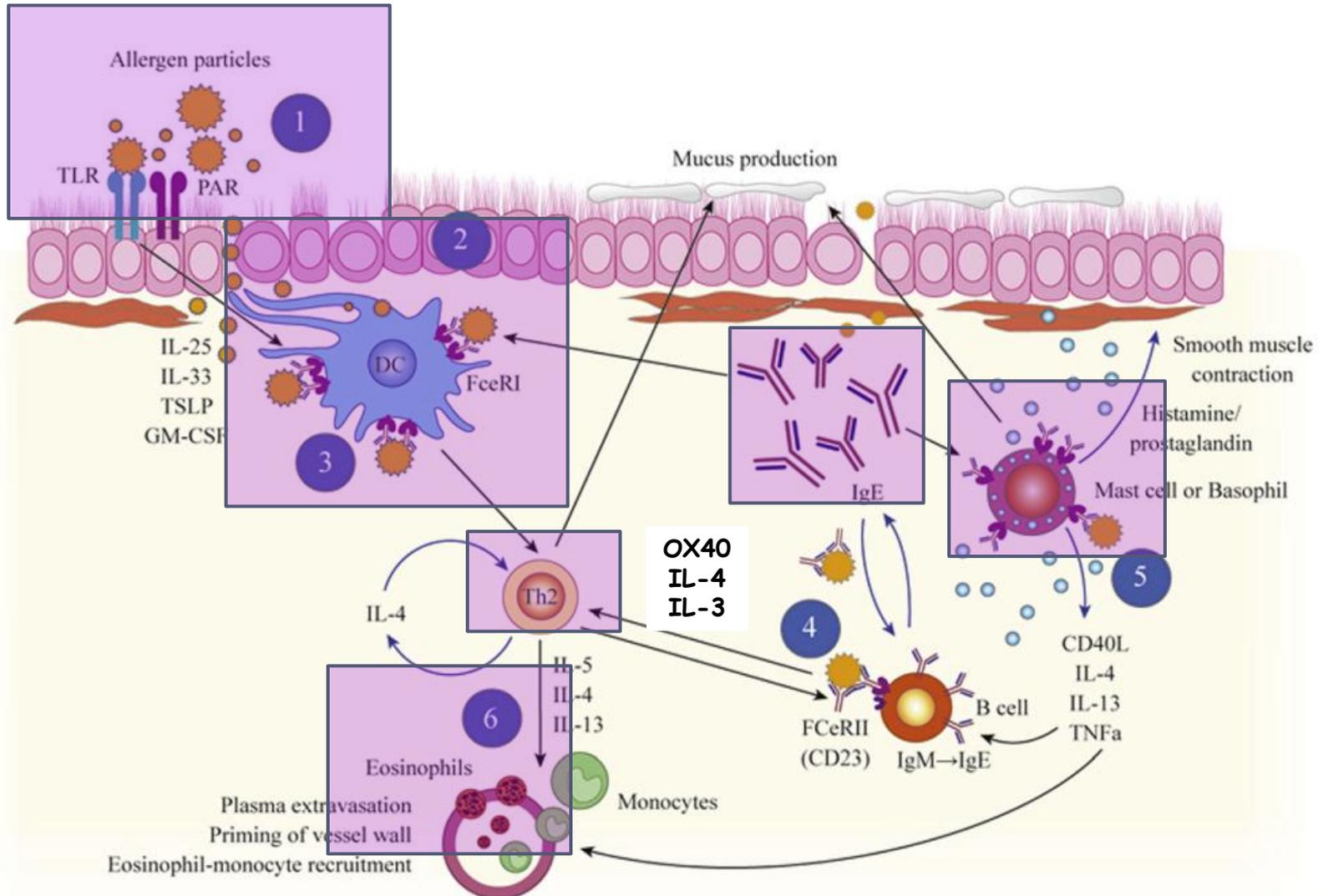
CCL, CC-chemokine ligand; DC, dendritic cell; DC-SIGN, DC-specific ICAM3-grabbing non-Integrin; GM-CSF, granulocyte/macrophage colony-stimulating factor; IL, interleukin; PAR, protease-activated receptor; T<sub>H</sub>2 cell, T helper 2 cell.

## ▶ En condiciones pro-inflamatorias

- ▶ Alérgenos que alteran la permeabilidad por afectar las uniones con las DC con las células epiteliales
- ▶ Contaminación con bajas dosis de LPS rompe la tolerancia a los aeroantígenos



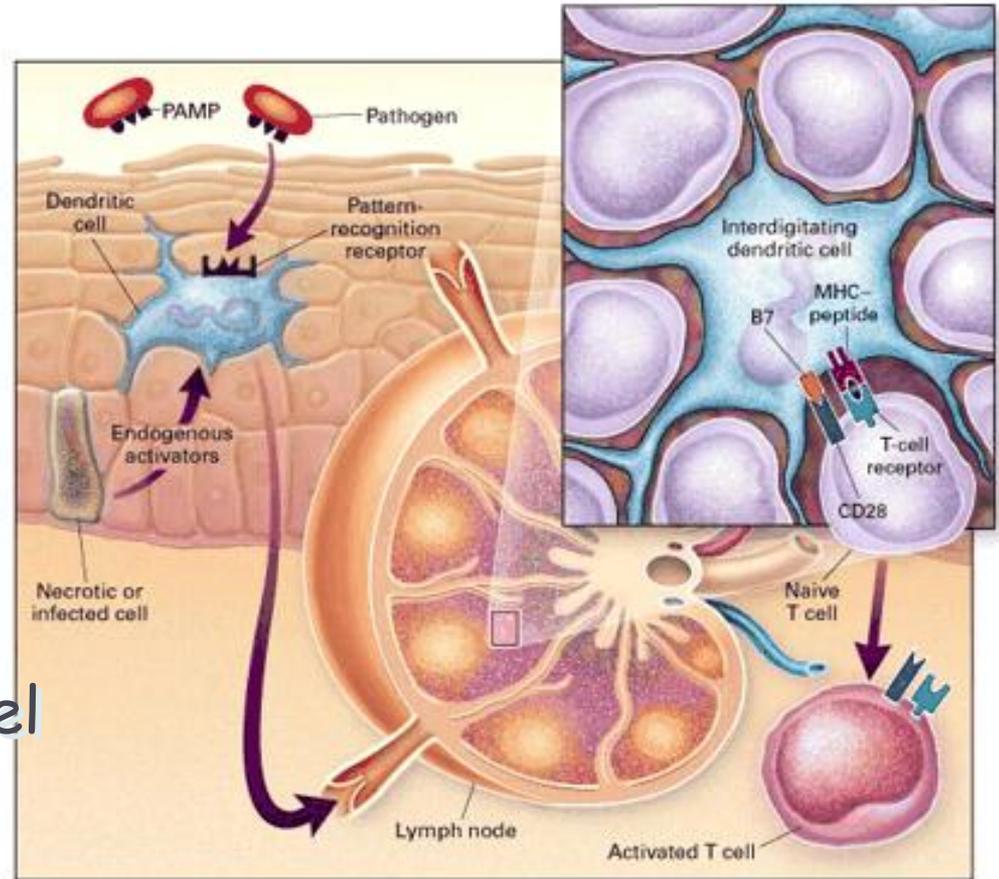
# Inmunopatogenia del asma



# HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma

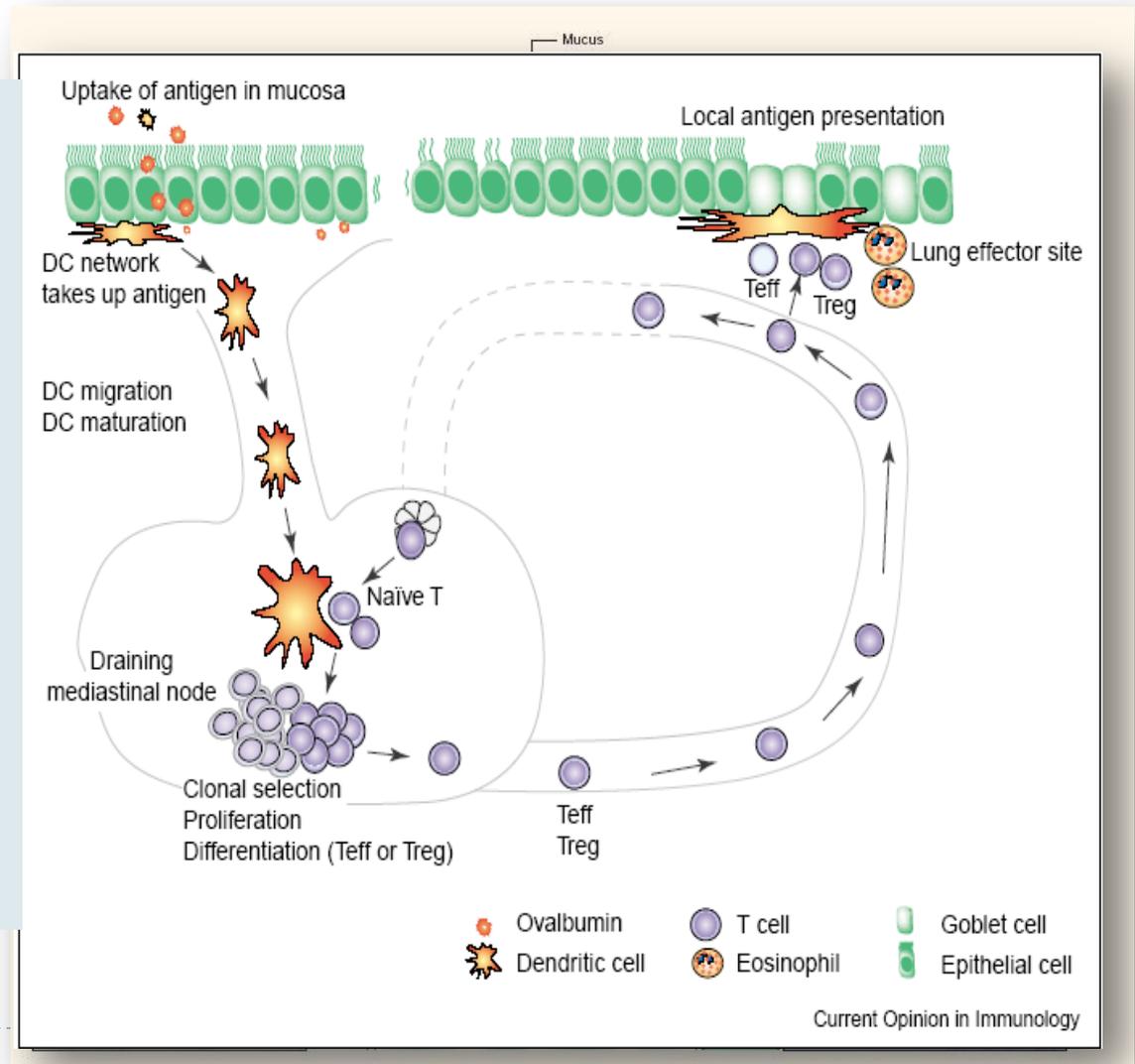
- ▶ Individuo genéticamente susceptible: Predisposición a responder  $T_H2$
- ▶ Condiciones ambientales
- ▶ Alergenos

Primer encuentro con el alérgeno, captado por las células dendríticas, drena hacia los nódulos linfáticos del mediastino, procesa y presenta los antígenos al linfocito T

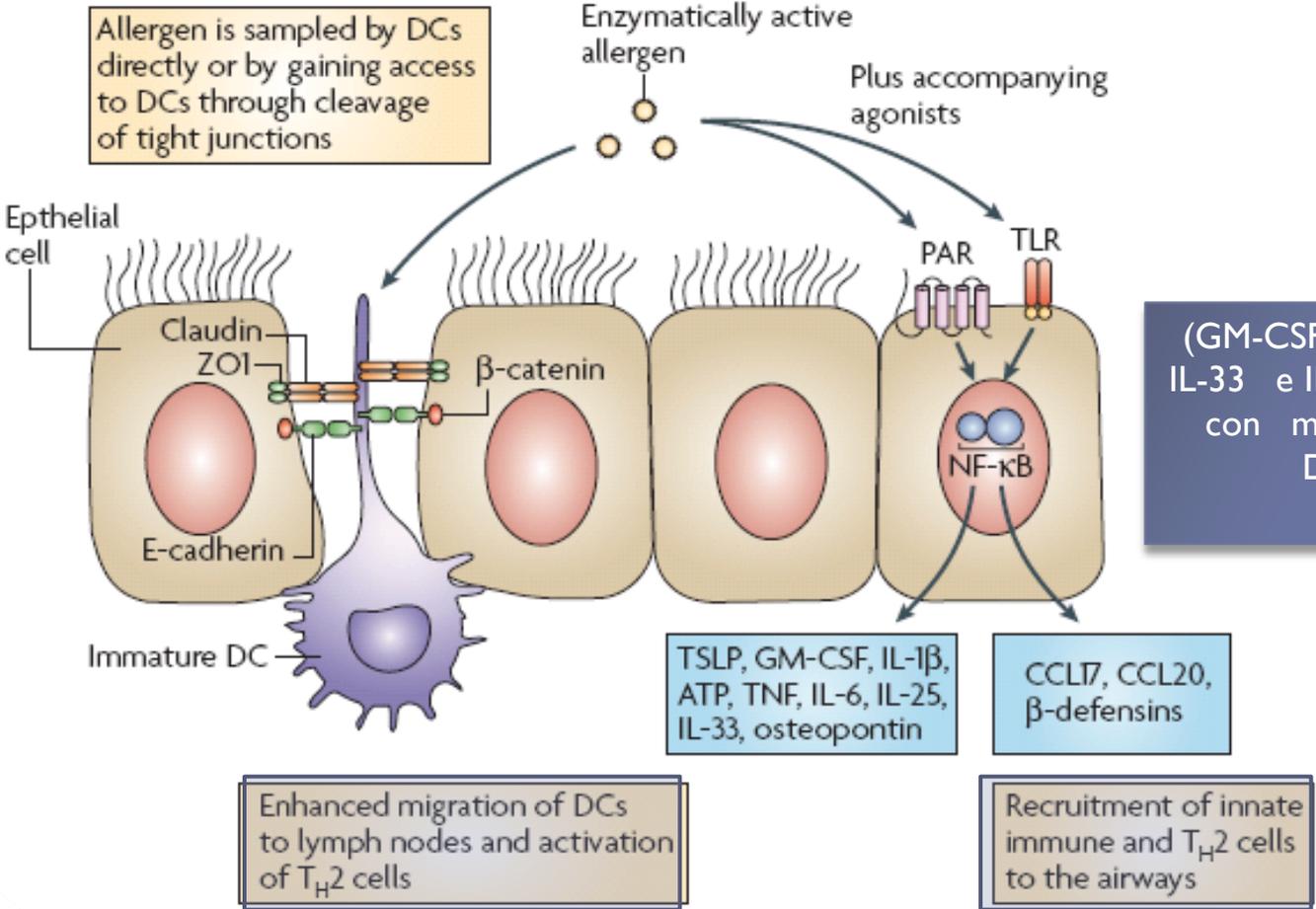


# HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma

- ▶ Células dendríticas responsables de la captura de Ag (fenotipo CD103+)
- ▶ Expresan además tight-junction proteins claudin-1, claudin-7 and zonula-2, le permite emitir digitación para la captura de Ag sin alterar la permeabilidad del epitelio



# Polarización de la respuesta inmune: Inmunopatogenia del asma



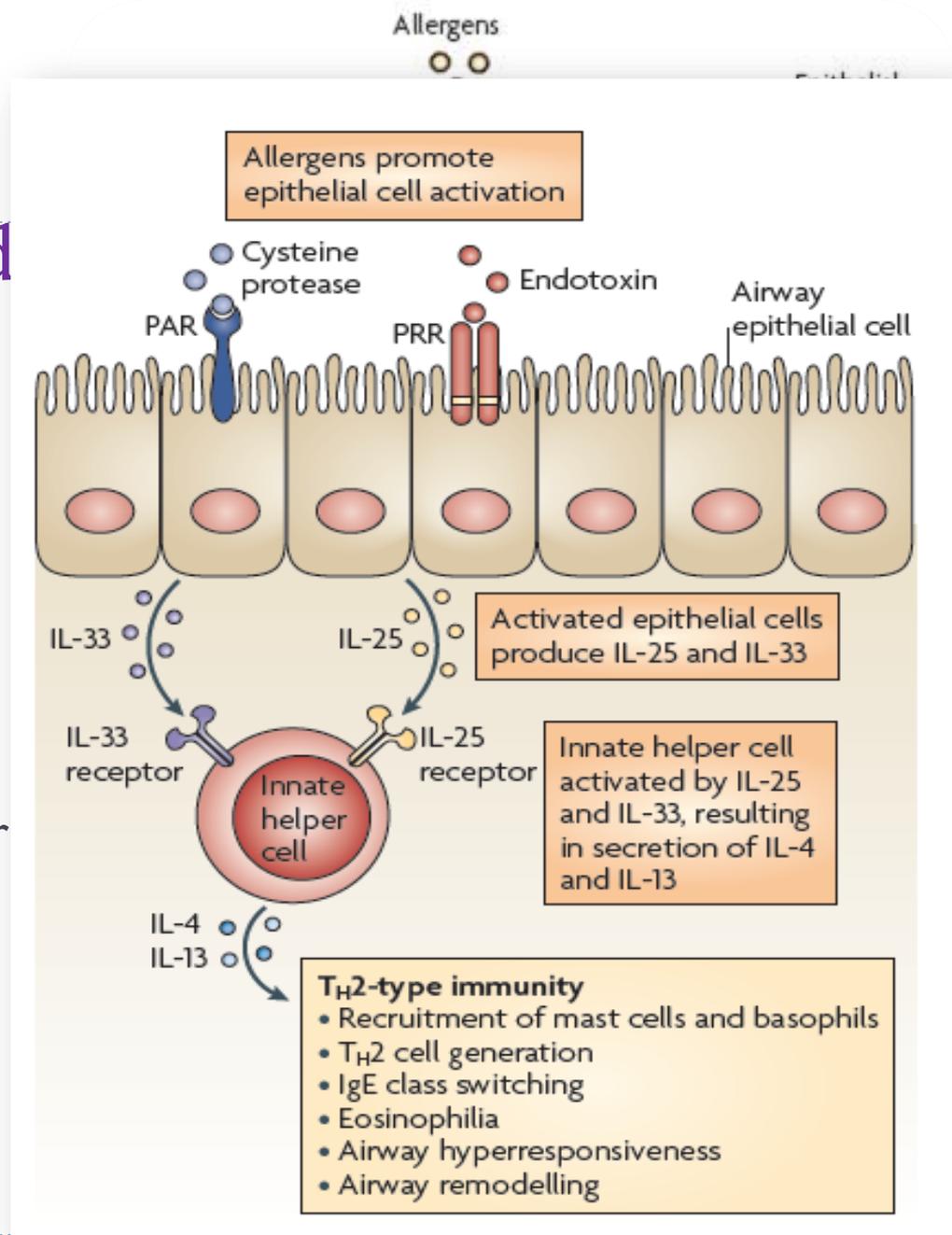
(GM-CSF, TSLP, IL-25, IL-33 e IL-1), contribuye con maduración de DCs y Th2

of TH2 cells to lymph nodes and activation

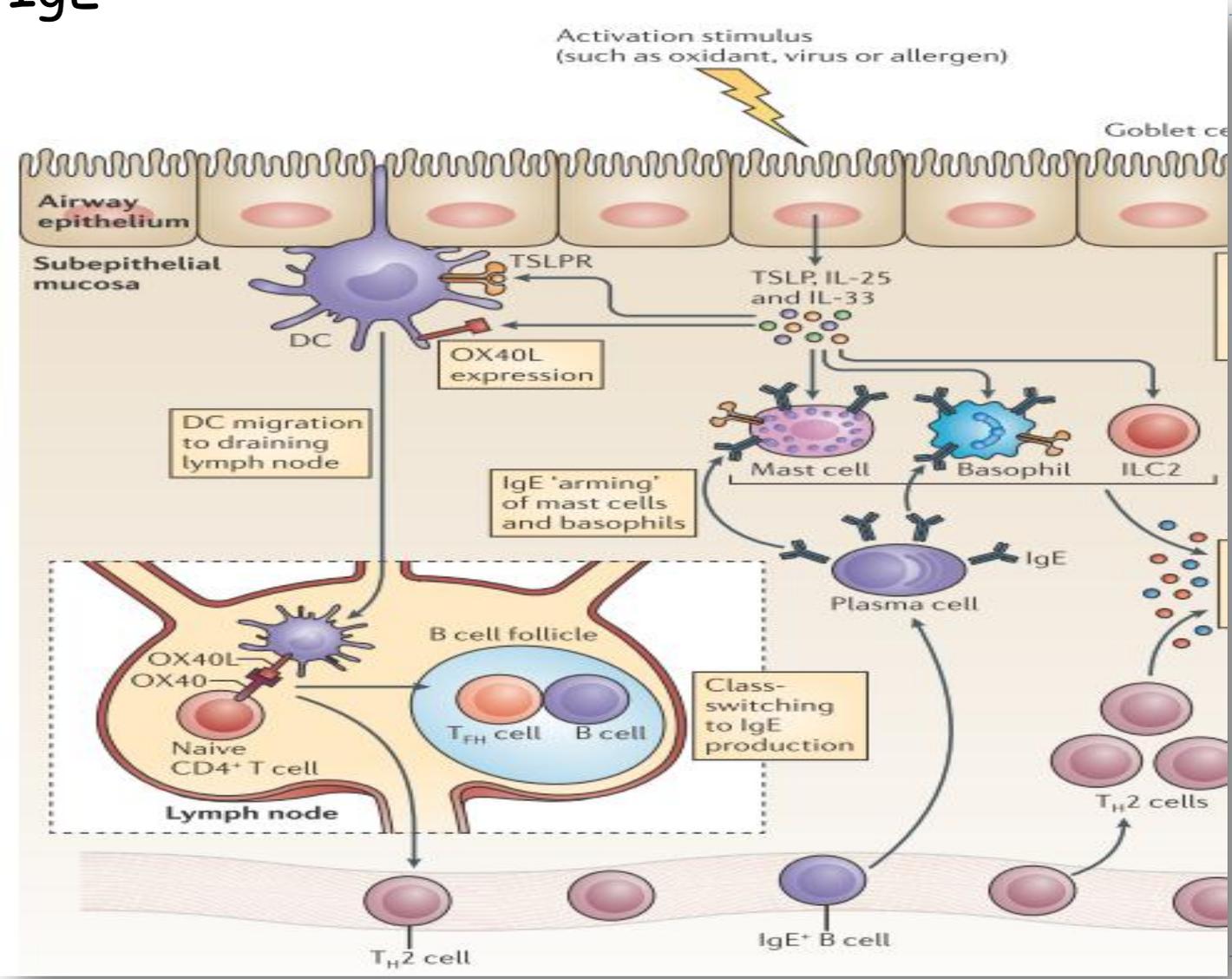
to the airways immune and TH2 cells

# Polarización de la respuesta inmune: Inmunopatogenia del asma

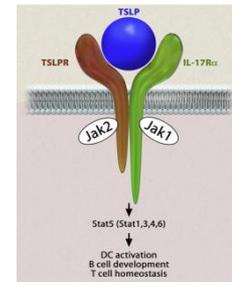
- ▶ Presentación antigénica
  - ▶ En presencia de TSLP (linfopoyetina del estroma tímico)
  - ▶ TSLP incrementa expresión e interacción OX40L, en DC
  - ▶ Activación de población Helper innata con patrón Th2
  - ▶ Desarrollo de respuesta Th2, ruptura de la tolerancia
  - ▶ Nueva población conocida como “**Células ayudadoras de la inmunidad innata de tipo 2**”



# Presentacion antigenica y cambio de isotipo IgE

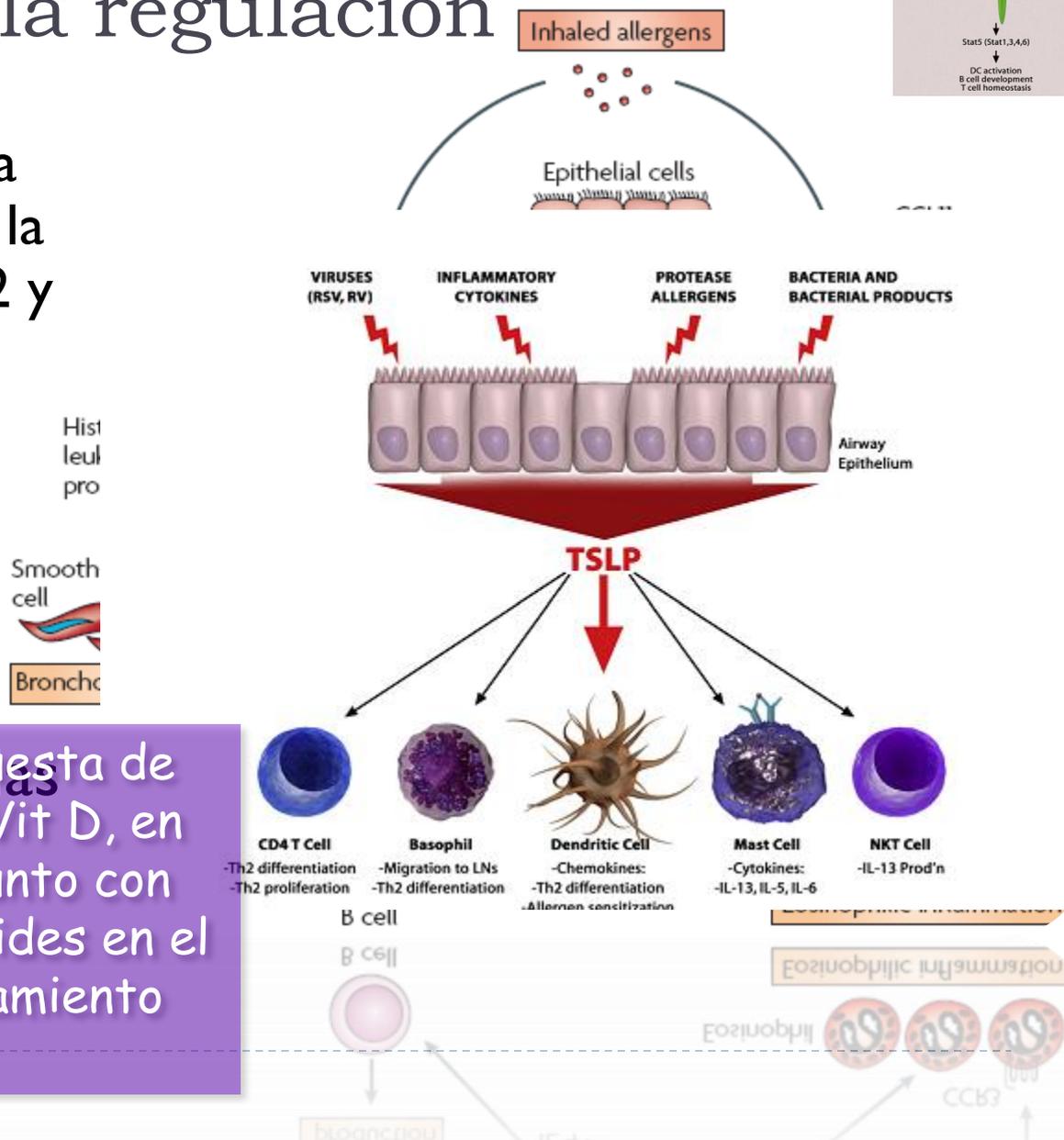


# Reclutamiento de células inflamatorias e inhibición de la regulación



- ▶ Linfopoyetina del estroma tímico (TSLP), conduce a la liberación de CCL17 y 22 y reclutamiento de Th2
- ▶ Células epiteliales liberan CCL11 que favorece reclutamiento de eosinófilos
- ▶ Defectos en el desarrollo de las células T reguladoras

Propuesta de usar Vit D, en conjunto con esteroides en el tratamiento

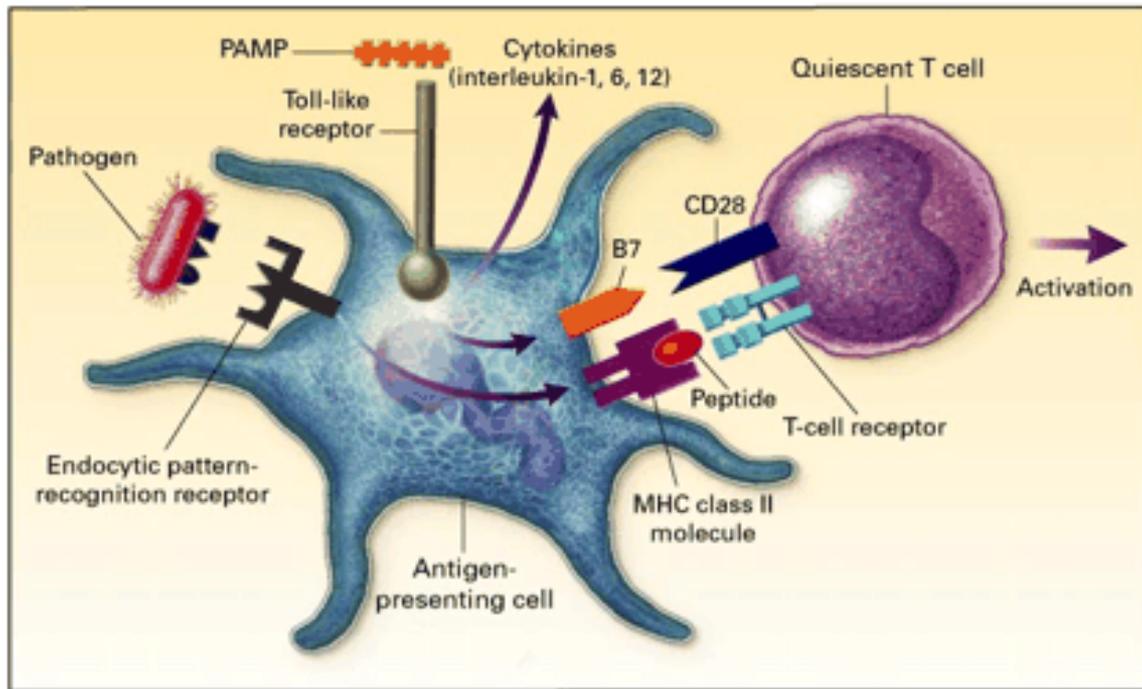


Hist  
leul  
pro

Smooth  
cell

Bronche

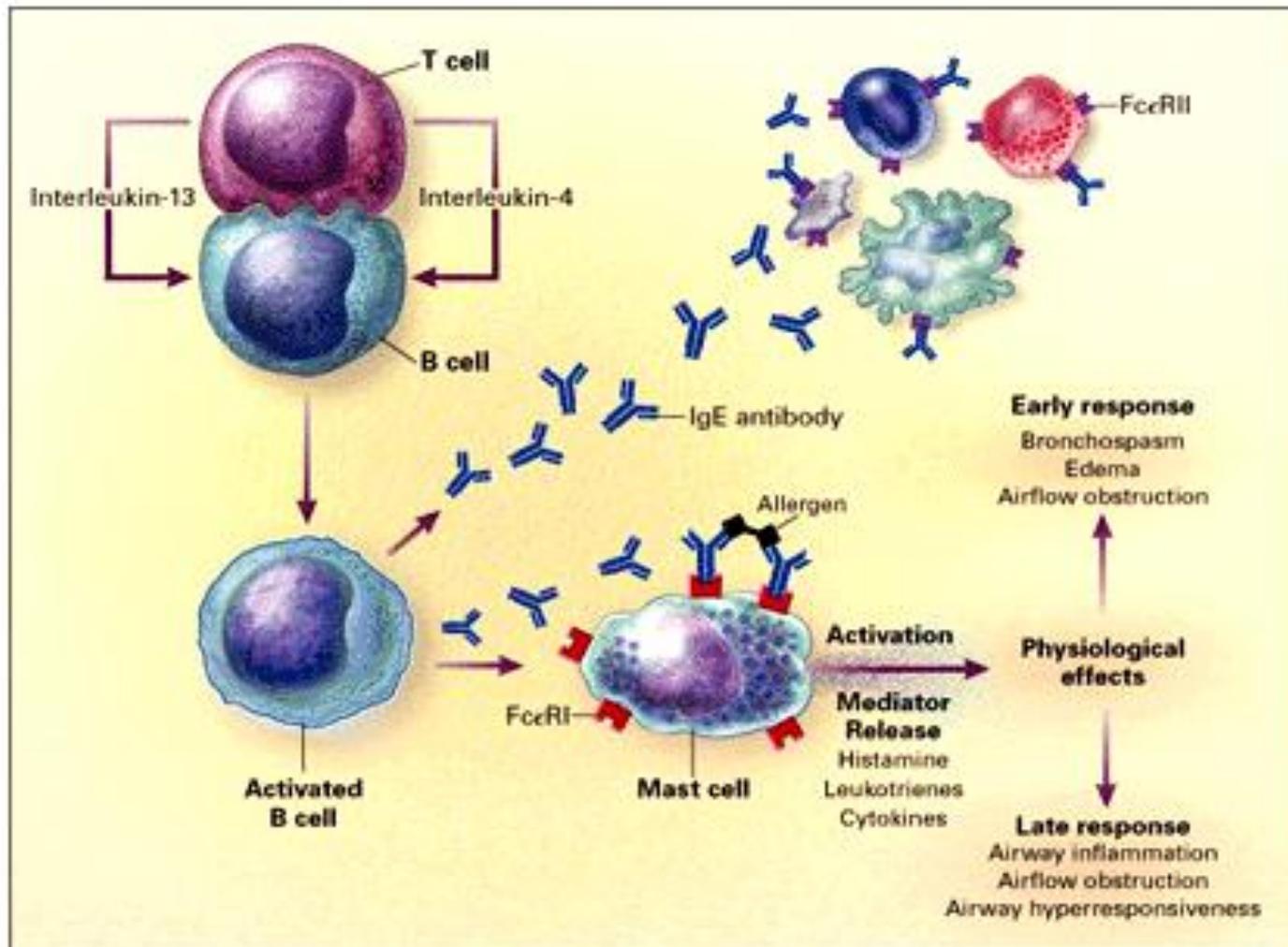
# HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma

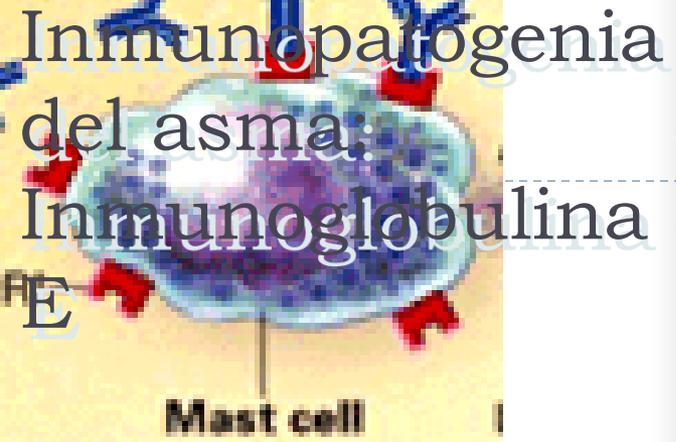


Polarización de la  
respuesta de tipo  $T_H2$

Activación de  
linfocitos B  
Cambio de isotipo de  
Inmunoglobulinas  
hacia IgE  
Generación de célula B  
de memoria y células  
plasmáticas

# HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma



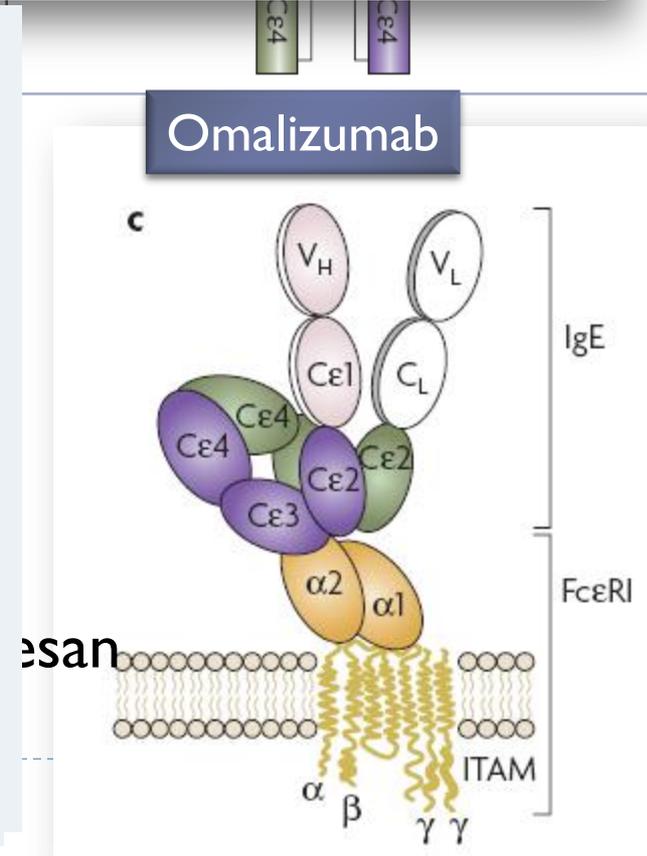


**TABLA III**  
EVOLUCIÓN DE LOS PACIENTES ASMÁTICOS SEGÚN EL GRUPO TERAPÉUTICO DE ACUERDO CON EL GRADO CLÍNICO Y EL ÍNDICE DE FRECUENCIA AL INGRESO, A LOS 3 Y A LOS 6 MESES DE TRATAMIENTO

	GRUPO A		GRUPO B		GRUPO C	
	GC	IF	GC	IF	GC	IF
Ingreso	3,28 (0,48)	15,6 (10)	3,16 (0,40)	9,2 (4,70)	3,16 (0,40)	15,5 (4,10)
3 Meses	2,14** (0,89)	2,8* (1,78)	1,66* (1,36)	1,66* (0,98)	1,88** (0,98)	1,66** (0,98)
6 Meses	0	0	0,66 (1,21)	0,80 (1,78)	1,00 (1,54)	0,66 (1,03)

Las cifras entre paréntesis corresponden a la desviación estándar. \*p<0,05. \*\*p<0,01.

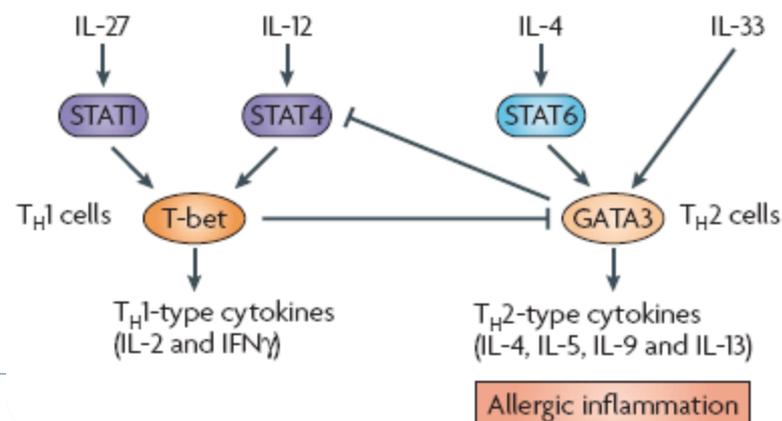
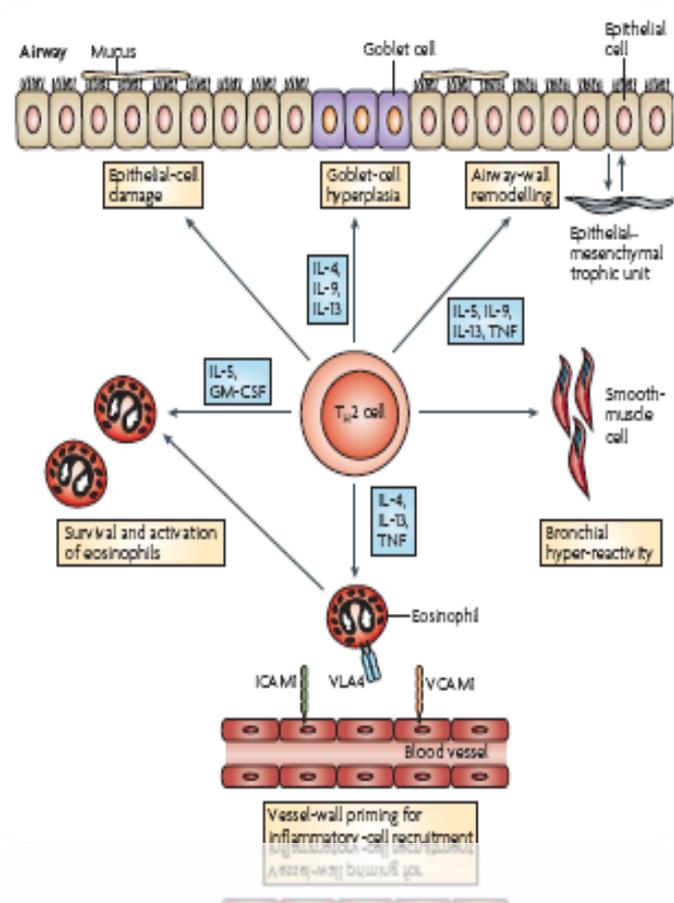
Fc RI expresado por los mastocitos y basófilos, media la desgranulación celular, la producción de eicosanoides y citocinas



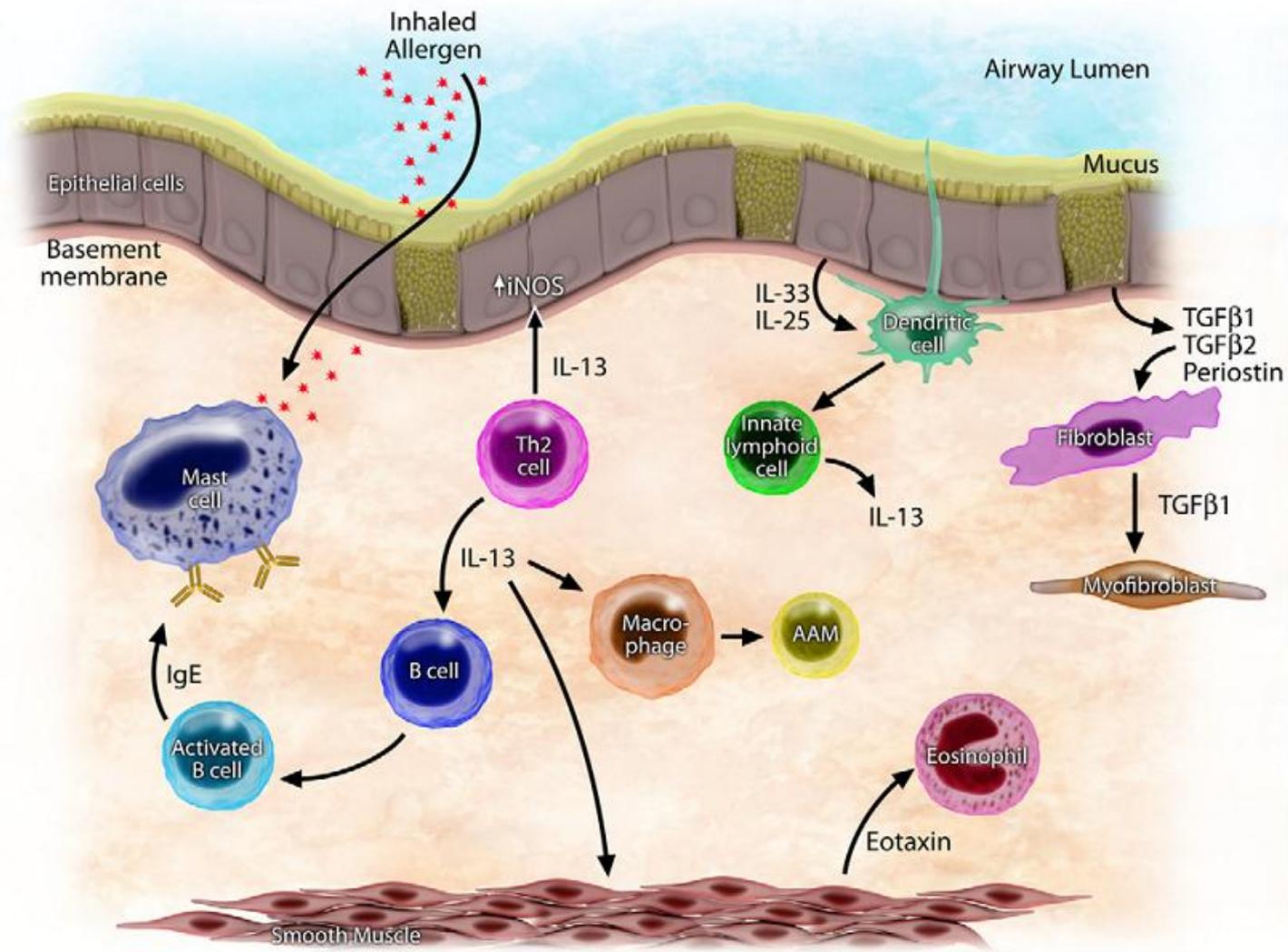
# HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma

## ▶ Linfocitos Th2

- ▶ Mediano reclutamiento y sobrevida de eosinófilos y mastocitos
- ▶ Hiperplasia de las células de goblet
- ▶ Hiperactividad bronquial asociado con la liberación de IL-9 e IL-13 que incrementan la excitabilidad del músculo liso bronquial
  - ▶ Resultado broncoconstricción por estímulos no específicos como el frío, o el ejercicio

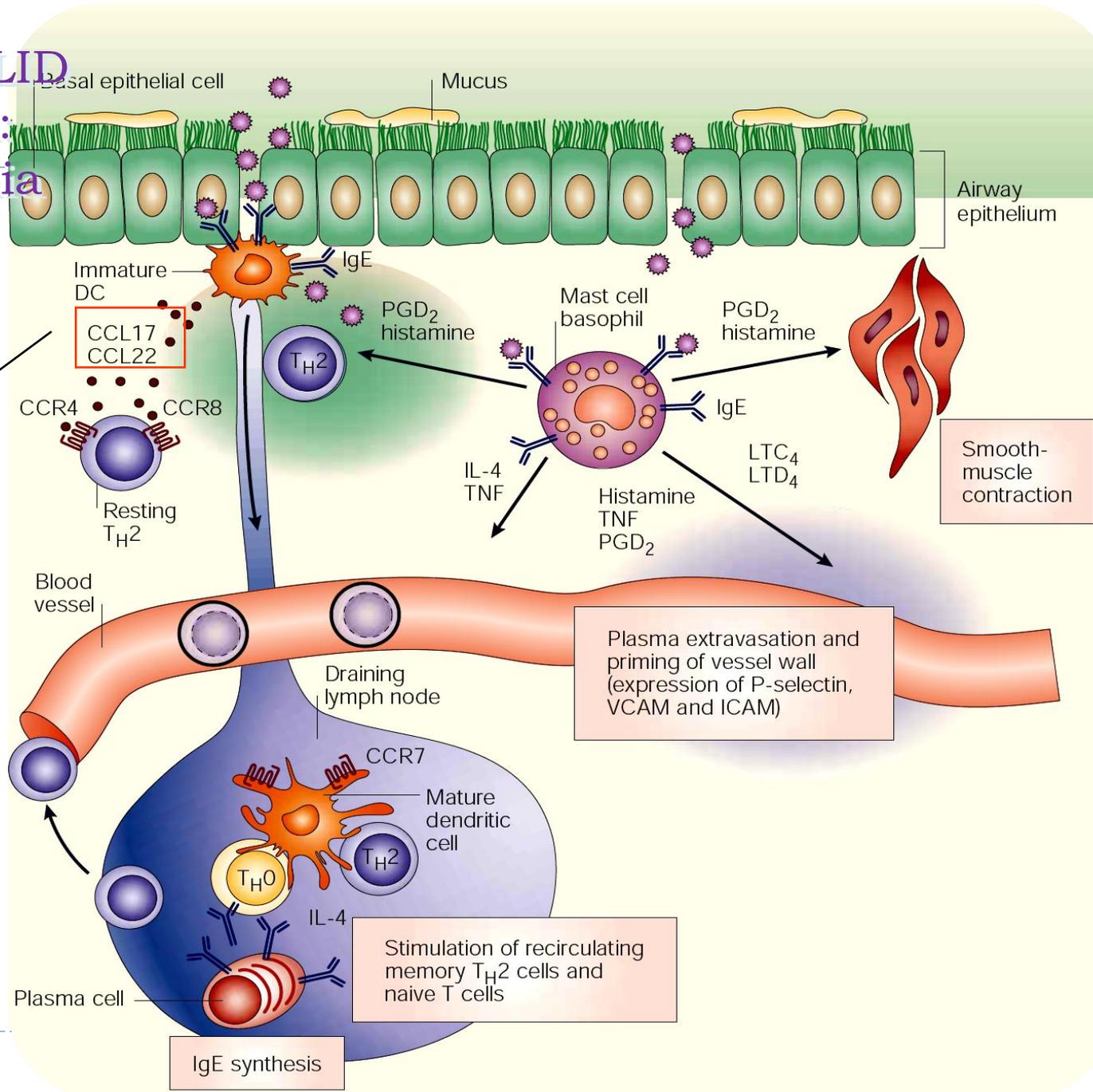


# Mecanismos de Inflamación eosinofílica inducida por interleukinas TH2



filos  
ial

# HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma



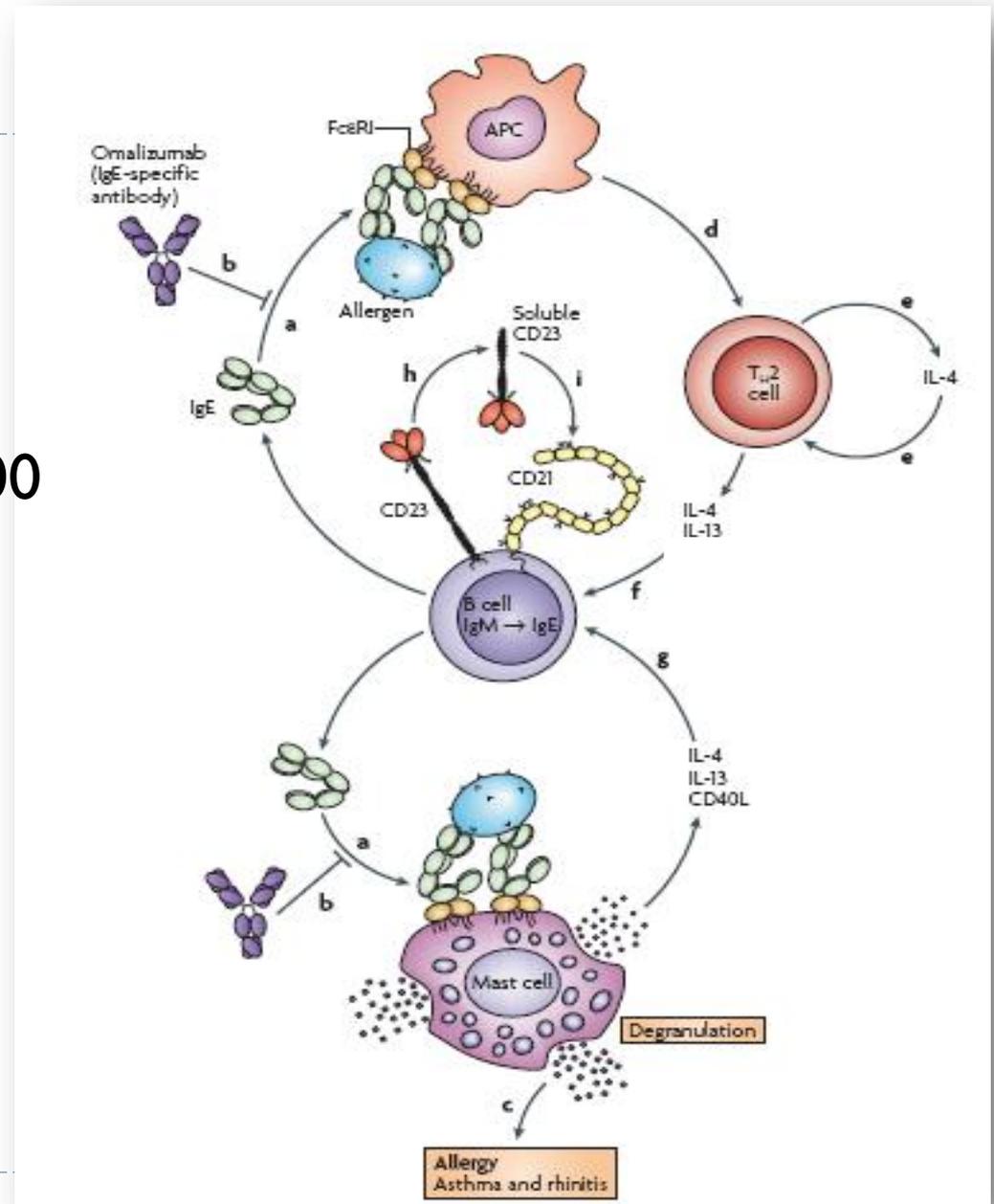
Reclutamiento de Th2 de memoria (CCL17, CCL18, CCL22)

Segundo encuentro con el alergen



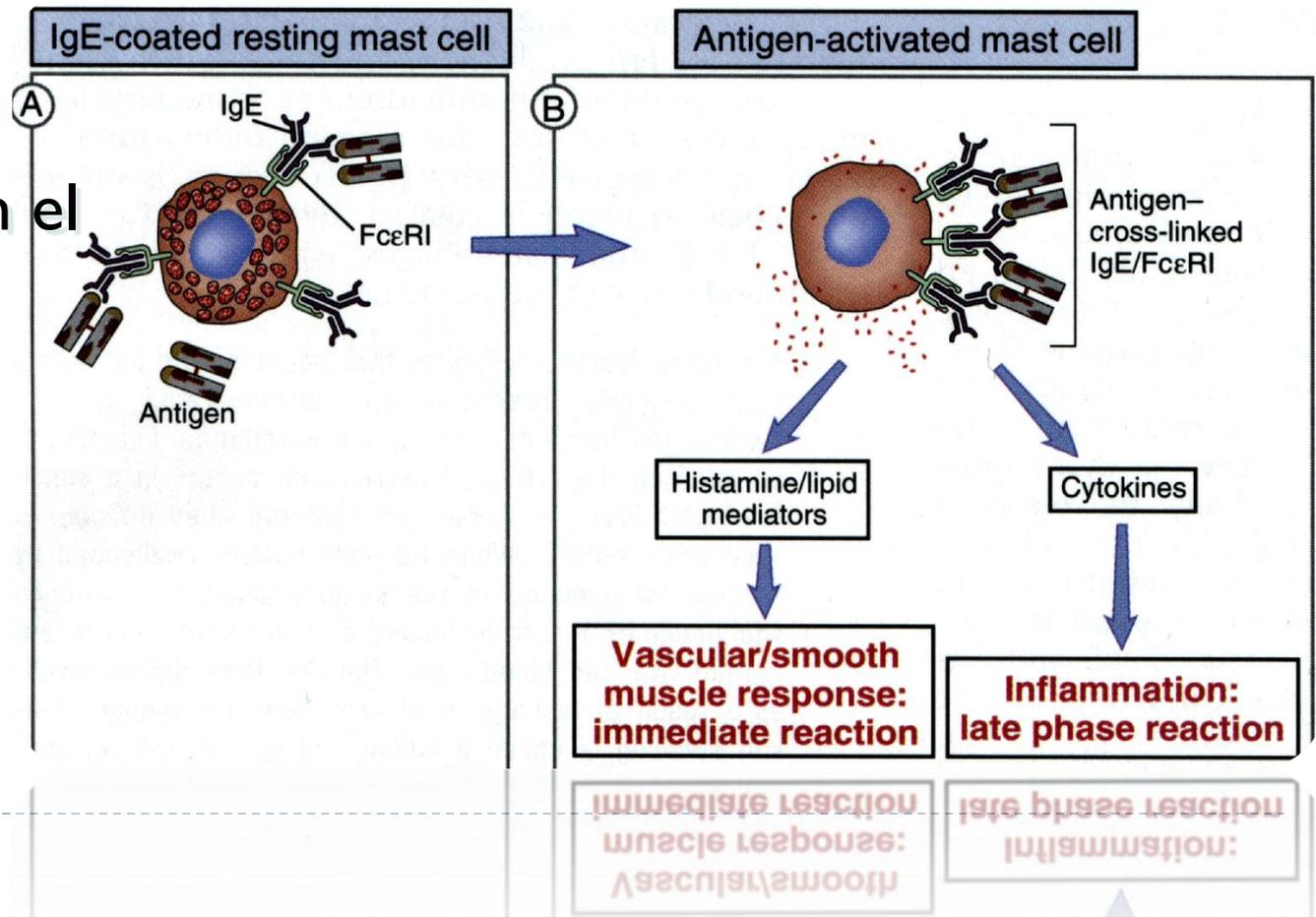
# Mastocitos sensibilizados

- ▶ Un mastocito expresan aproximadamente 500000 receptores Fce en su superficie

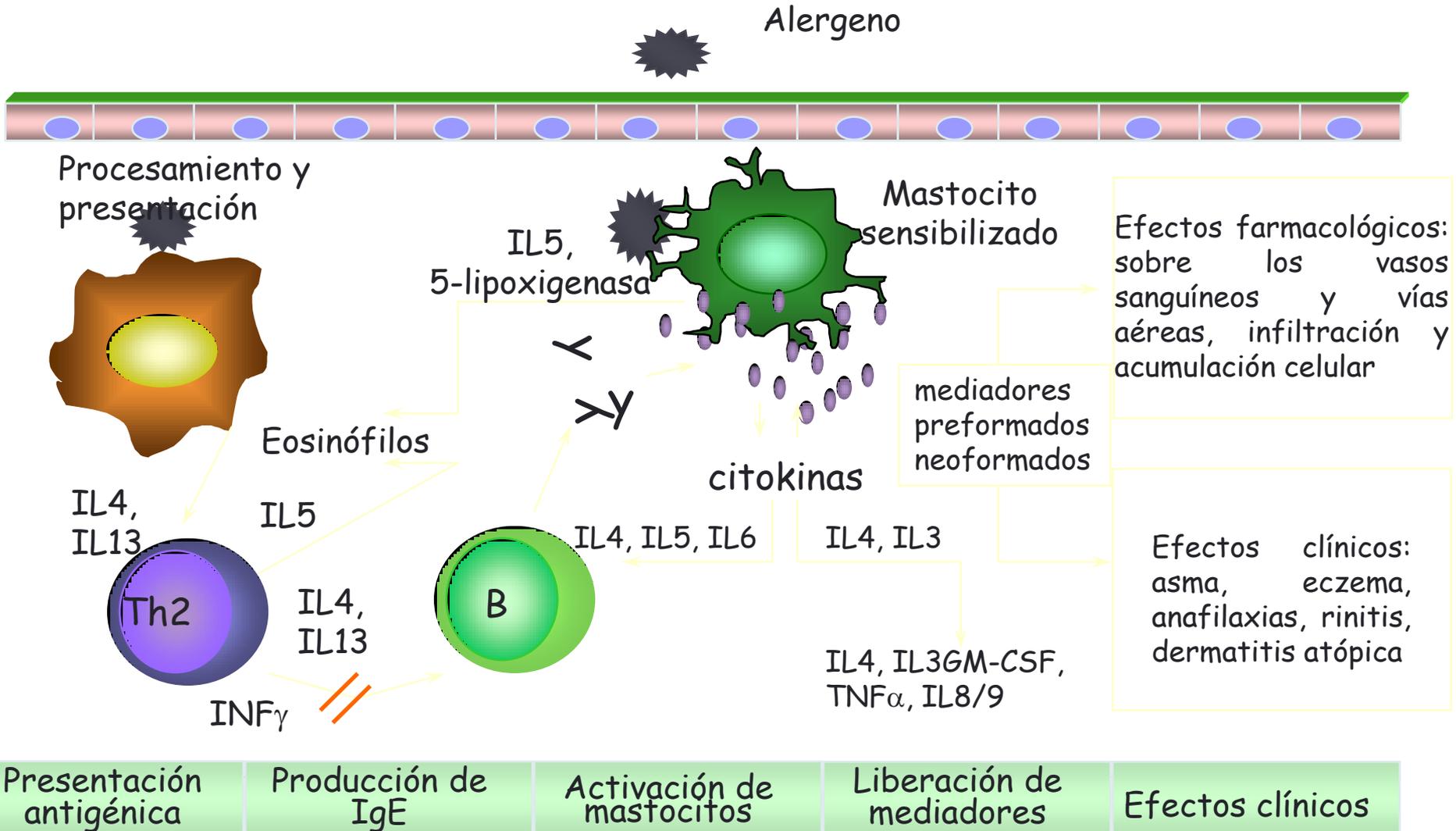


# HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma

- ▶ Segundo encuentro con el alérgeno



# Inmunopatogenia del asma: RESPUESTA INFLAMATORIA



Presentación antigénica	Producción de IgE	Activación de mastocitos	Liberación de mediadores	Efectos clínicos
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# Inmunopatogenia del asma: Participación de los Mastocitos

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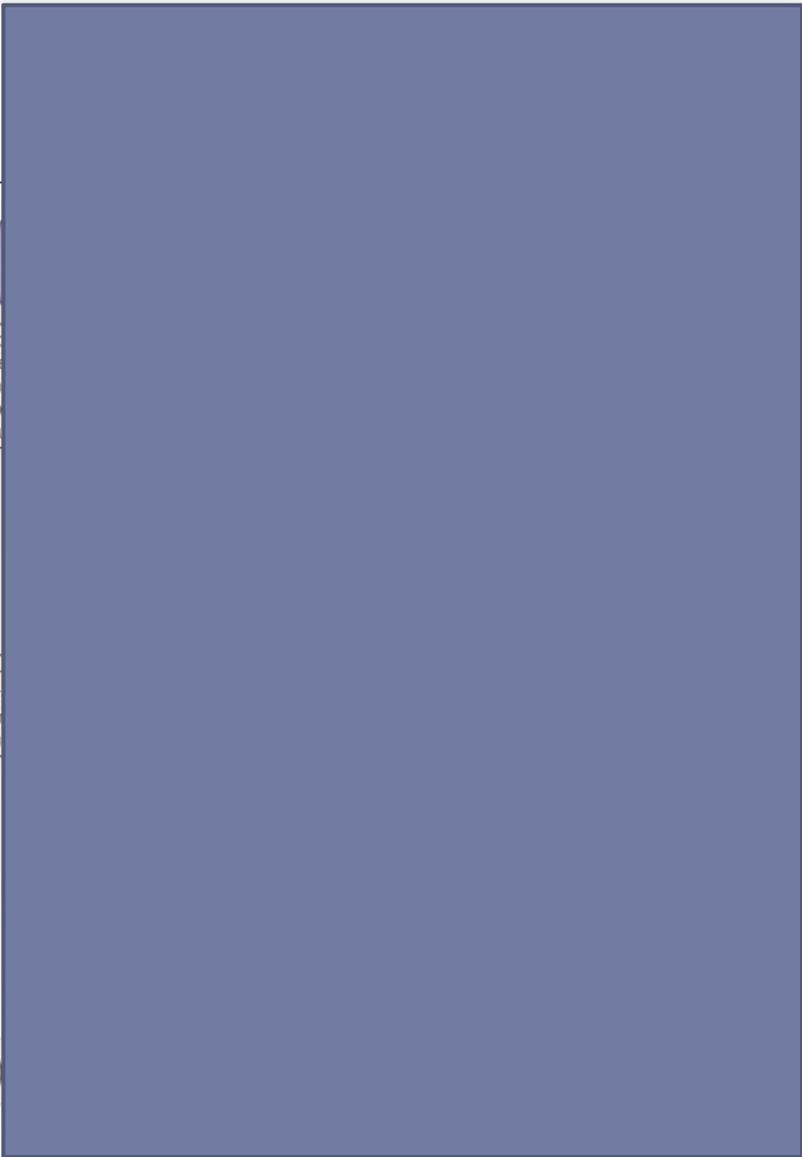
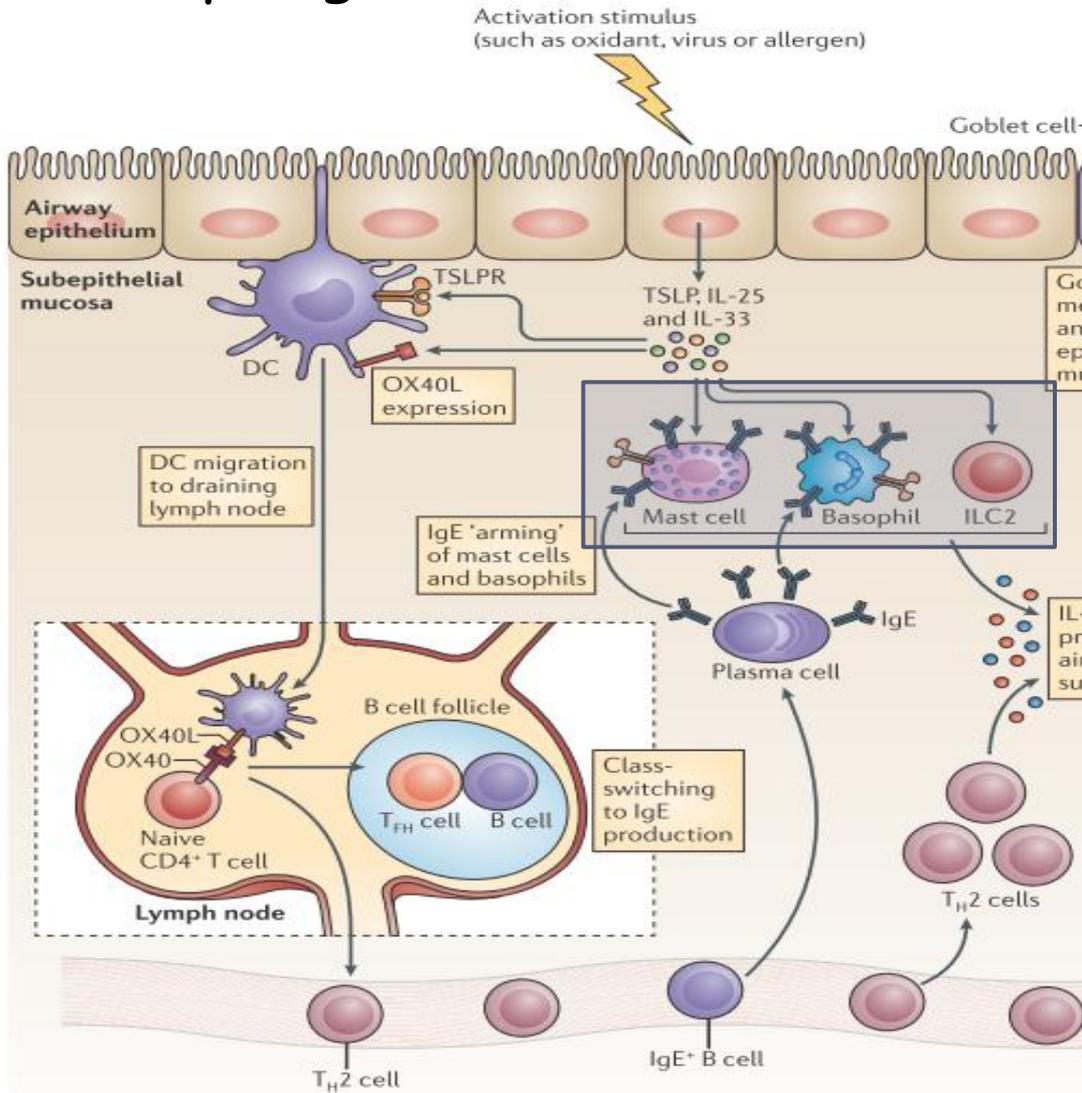
- ▶ Degranulación de mastocitos
  - ▶ Entrecruzamiento de receptores FcεRI
  - ▶ C3a
  - ▶ ACTH, codeína, morfina, sustancia P
- ▶ Mediadores preformados
- ▶ Mediadores neoformados



# Inmunopatogenia del asma: Participación de los leukotrienos

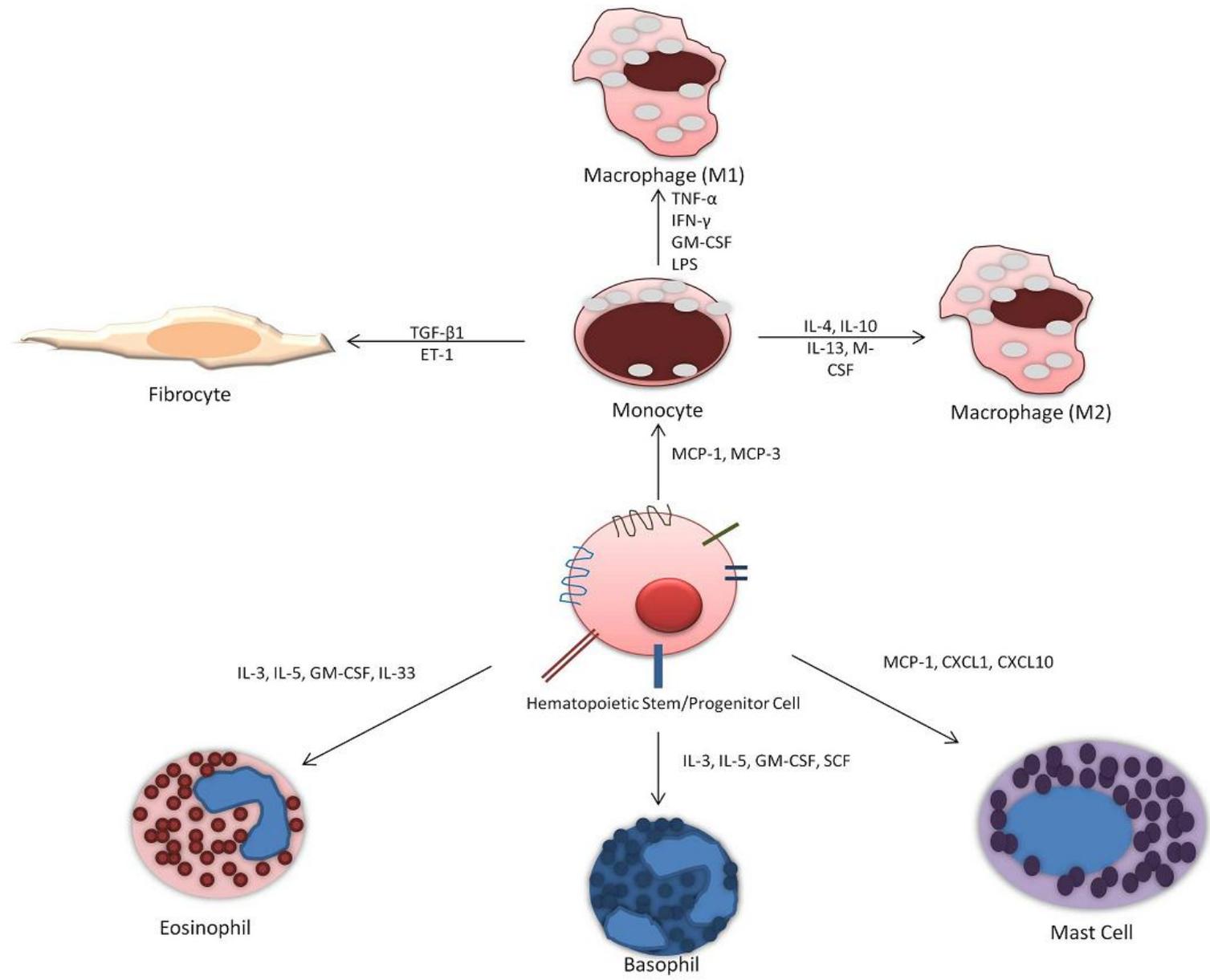


# Presentacion antigenica y cambio de isotipo IgE



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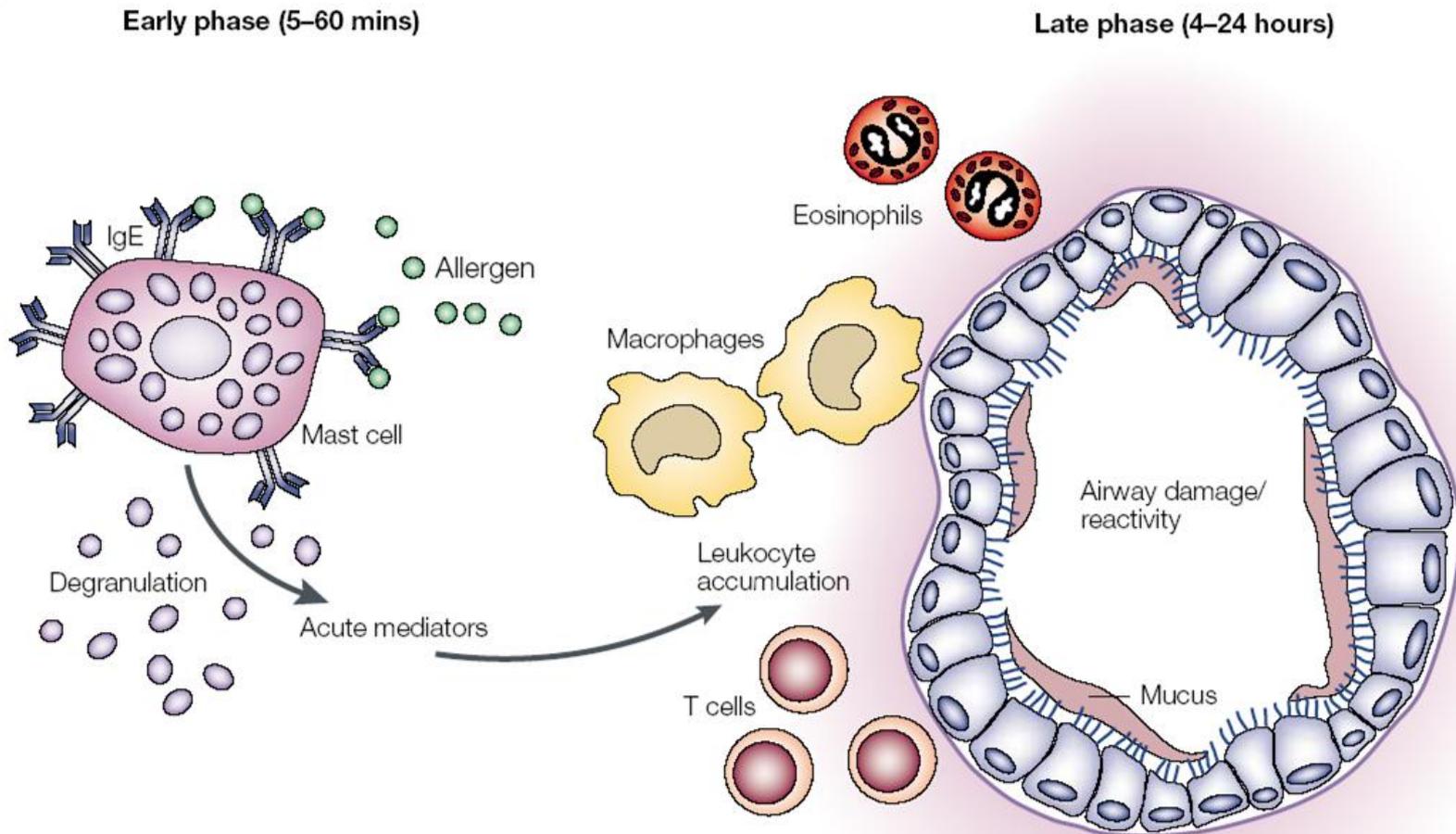
▶ HS  
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**FIGURE 2 | Differentiation of hematopoietic progenitor cells into immune cells: HSPCs can potentially differentiate into distinct immune cells *in situ* depending on the presence of locally elevated factors and cytokines.**

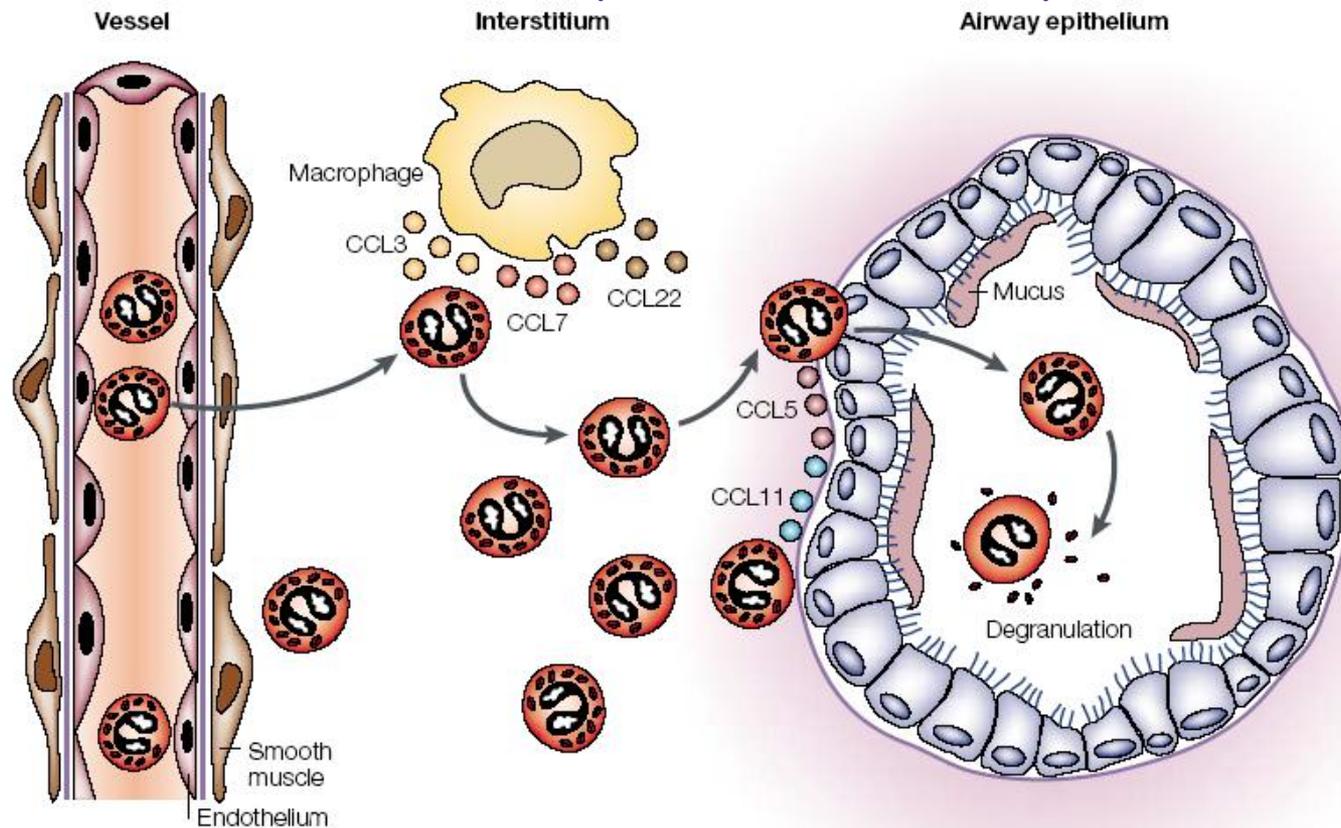
# HIPERSENSIBILIDAD INMEDIATA:

## Inmunopatogenia del asma



# Inmunopatogenia del asma: participación de las quemokinas

Principales Fuentes: Células epiteliales y los  
macrófagos alveolares  
Reclutan eosinófilos y linfocitos de patrón Th2



# Inmunopatogenia del asma:

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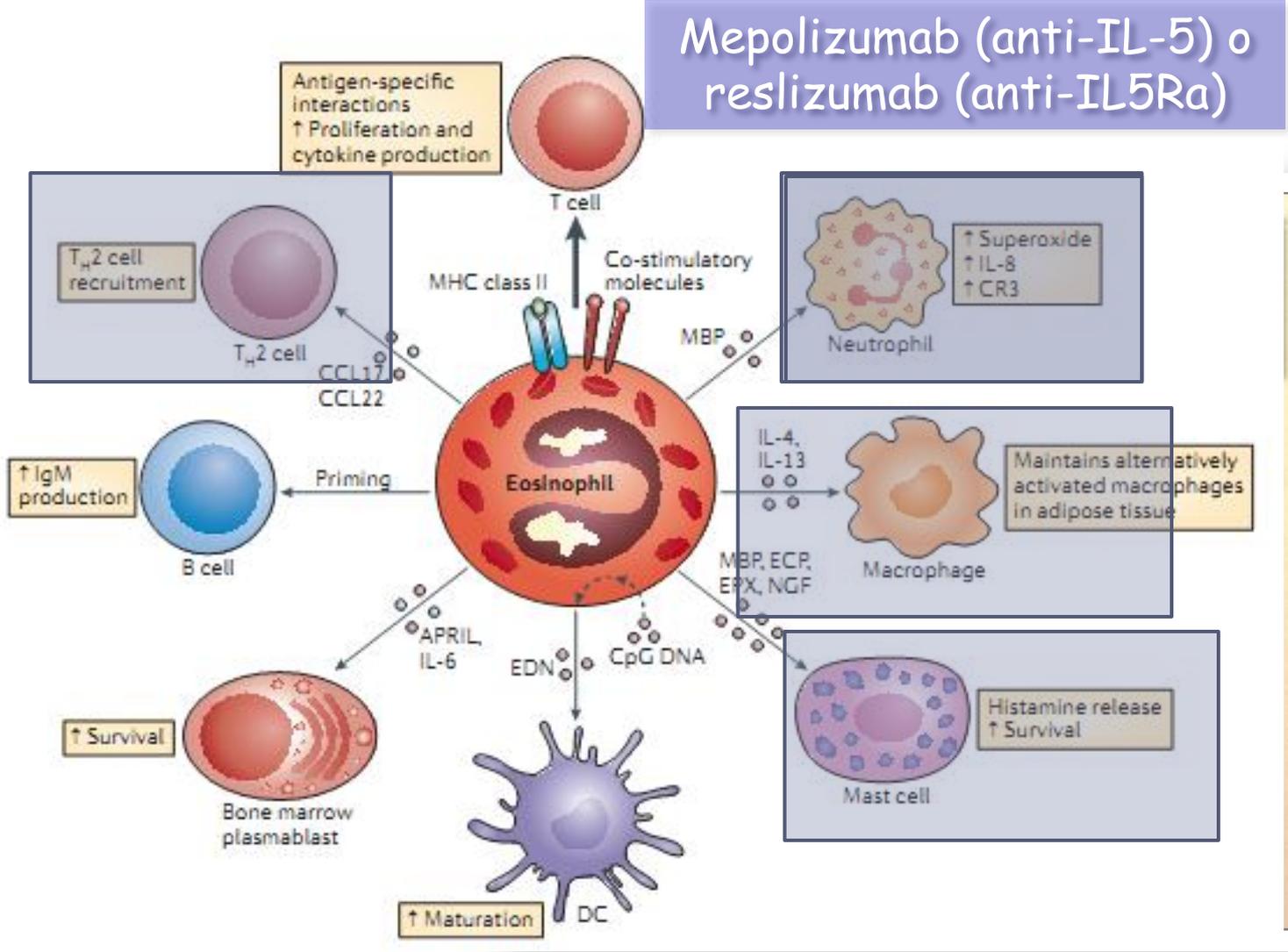
## Respuesta inflamatoria

- ▶ 2 a 4 horas y máxima a las 24 horas:
  - ▶ Acúmulo de Neutrófilos, eosinófilos, basófilos y células T CD4+ (fundamentalmente Th2)
  - ▶ TNF liberado por los mastocitos incrementa la expresión de moléculas de adhesión en células endoteliales:
    - ▶ E-selectin e ICAM



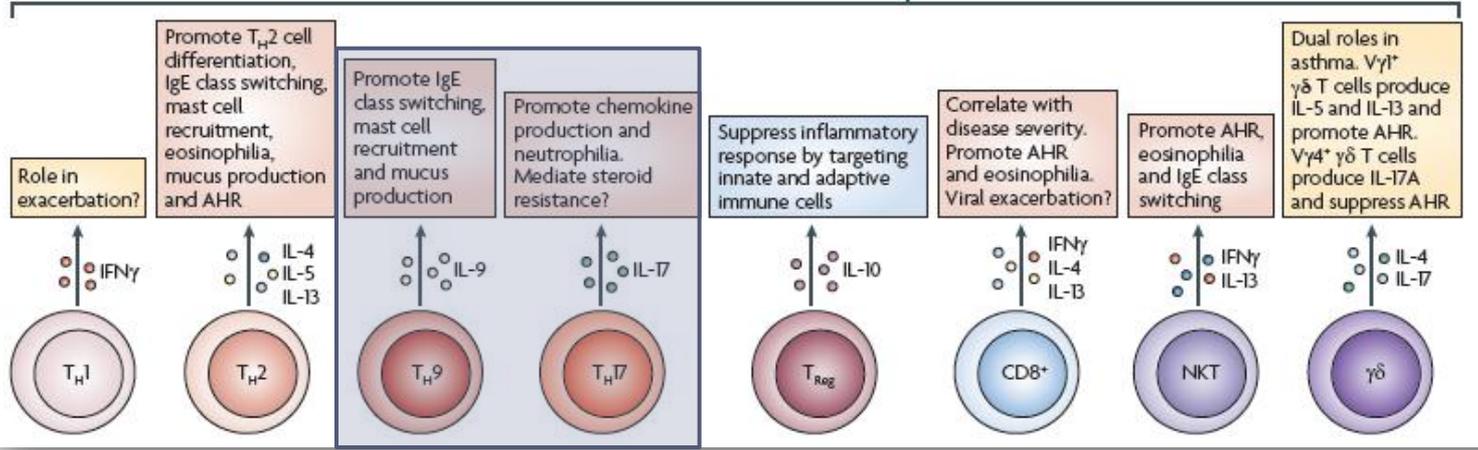
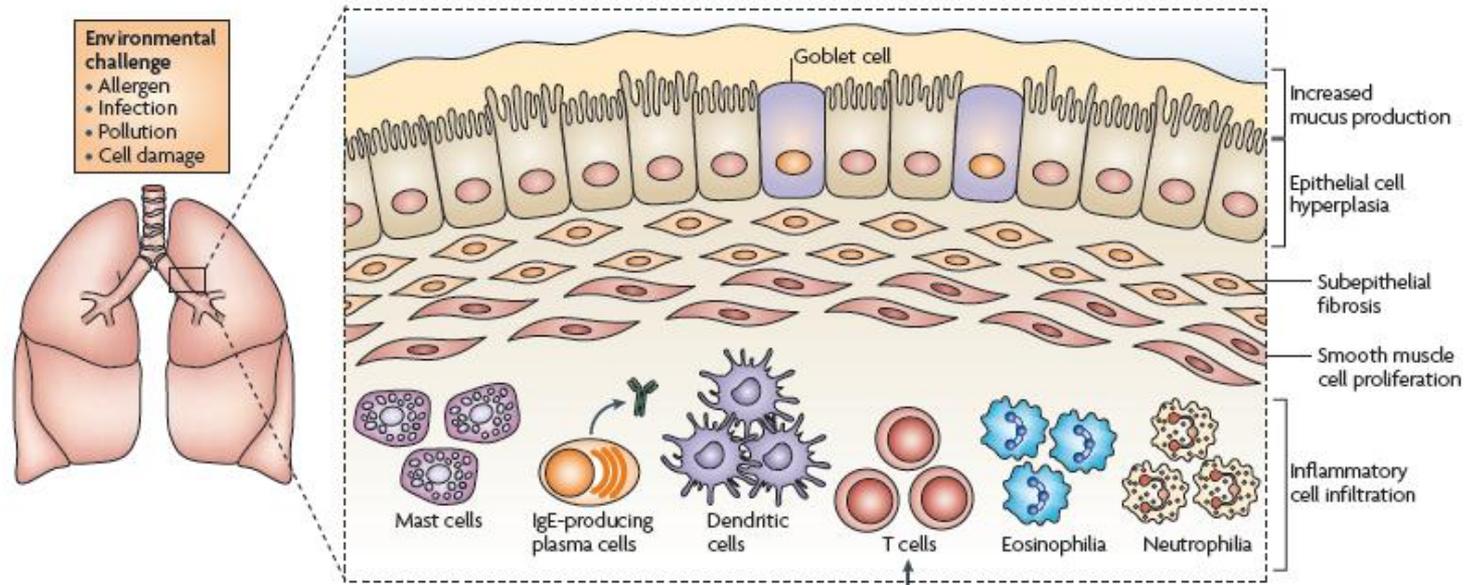
# Inmunopatogenia del asma: EOSINOFILOS

- ▶ Eosinofilia
- ▶ Respuesta
- ▶ Atracción
- ▶ CCL2
- ▶ IL-5 factor
- ▶ y citoquinas
- ▶ TSLP
- ▶ expresión
- ▶ Proteína
- ▶ de membrana
- ▶ nerviosa
- ▶ Hipersensibilidad
- ▶ Oxidativa



# Reclutamiento de células pro-inflamatorias

- ▶ Pacientes con asma severa cursan con infiltración de neutrófilos, mediado por TH17
- ▶ TH17 media resistencia a los esteroides



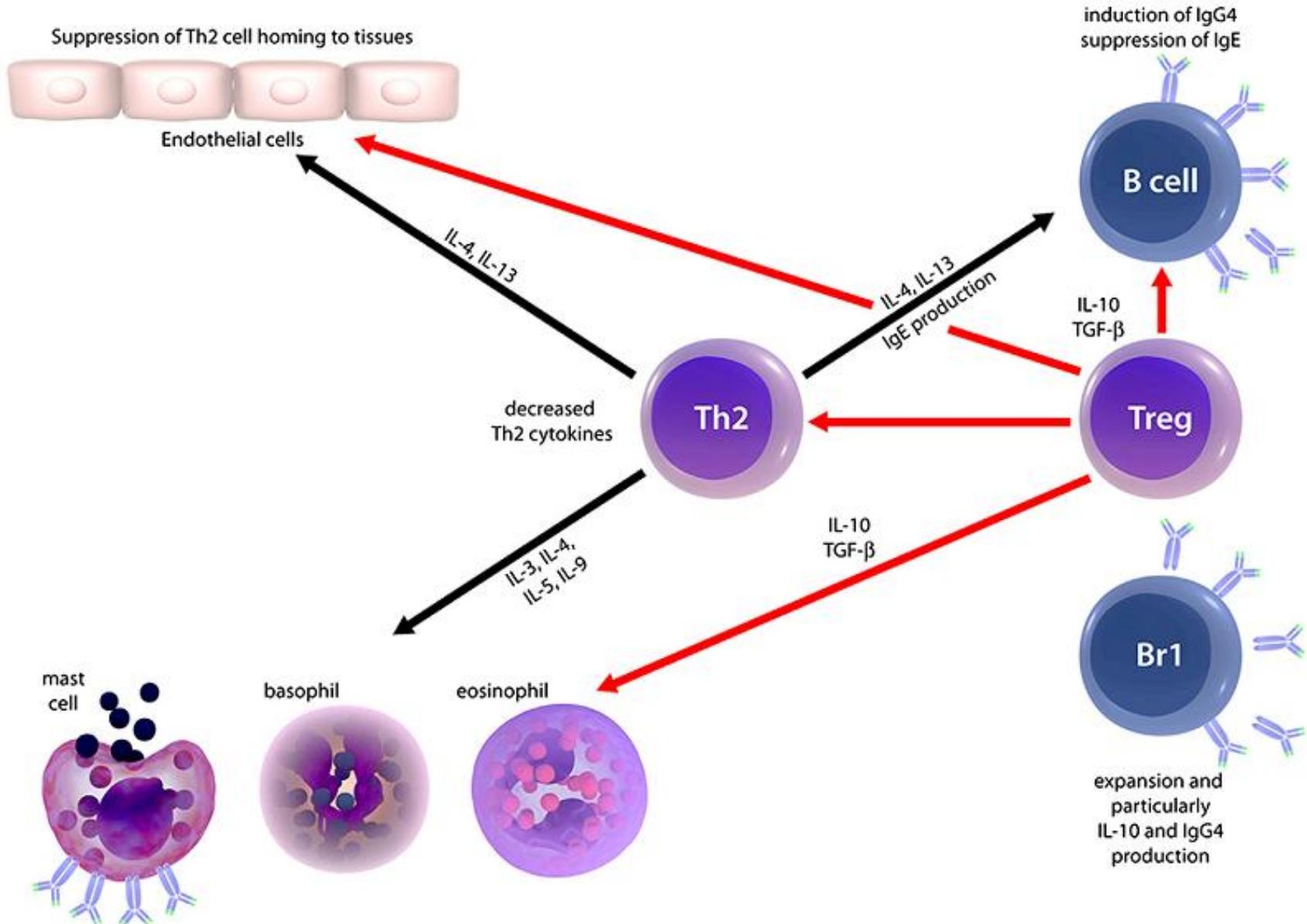
# Terapia biológica e inmunoterapia

Table 1 | Summary of available data from trials of treatments directed at type 2 inflammation in asthma\*

Therapeutic antibody	Isotype	Targeted epitope	Relative affinity	Main effects in human asthma trials
Omalizumab (Genentech/Roche and Novartis)	Humanized IgG1	IgE (CH2 and CH3 domains)	0.06 nM <sup>78</sup>	Decrease in asthma exacerbation rates and reductions in maintenance doses of oral corticosteroids <sup>36,37</sup> . Small effects on FEV1 and asthma symptoms.
Mepolizumab (GlaxoSmithKline)	Humanized IgG1	IL-5	NA	Decrease in asthma exacerbation rates when used to treat patients with asthma who have persistent eosinophilia despite corticosteroid treatment <sup>27-29</sup> .
Benralizumab (MedImmune/AstraZeneca)	Humanized IgG1	IL-5R $\alpha$	NA	Decrease in asthma exacerbation rates when used to treat patients with asthma who have persistent eosinophilia despite corticosteroid treatment <sup>45</sup> .
Reslizumab (Teva Pharmaceutical Industries)	Humanized IgG4	IL-5	20 pM	Improvements in airway function and a trend towards greater asthma control when used to treat patients with asthma who have persistent eosinophilia despite corticosteroid treatment <sup>46</sup> .
Lebrikizumab (Genentech/Roche)	Human IgG4	IL-13 (IL-4R $\alpha$ -binding epitope)	<10 pM <sup>79</sup>	No effect on FEV1 in steroid-naïve individuals with asthma <sup>47</sup> . Improvements in FEV1 and asthma exacerbations in steroid-treated patients with moderate and severe asthma <sup>48</sup> . Greatest effects in patients with high serum periostin levels.
GSK679586 (GlaxoSmithKline)	Human IgG1	IL-13R $\alpha$ 1 and IL-13R $\alpha$ 2	300–400 pM <sup>80</sup>	No improvement in FEV1 or exacerbations in patients with moderate to severe asthma.
Tralokinumab (MedImmune/AstraZeneca)	Human IgG4	IL-13R $\alpha$ 1 and IL-13R $\alpha$ 2	165 pM <sup>81</sup>	Limited effects on FEV1 but effective in reducing asthma exacerbations. Greatest effects in patients with high serum periostin levels.
Dupilumab (Regeneron Pharmaceuticals)	Human IgG4	IL-4R $\alpha$	NA	Maintenance of asthma control and FEV1 when corticosteroid dose is tapered in patients with moderate to severe asthma <sup>30</sup> . Effects are greatest in patients with high blood eosinophil levels.

\*The table is restricted to data from Phase II trials or beyond. FEV1, forced expired volume in 1 second; IL, interleukin; IL-5R $\alpha$ ,  $\alpha$ -chain of the IL-5 receptor; NA, not applicable.

# Papel de la inmunoterapia



# Perspectivas futuras



## Novel immunotherapy vaccine development

Marek Jutel<sup>a,b</sup> and Cezmi A. Akdis<sup>c</sup>

Curr Opin Allergy Clin Immunol 2014, 14:557-563

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Review

Vitamin E and D regulation of allergic asthma immunopathogenesis <sup>☆</sup>

Joan M. Cook-Mills <sup>\*</sup>, Pedro C. Avila

Allergy-Immunology Division, Northwestern University Feinberg School of Medicine, Chicago, IL, United States



*Current perspectives*

**Worms as therapeutic agents for allergy and asthma:  
Understanding why benefits in animal studies have not  
translated into clinical success**

Holly Evans, BS, and Edward Mitre, MD *Bethesda, Md*

(J Allergy Clin Immunol 2014; nnn : nnn - nnn .)

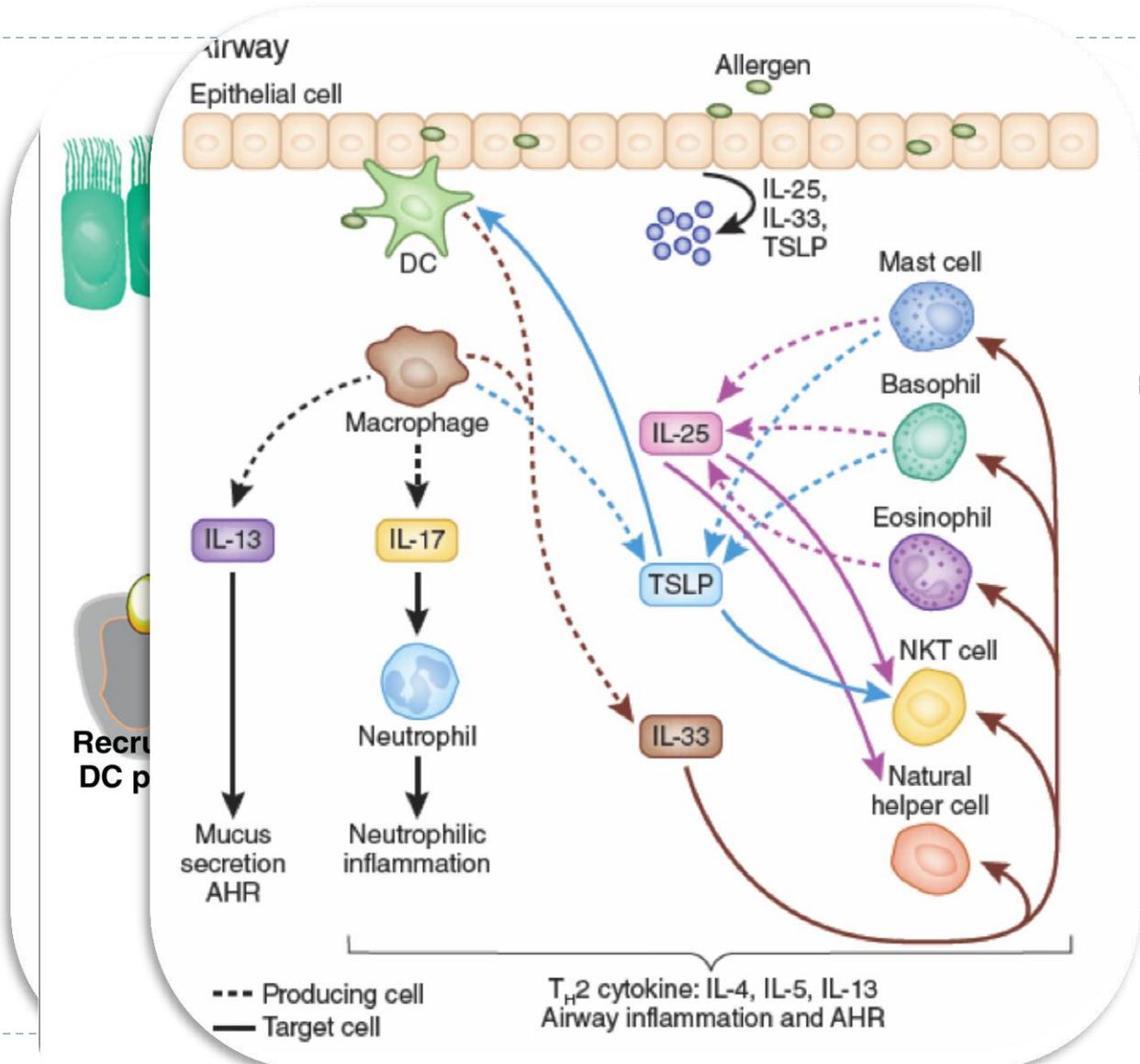
# Inmunopatogenia del asma: Resumen

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- ▶ Individuo genéticamente predispuesto
- ▶ Alergenos
- ▶ Producción de IgE por el linfocito B durante el primer contacto
- ▶ Unión de la IgE a los receptores Fc $\epsilon$  en mastocitos y basófilos
- ▶ Reintroducción del Ag y entrecruzamiento de los receptores sobre los mastocitos
- ▶ Liberación de mediadores inflamatorios y reclutamiento de células (eosinófilos)
- ▶ Manifestaciones clínicas

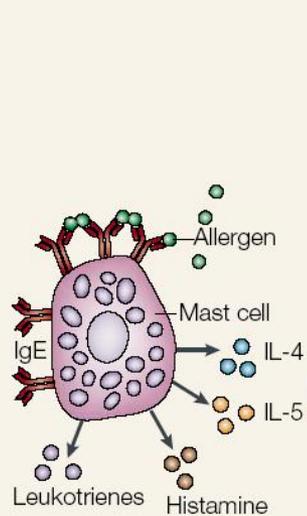


# Inmunopatogenia del Asma: RESUMEN

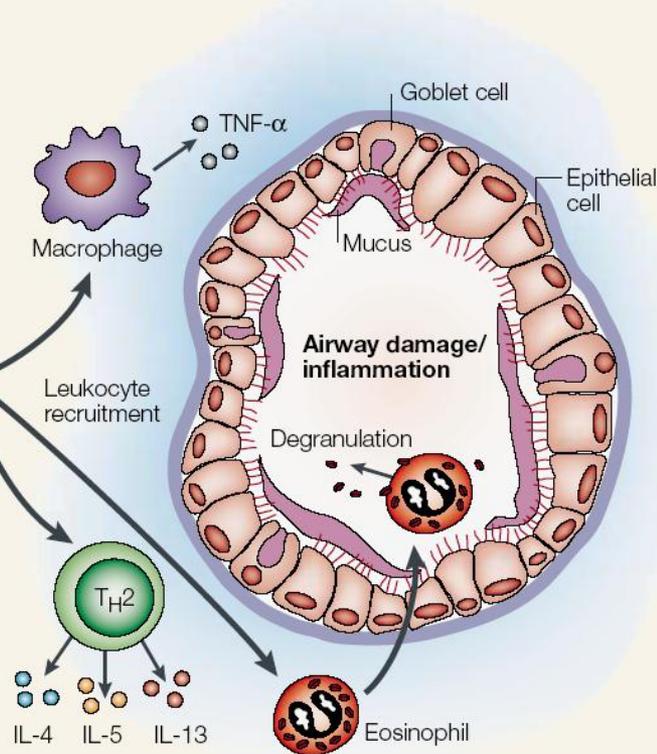


# Inmunopatogenia del Asma: RESUMEN

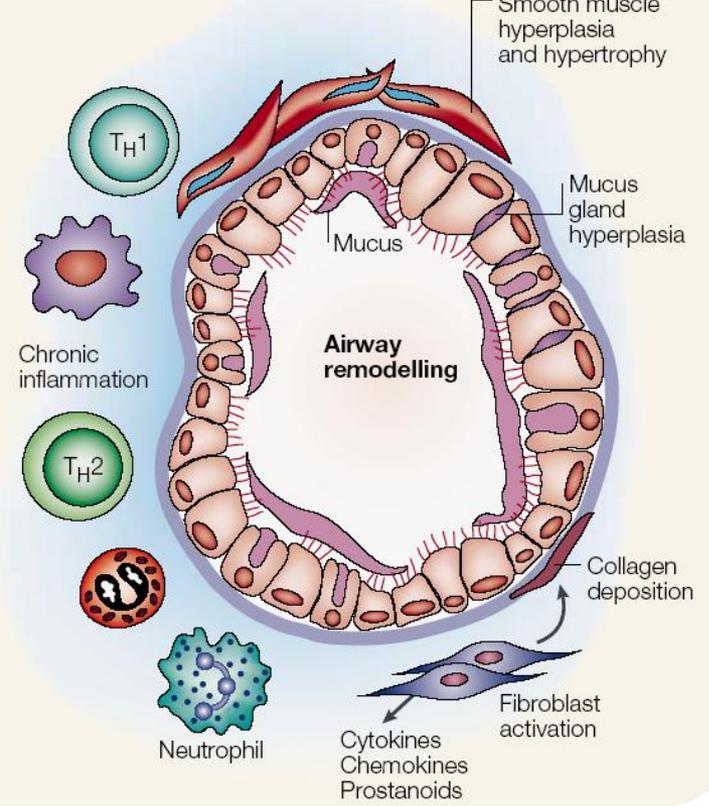
## a Acute phase



## b Chronic phase



## c Remodelling



IL-4 IL-5 IL-13

Eosinophil

Neutrophil

Cytokines

activation