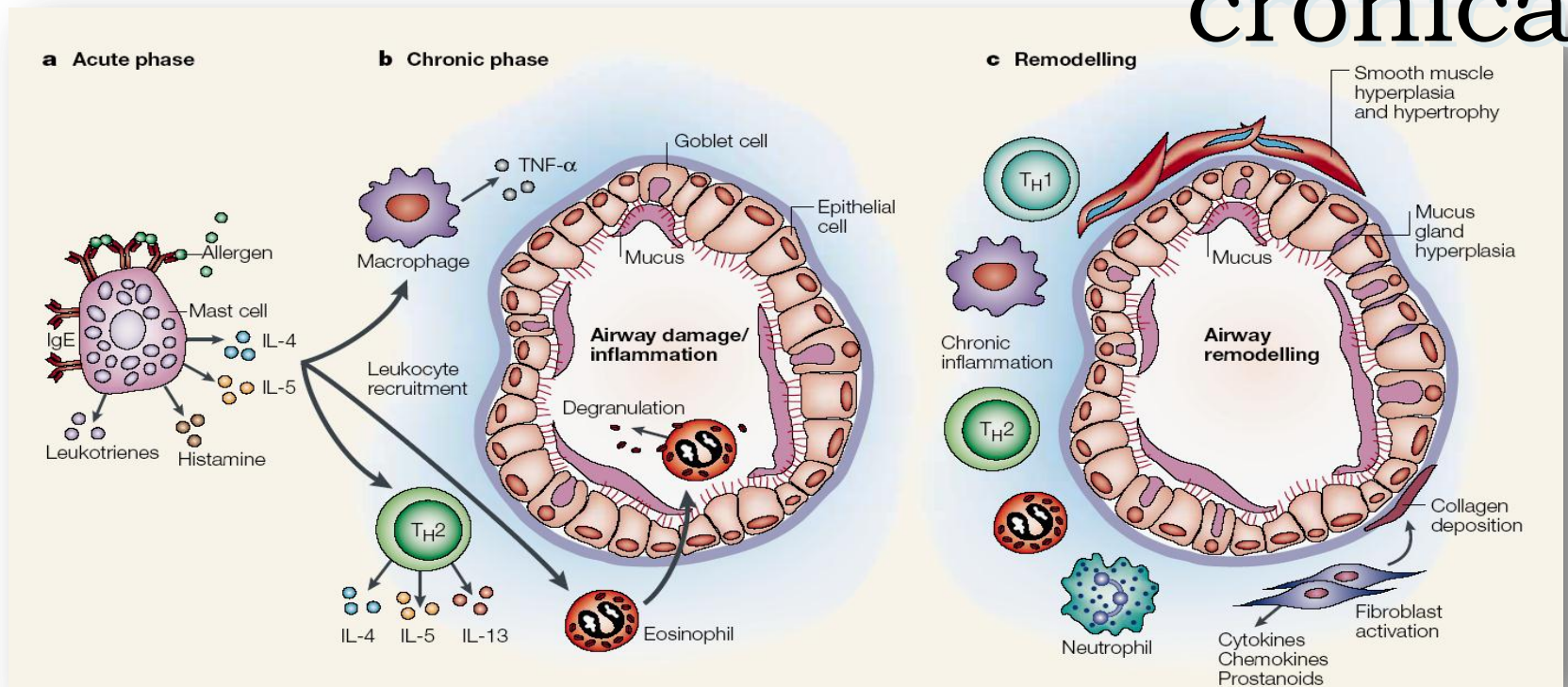


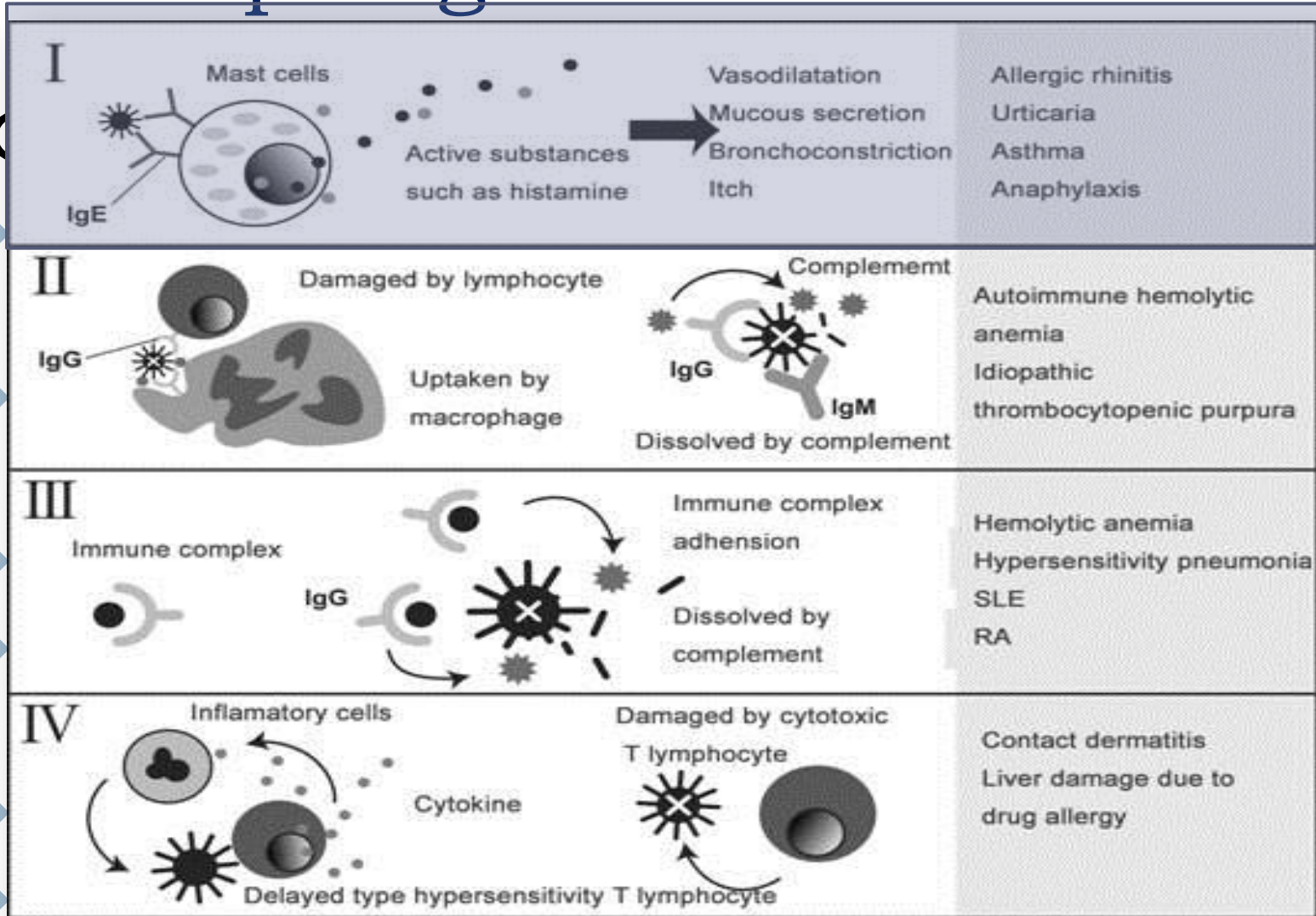
Hipersensibilidad Tipo I inmediata: Inmunopatogenia del asma crónica



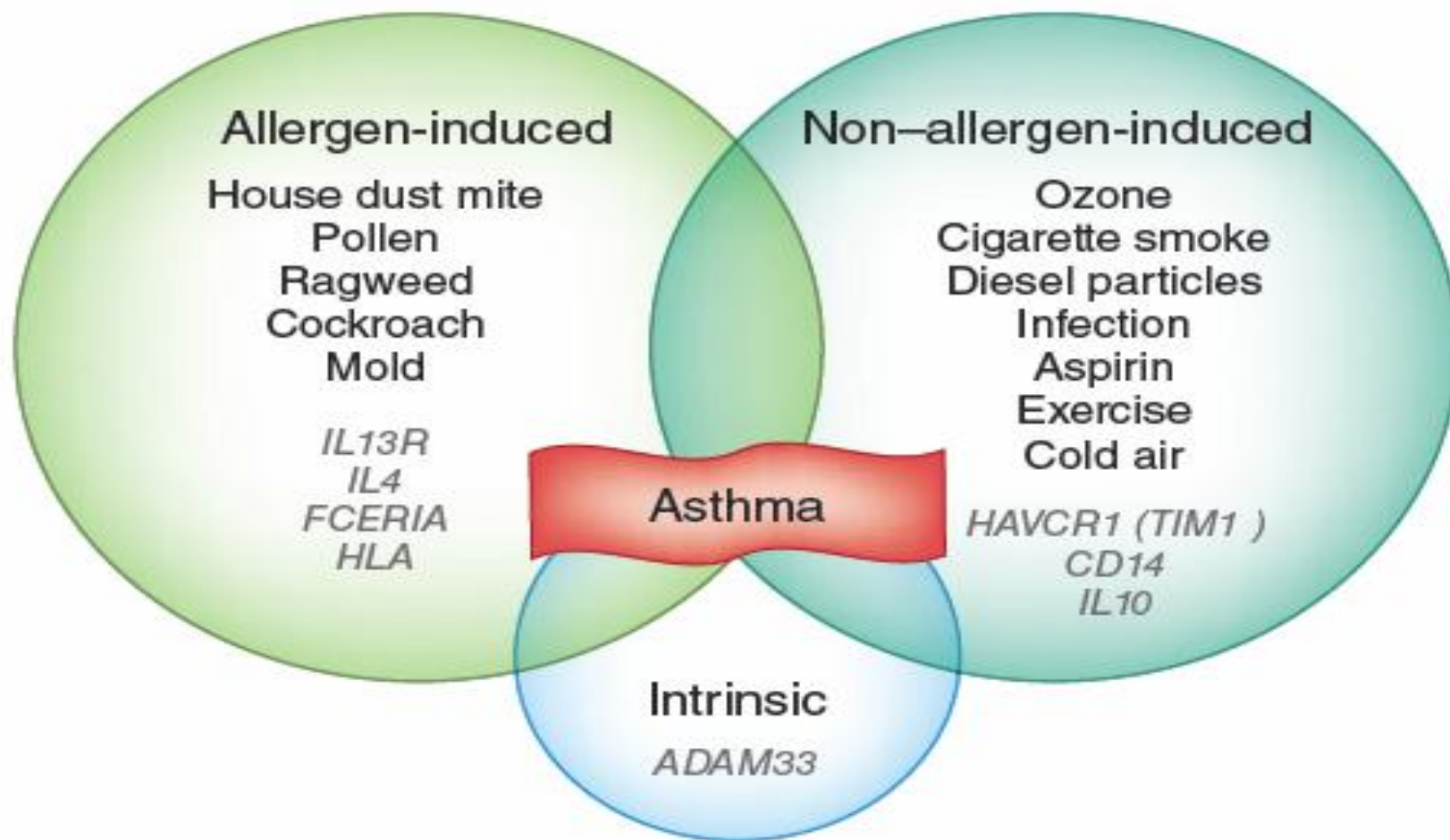
Siham Salmen Halabi

Instituto de Inmunología Clínica 2015

Inmunopatogenia del asma crónica

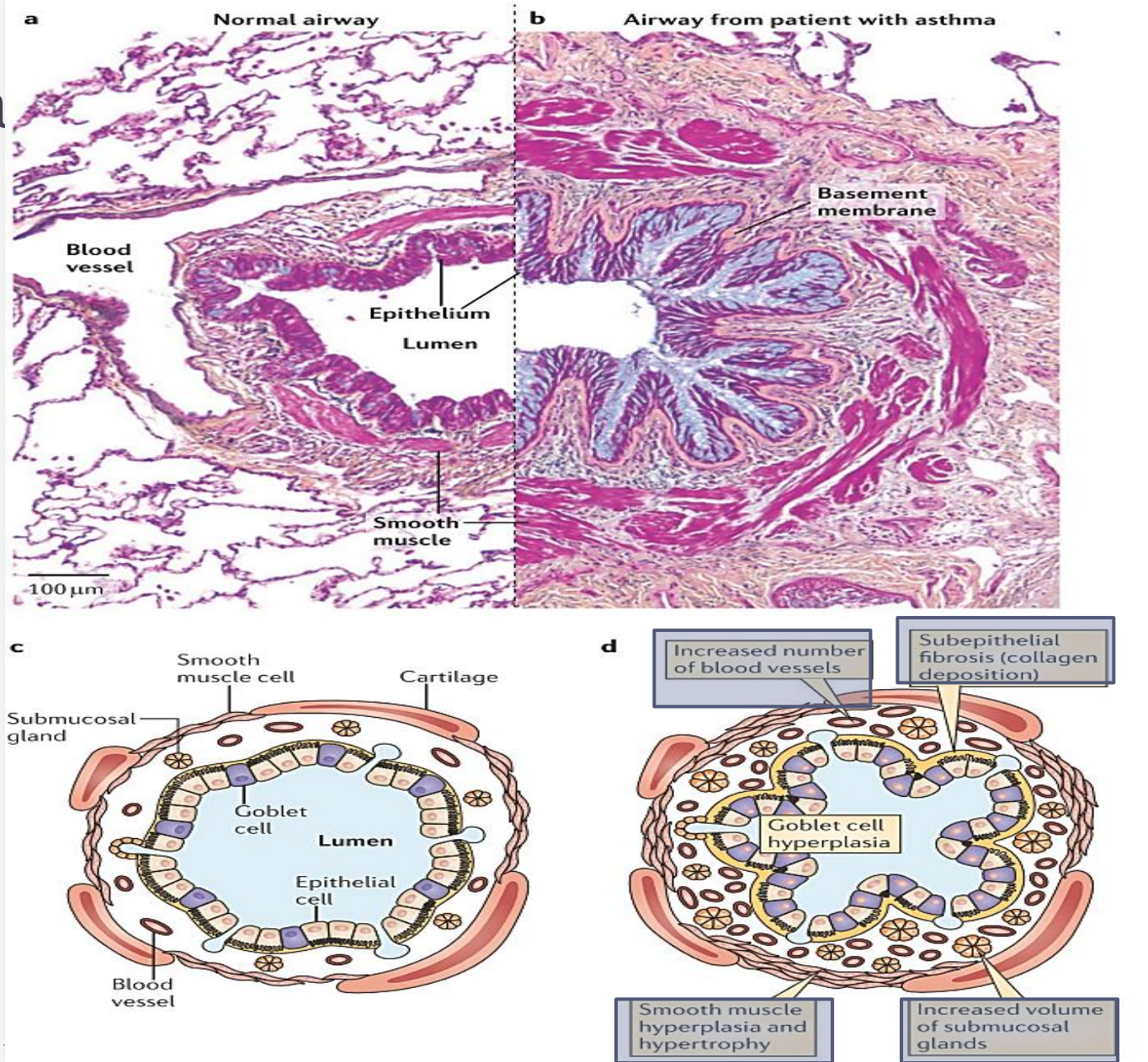


HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma

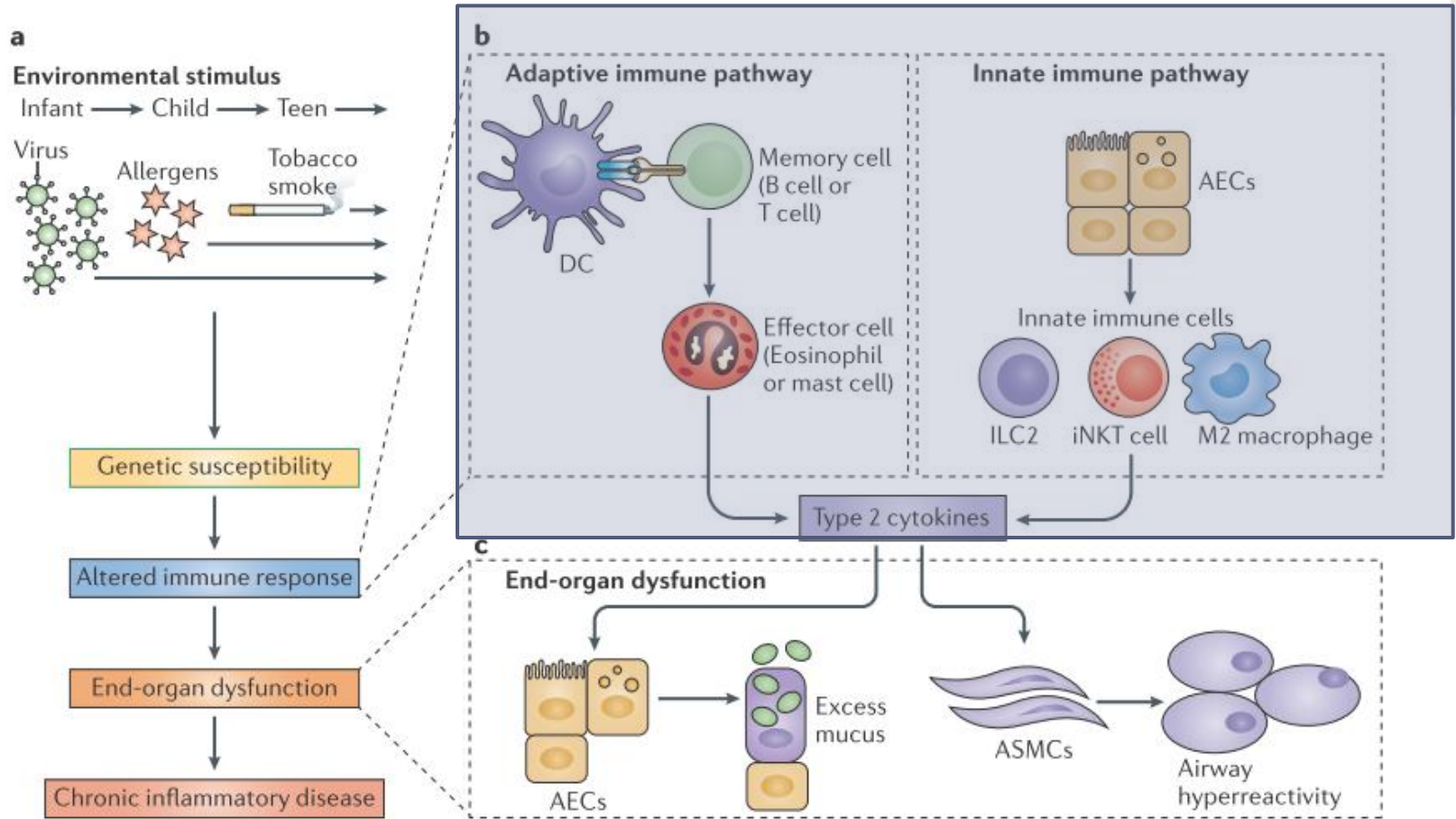


Es la enfermedad respiratoria crónica mas frecuente (10% adultos y 20% niños): 300 millones de personas en el mundo

Cambios a nivel de la mucosa bronquial Asma crónica

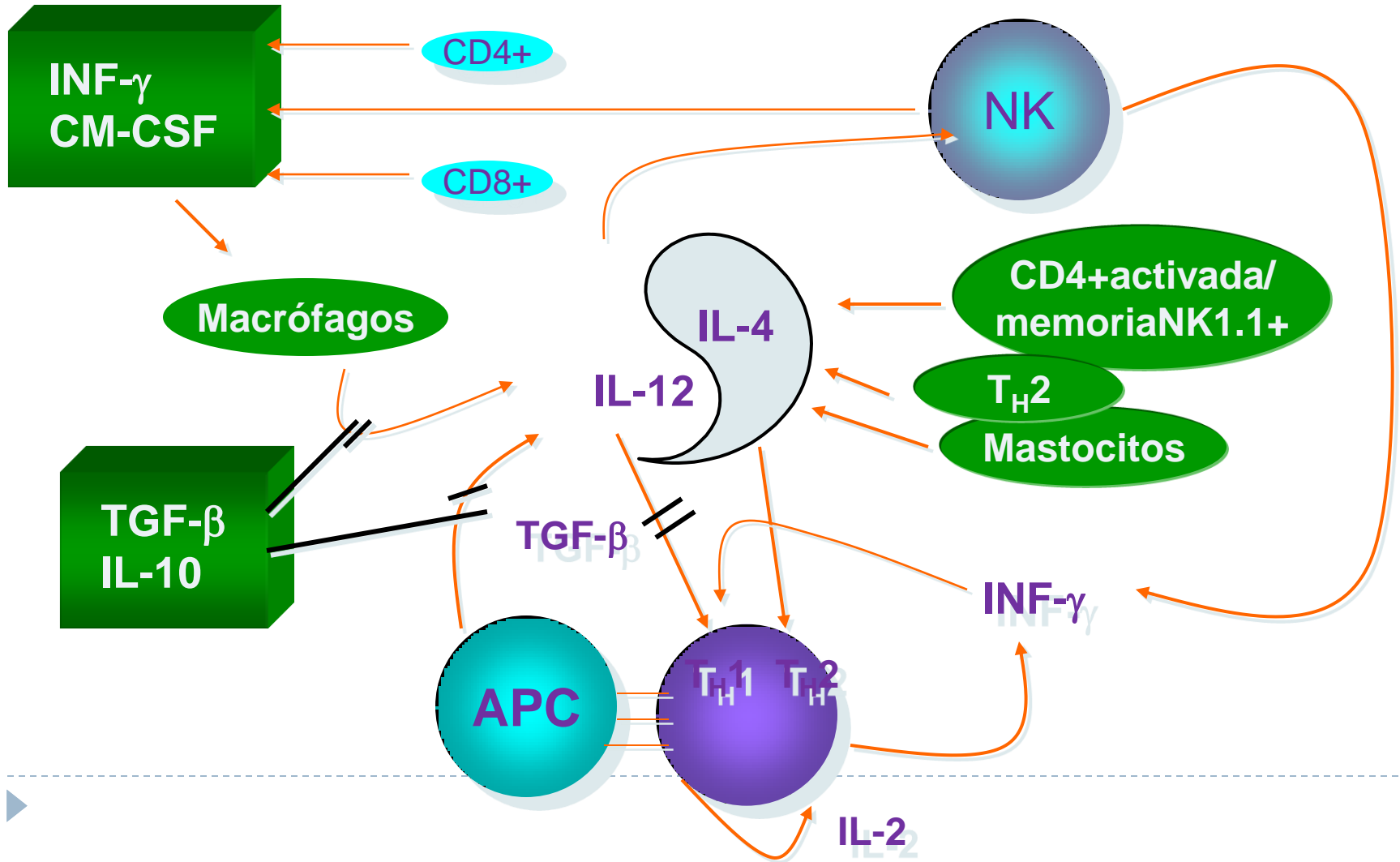


HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma



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 γ SCF, NFkB STAT6	Aumenta la transcripción de IL4 y genes HLAD Factor transcripcional regulado por IL Interacción con complejos MHC-péptidos	Asma, atopia, Niveles de IgE " " "
	9q34y 19.13.3	TCRA, TCRD NFkB-I C5 y C5R	Activa genes moduladores de la RI Incrementa IL-12

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- α/β production [68]	4E-BP1
miR-150	ACD	Nanovesicles containing miR-150 induced antigen-specific tolerance in ACD model in mice [84•]	

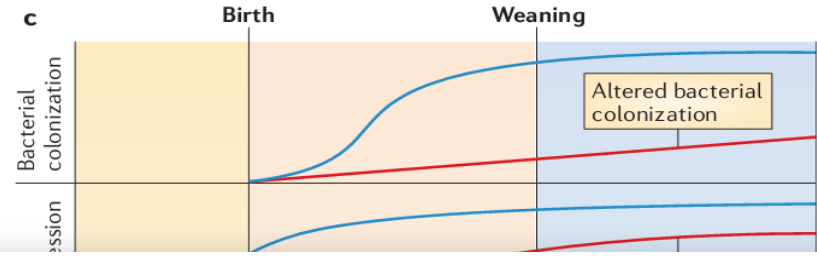
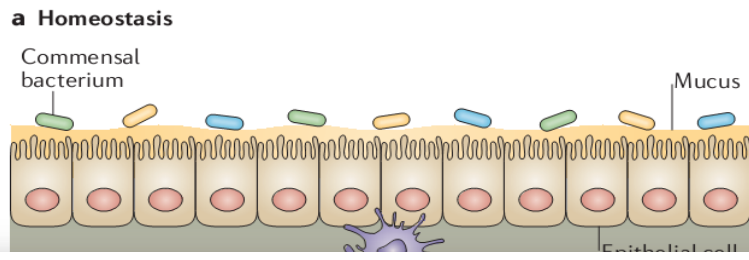
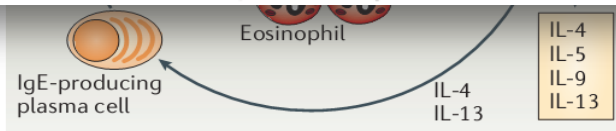


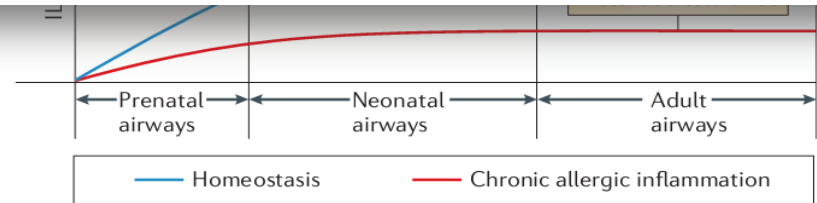
Table 1 | **Microorganisms affect the development of experimental and clinical asthma**

Source and route of microbial exposure	Examples of bacteria	Effect on asthma
Environmental microorganisms	<ul style="list-style-type: none"> • <i>Acinetobacter lwoffii</i> • <i>Eurotium</i> spp. • <i>Penicillium</i> spp. 	<ul style="list-style-type: none"> • Transgenerational protection from experimental asthma • Asthma-protected children are exposed to a high level of bacteria and fungi/spores^{103,146}
Respiratory microbiota	<ul style="list-style-type: none"> • Proteobacteria • <i>Bacteroides</i> spp. 	<ul style="list-style-type: none"> • Altered microbial colonization pattern of the respiratory mucosa in asthmatics and patients with COPD⁹
Intestinal microbiota	<ul style="list-style-type: none"> • Lactobacillae • Bifidobacteriae • <i>Bacteroides</i> spp. • <i>Clostridium</i> spp. 	<ul style="list-style-type: none"> • Altered quantitative distribution pattern of certain culturable microbial strains in young asthmatic patients¹²¹⁻¹²⁵ • Depletion of gut microbiota exacerbates experimental asthma¹²⁷
Urogenital microbiota	<ul style="list-style-type: none"> • Vaginal microorganisms 	<ul style="list-style-type: none"> • Indirect evidence from a model of Caesarean section; cause-effect relationship needs to be established¹²⁹⁻¹³¹

COPD, chronic obstructive pulmonary disease.



NATURE REVIEWS | IMMUNOLOGY VOLUME 12 | JANUARY 2012



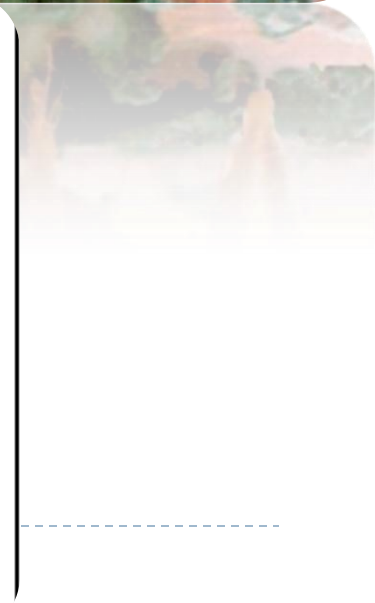
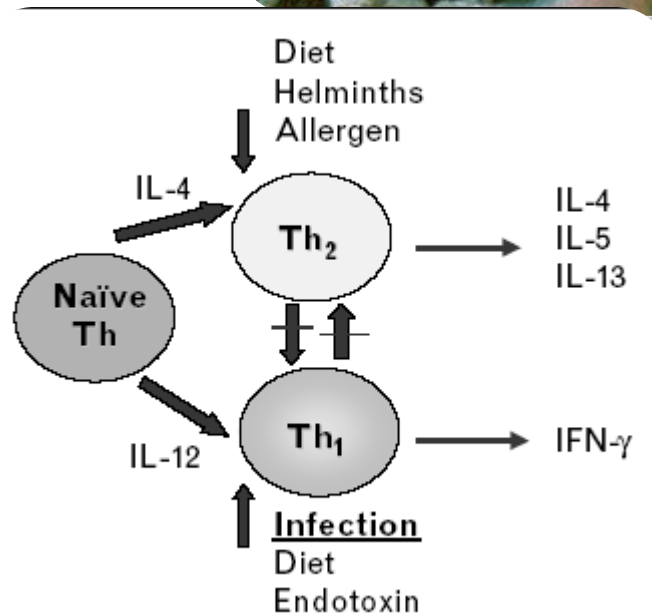
HIPERSENSIBILIDAD INMEDIATA:

Inmunopatogenia del asma Alergenos

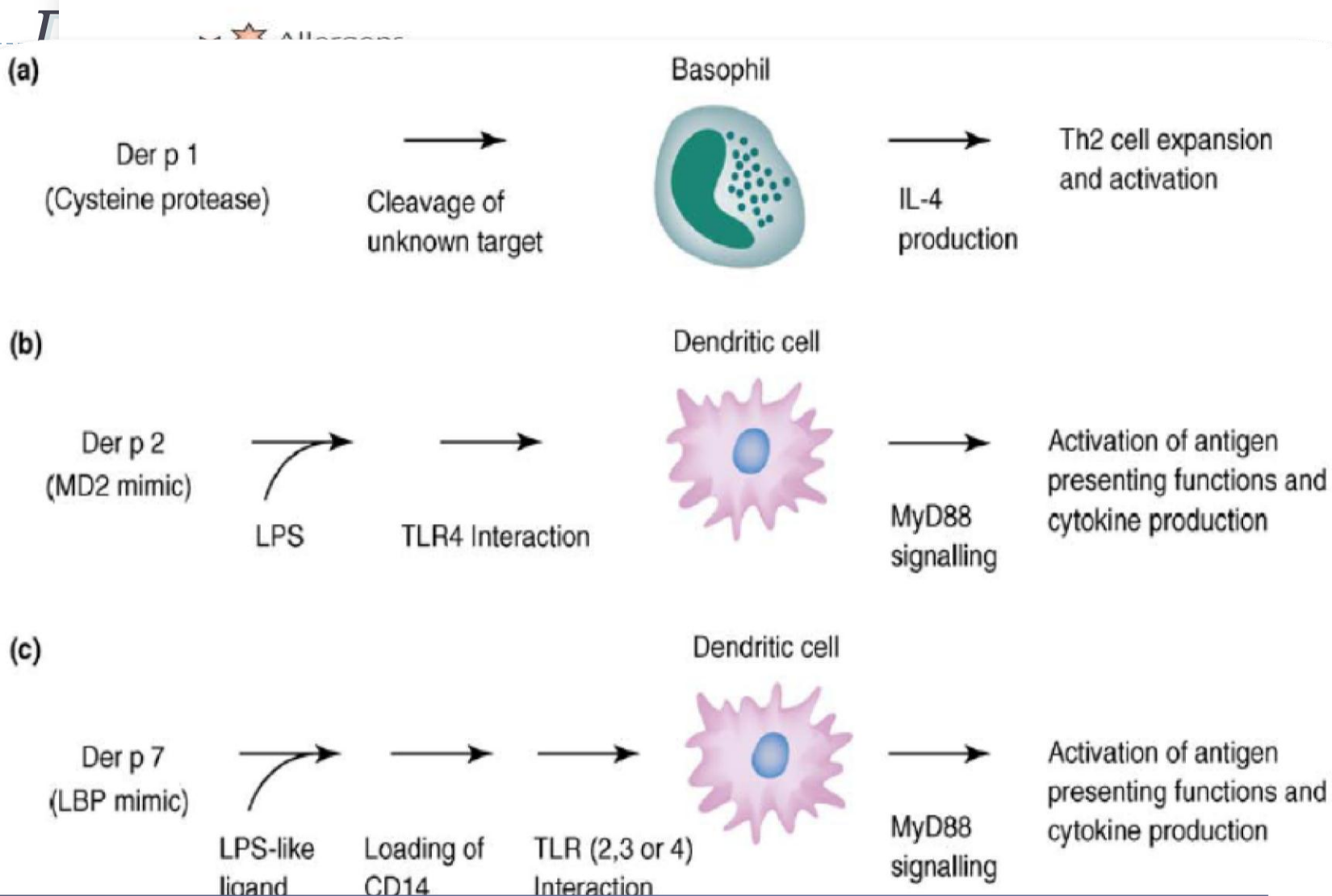
- ▶ Acaros (Derp I y 2)
 - ▶ Proteasas, quitinas
- ▶ Cucarachas (Bla g 2)
 - ▶ Quitinas
- ▶ Hongos saprófitos
 - ▶ Quitinas
- ▶ glicanos, endotoxina

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 _H 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 _H 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 _H 2-cell responses	81
Ragweed pollen Birch pollen	Amb a Bet v	Induction of chemokines	Recruitment of T _H 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

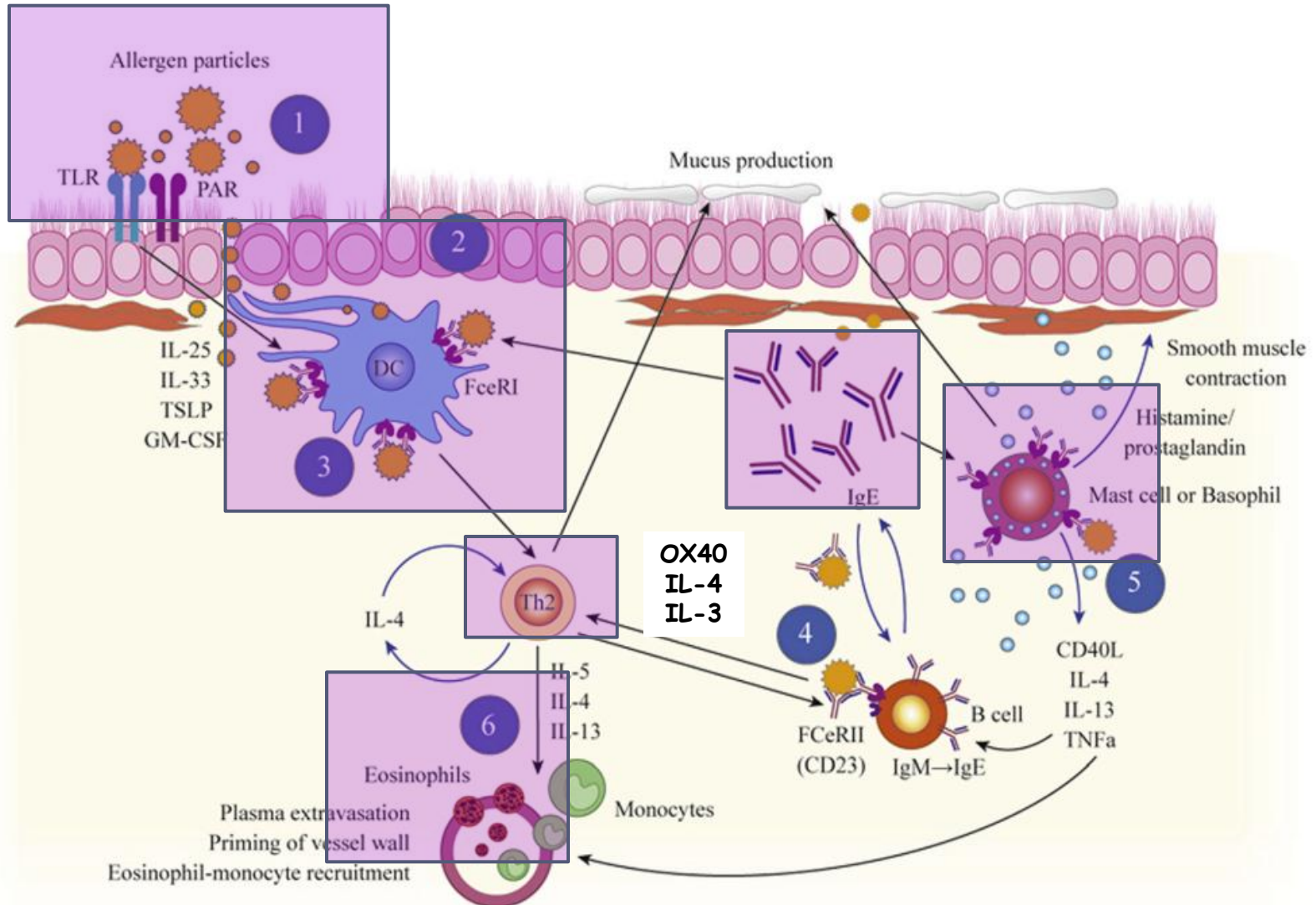
CCL, CC-chemokine ligand; DC, dendritic cell; DC-SIGN, DC-specific ICAM3-grabbing non-Integrin; GM-CSF, granulocyte/macrophage colony-stimulating factor; IL, interleukin; PAR, protease-activated receptor; T_H2 cell, T helper 2 cell.

▶ 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



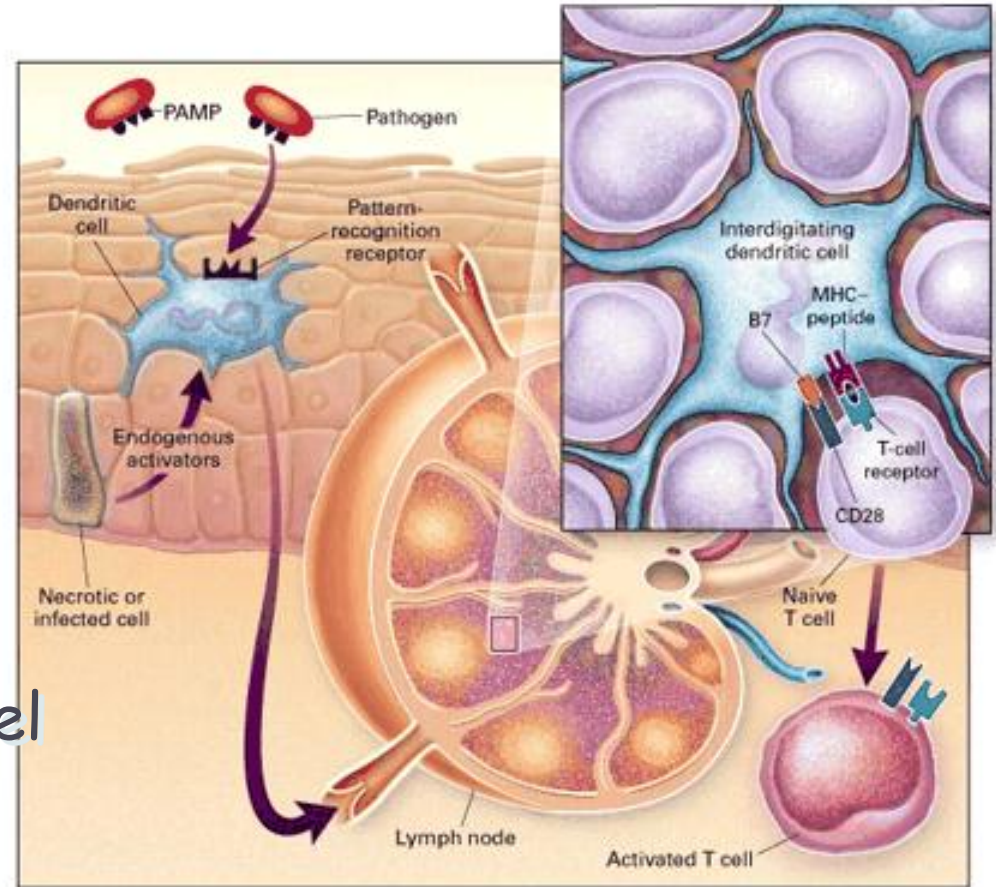
Inmunopatogenia del asma



HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma

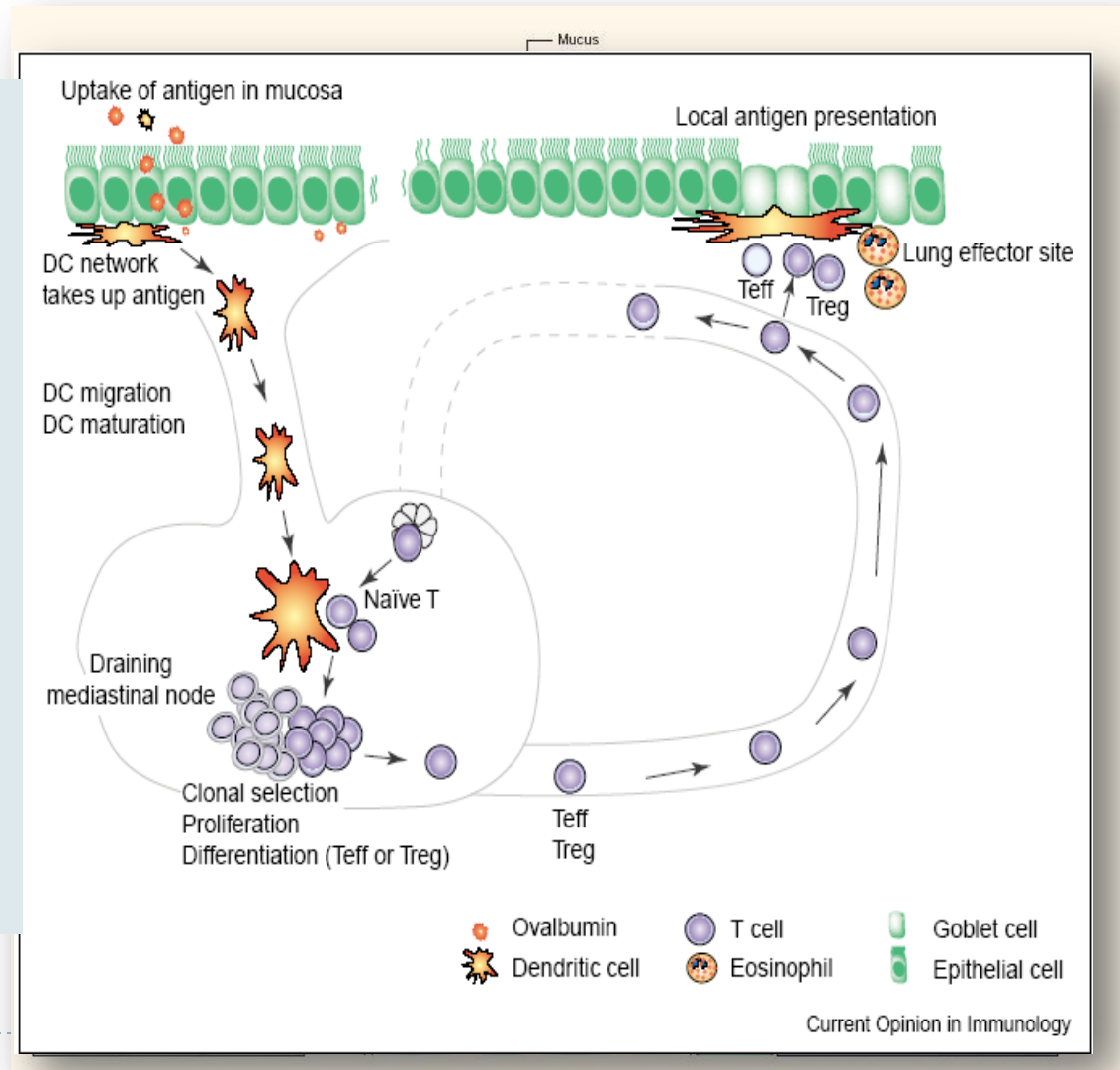
- ▶ Individuo genéticamente susceptible: Predisposición a responder T_H2
- ▶ Condiciones ambientales
- ▶ Alergenos

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

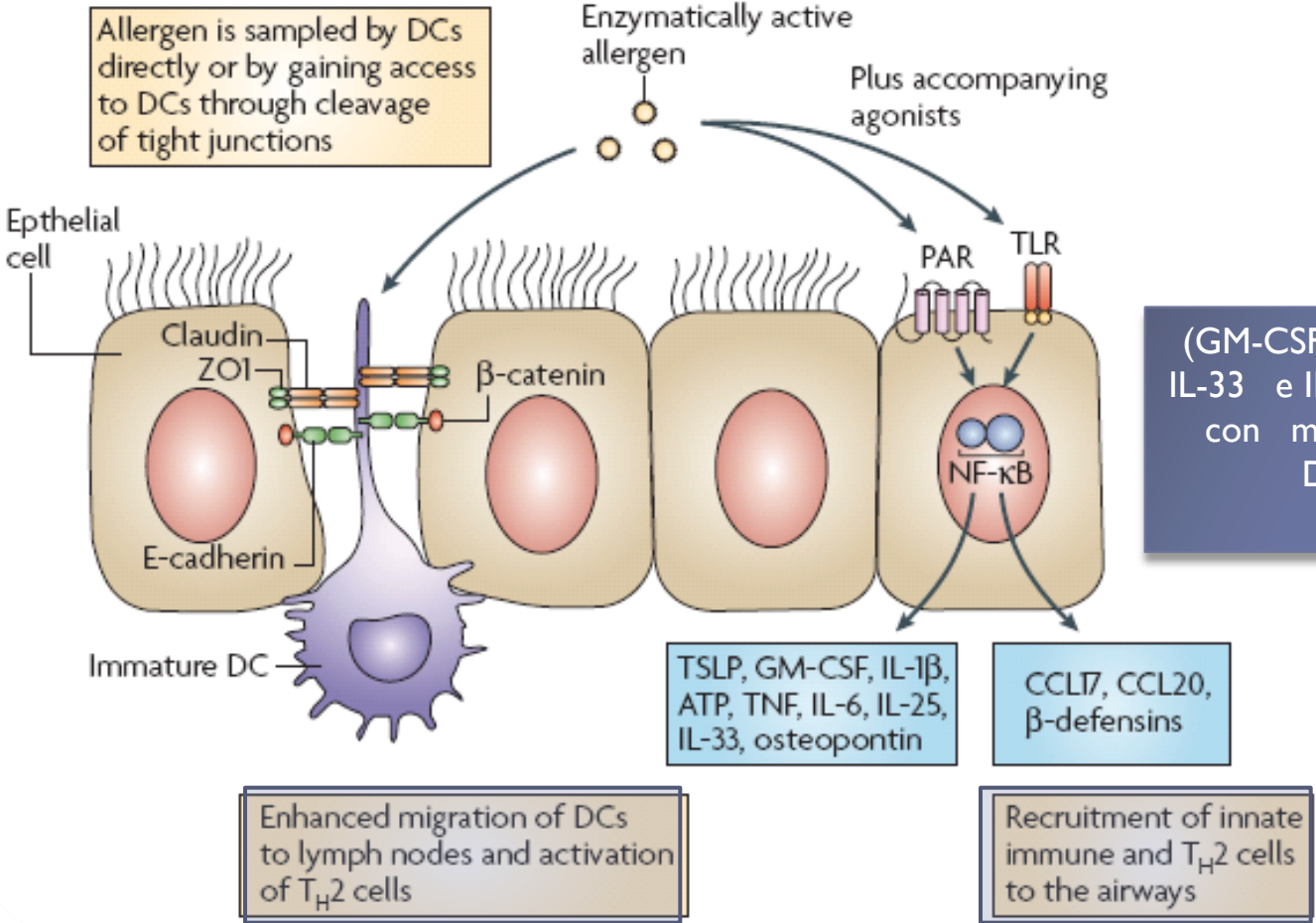


HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma

- ▶ 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



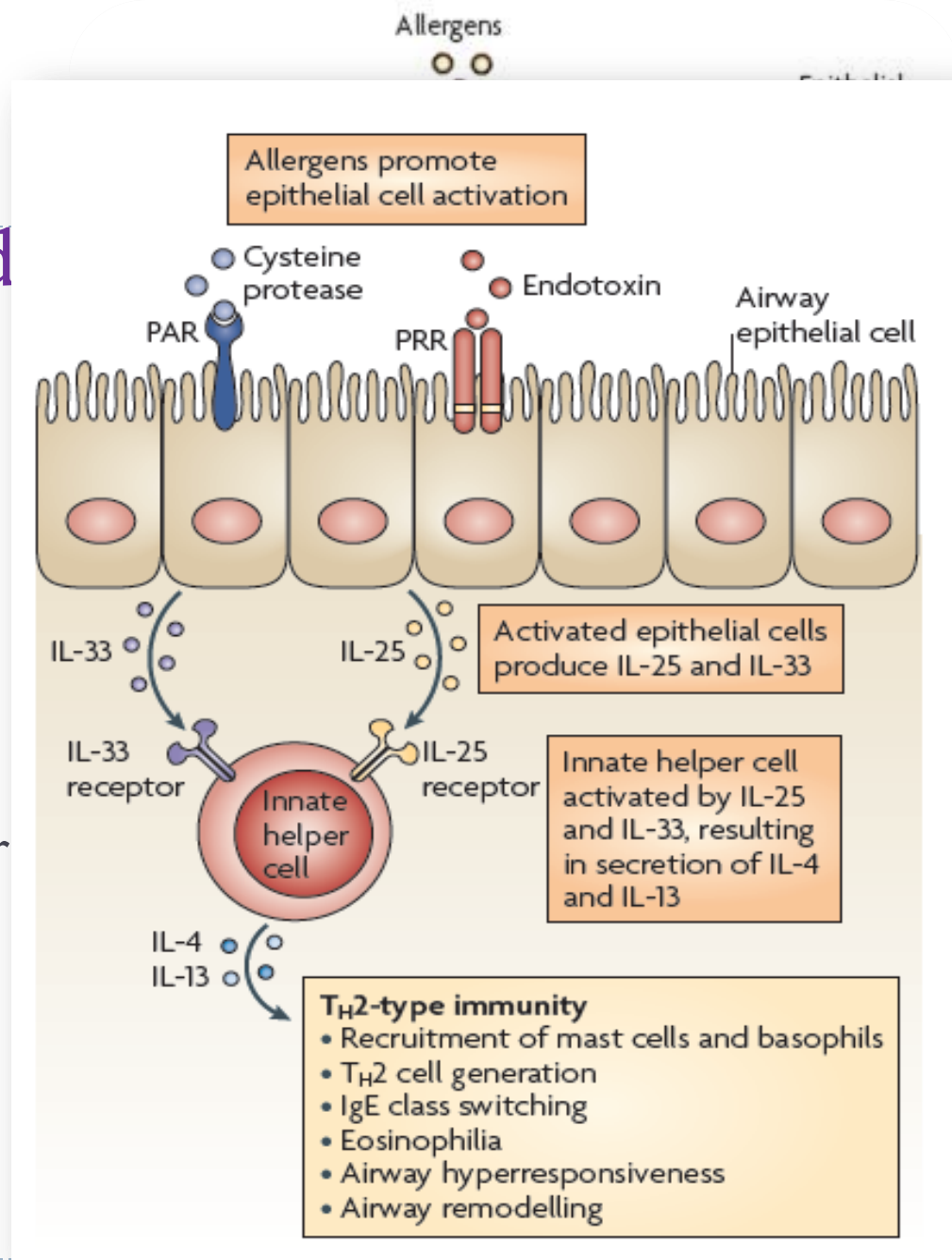
(GM-CSF, TSLP, IL-25, IL-33 e IL-1), contribuye con maduración de DCs y Th2

of TH2 cells to lymph nodes and activation

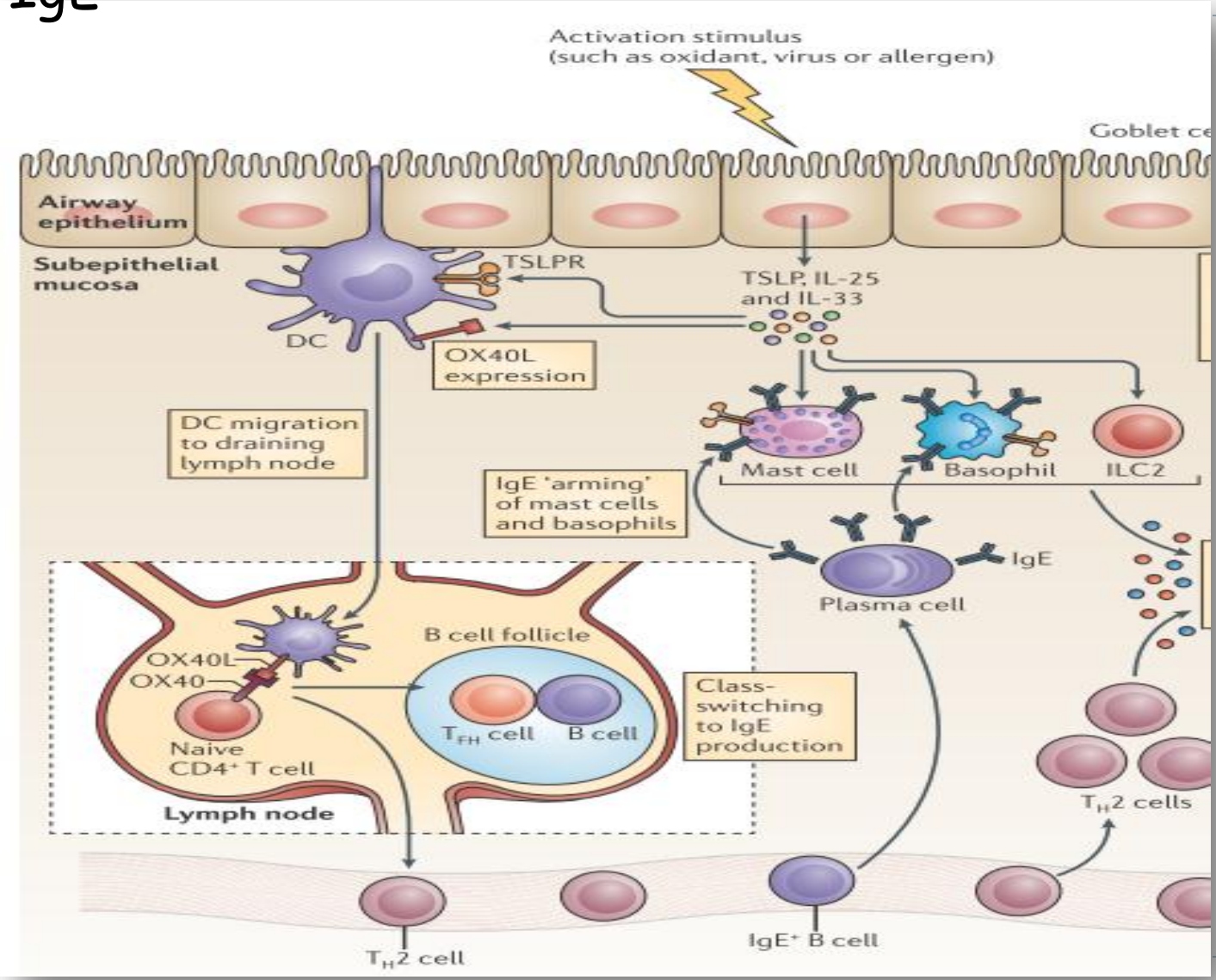
to the airways immune and TH2 cells

Polarización de la respuesta inmune: Inmunopatogenia del asma

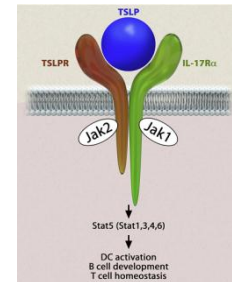
- ▶ Presentación antigénica
 - ▶ En presencia de TSLP (linfopoyetina del estroma tímico)
 - ▶ TSLP incrementa expresión e interacción OX40L, en DC
 - ▶ Activación de población Helper innata con patrón Th2
 - ▶ Desarrollo de respuesta Th2, ruptura de la tolerancia
 - ▶ Nueva población conocida como “**Células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



Presentacion antigenica y cambio de isotipo IgE

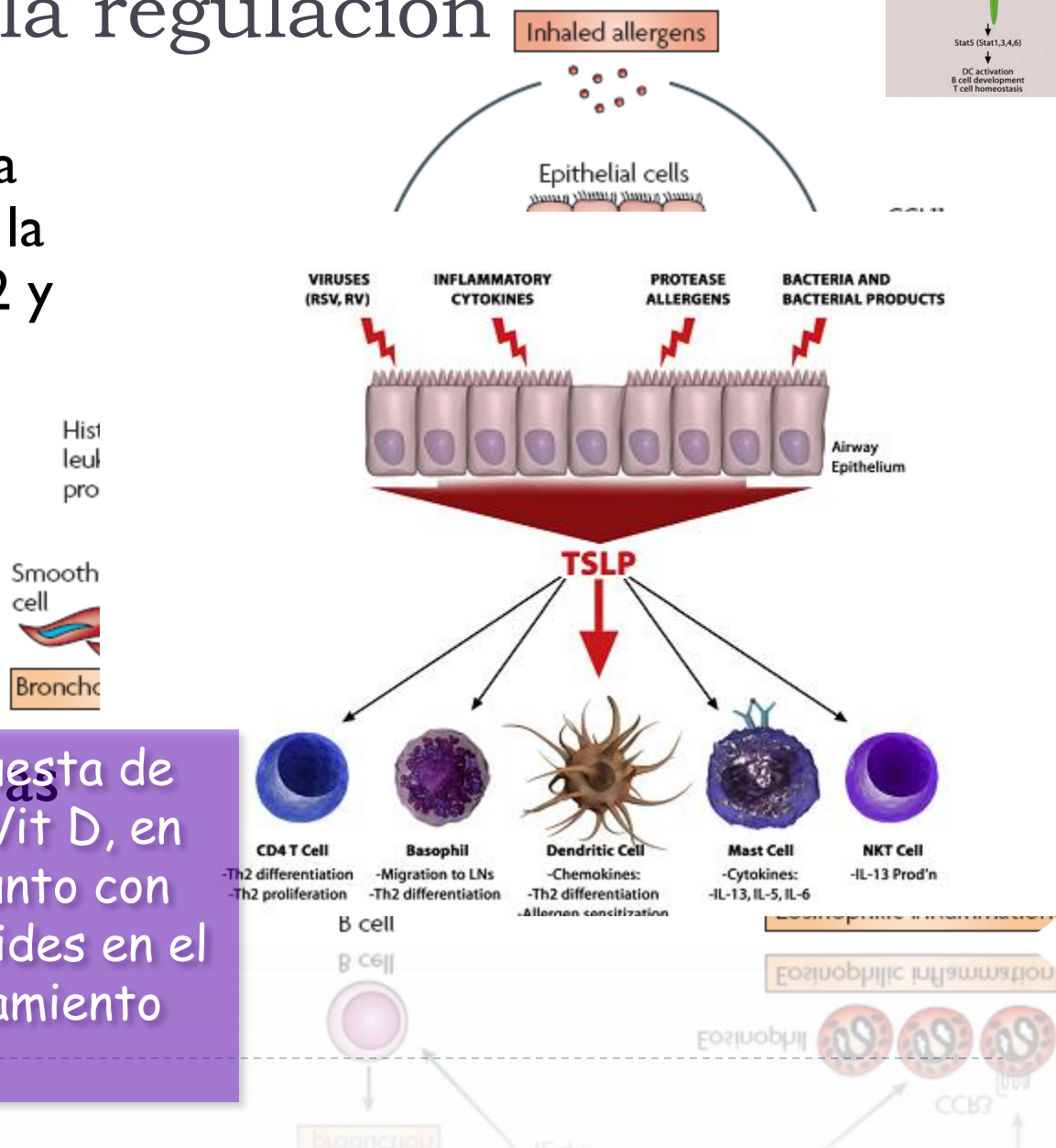


Reclutamiento de células inflamatorias e inhibición de la regulación



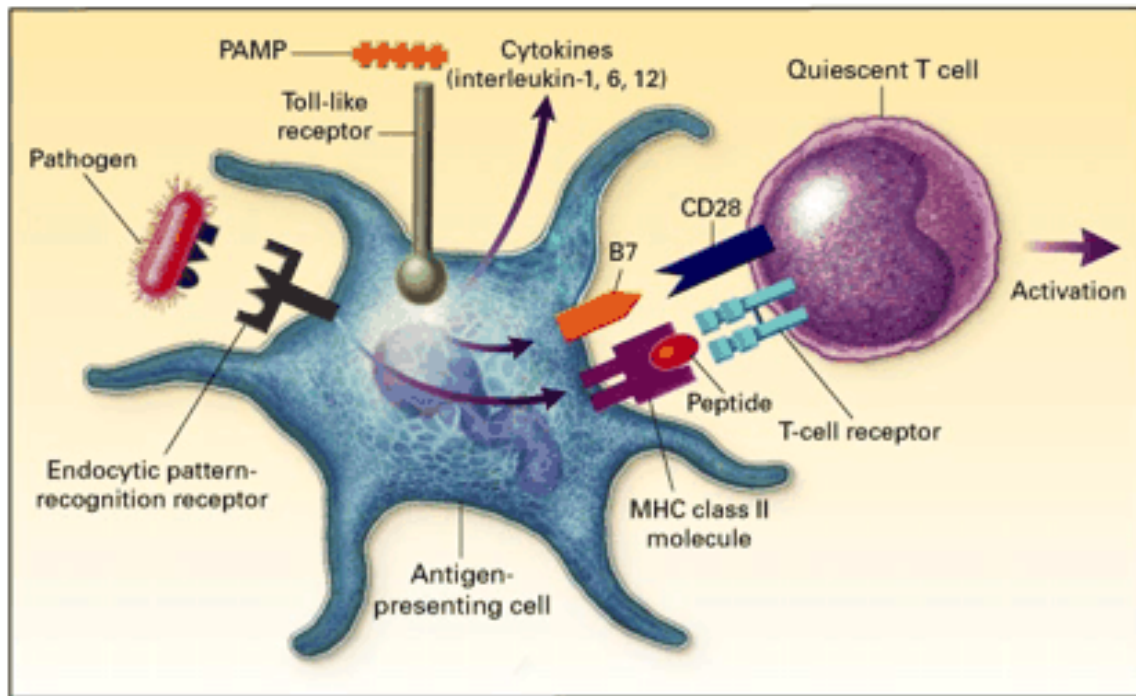
- ▶ Linfopoyetina del estroma tímico (TSLP), conduce a la liberación de CCL17 y 22 y reclutamiento de Th2
- ▶ Células epiteliales liberan CCL11 que favorece reclutamiento de eosinófilos
- ▶ Defectos en el desarrollo de las células T reguladoras

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



HIPERSENSIBILIDAD INMEDIATA:

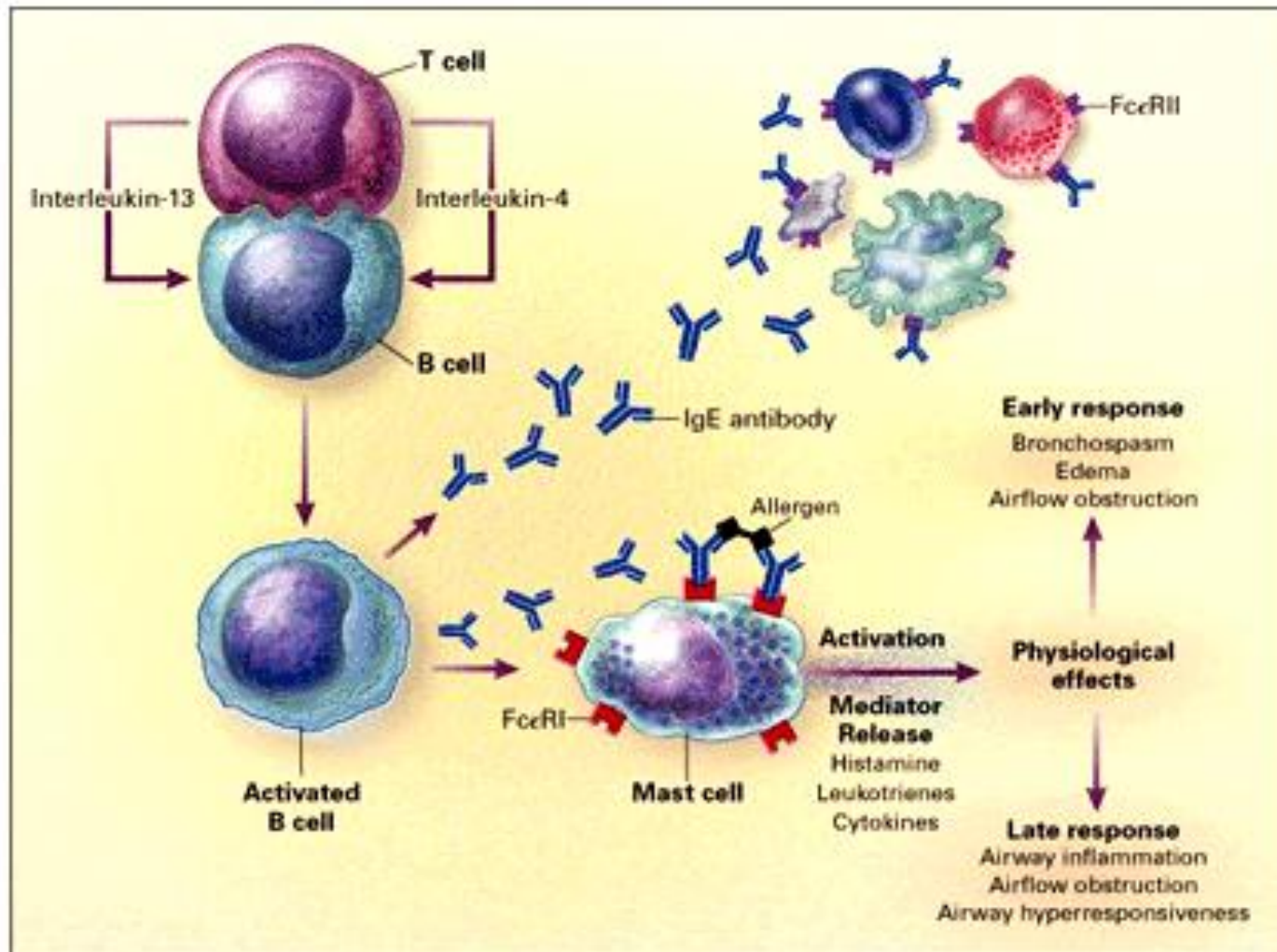
Inmunopatogenia del asma



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



Inmunopatogenia del asma: Inmunoglobulina E

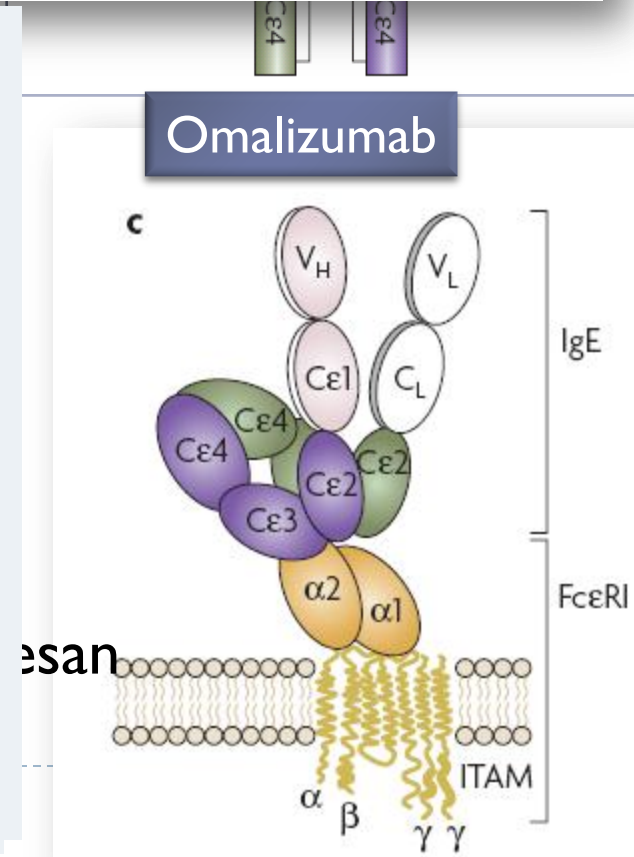


TABLA III
EVOLUCIÓN DE LOS PACIENTES ASMÁTICOS SEGÚN EL GRUPO TERAPÉUTICO DE ACUERDO CON EL GRADO CLÍNICO Y EL ÍNDICE DE FRECUENCIA AL INGRESO, A LOS 3 Y A LOS 6 MESES DE TRATAMIENTO

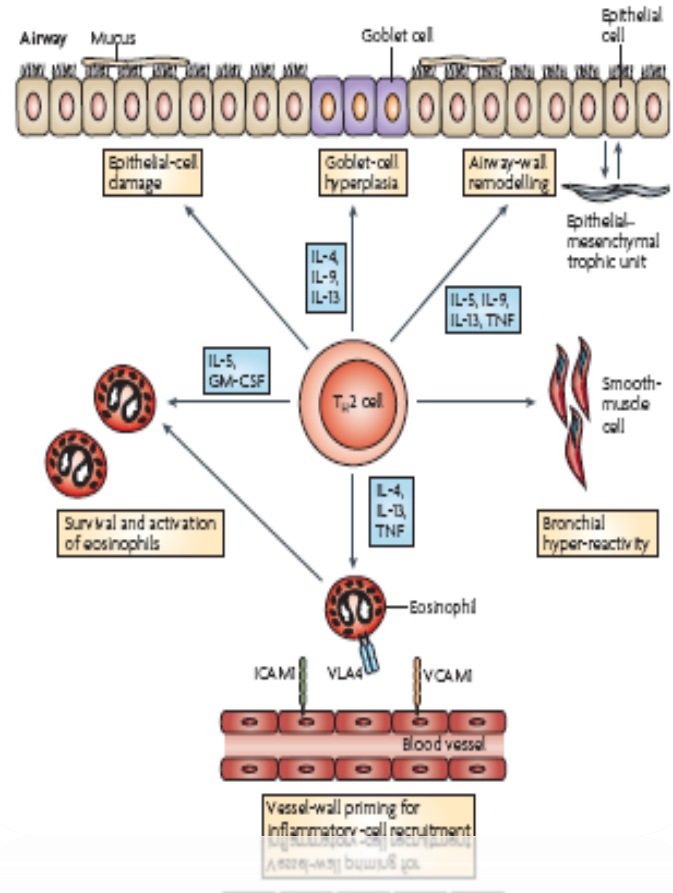
	GRUPO A		GRUPO B		GRUPO C	
	GC	IF	GC	IF	GC	IF
Ingreso	3,28 (0,48)	15,6 (10)	3,16 (0,40)	9,2 (4,70)	3,16 (0,40)	15,5 (4,10)
3 Meses	2,14** (0,89)	2,8* (1,78)	1,66* (1,36)	1,66* (0,98)	1,88** (0,98)	1,66** (0,98)
6 Meses	0	0	0,66 (1,21)	0,80 (1,78)	1,00 (1,54)	0,66 (1,03)

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

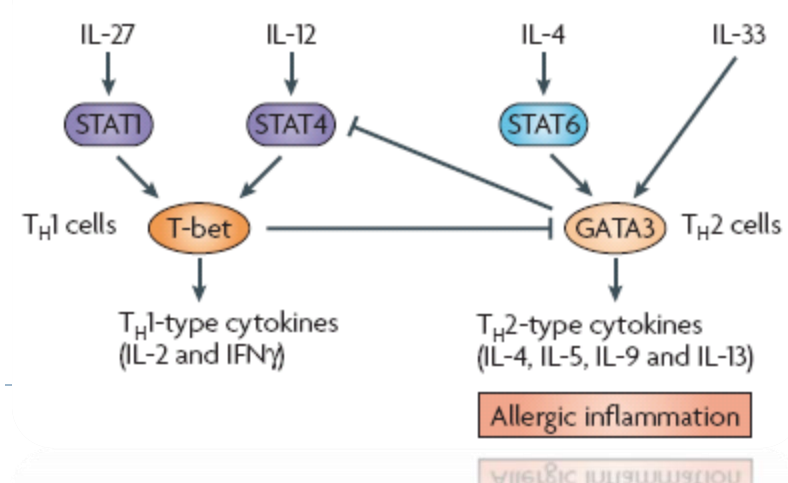


HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma

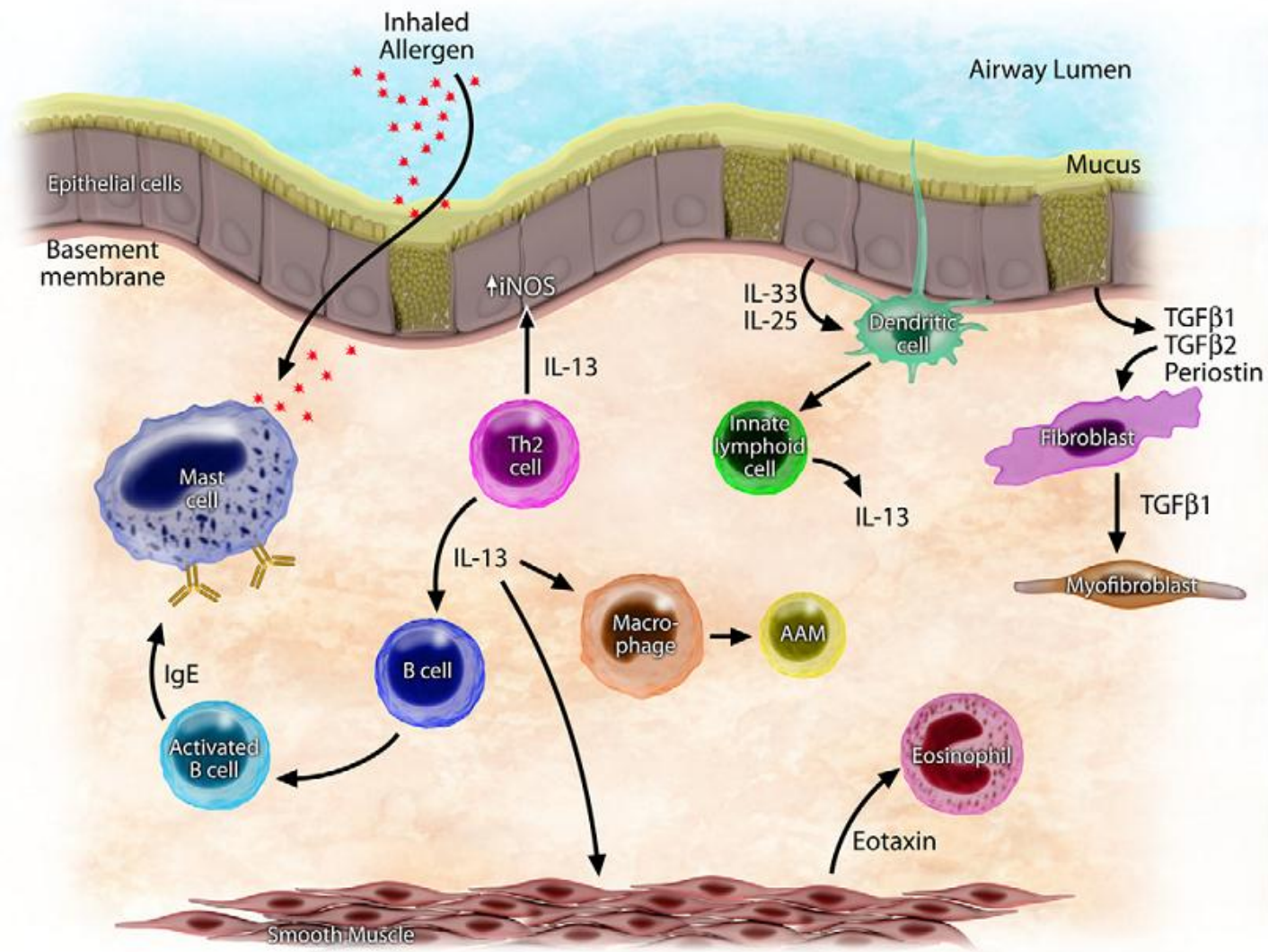


▶ Linfocitos Th2

- ▶ Median reclutamiento y sobrevida de eosinofilos y mastocitos
- ▶ Hiperplasia de las células de globet
- ▶ Hiperactividad bronquial asociado con la liberación de IL-9 e IL-13 que incrementan la excitabilidad del musculo liso bronquial
 - ▶ Resultado bronconstriccion por estímulos no específicos como el frio, o el ejercicio

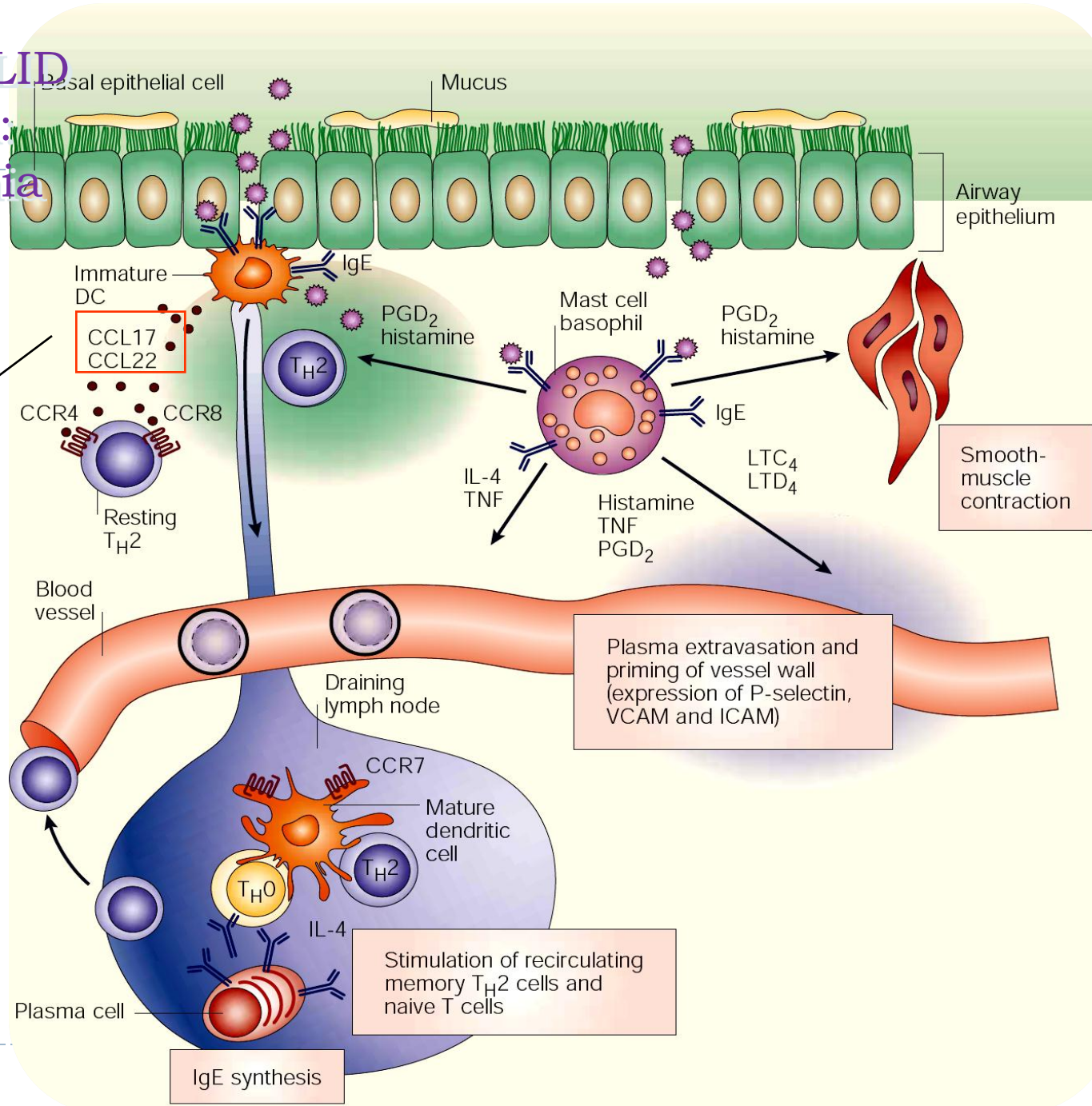


Mecanismos de Inflamación eosinofílica inducida por interleukinas TH2



filos
ial

HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma



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

Segundo encuentro con el alergen

IgE synthesis

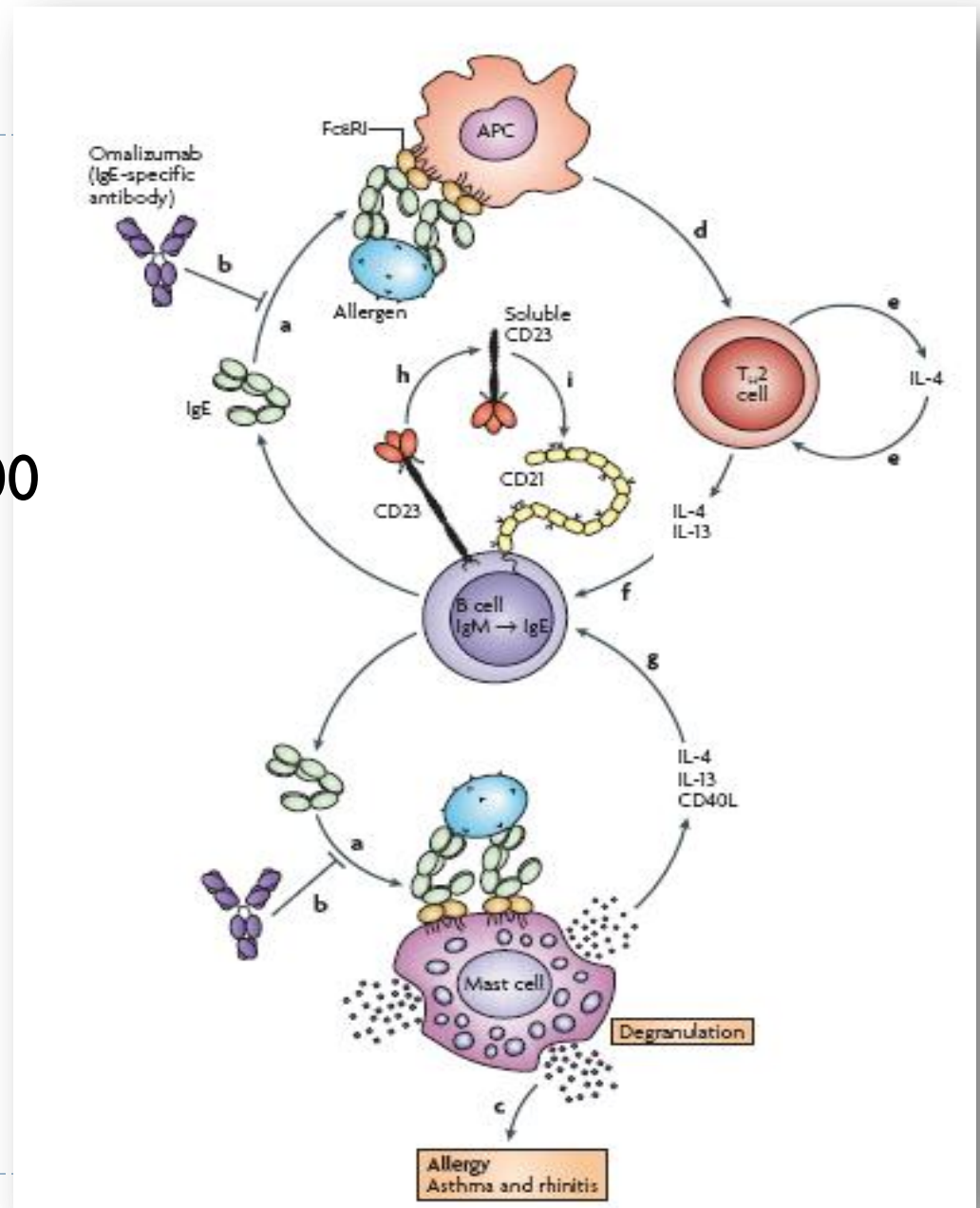
Plasma extravasation and priming of vessel wall (expression of P-selectin, VCAM and ICAM)

Stimulation of recirculating memory Th2 cells and naive T cells

Smooth-muscle contraction

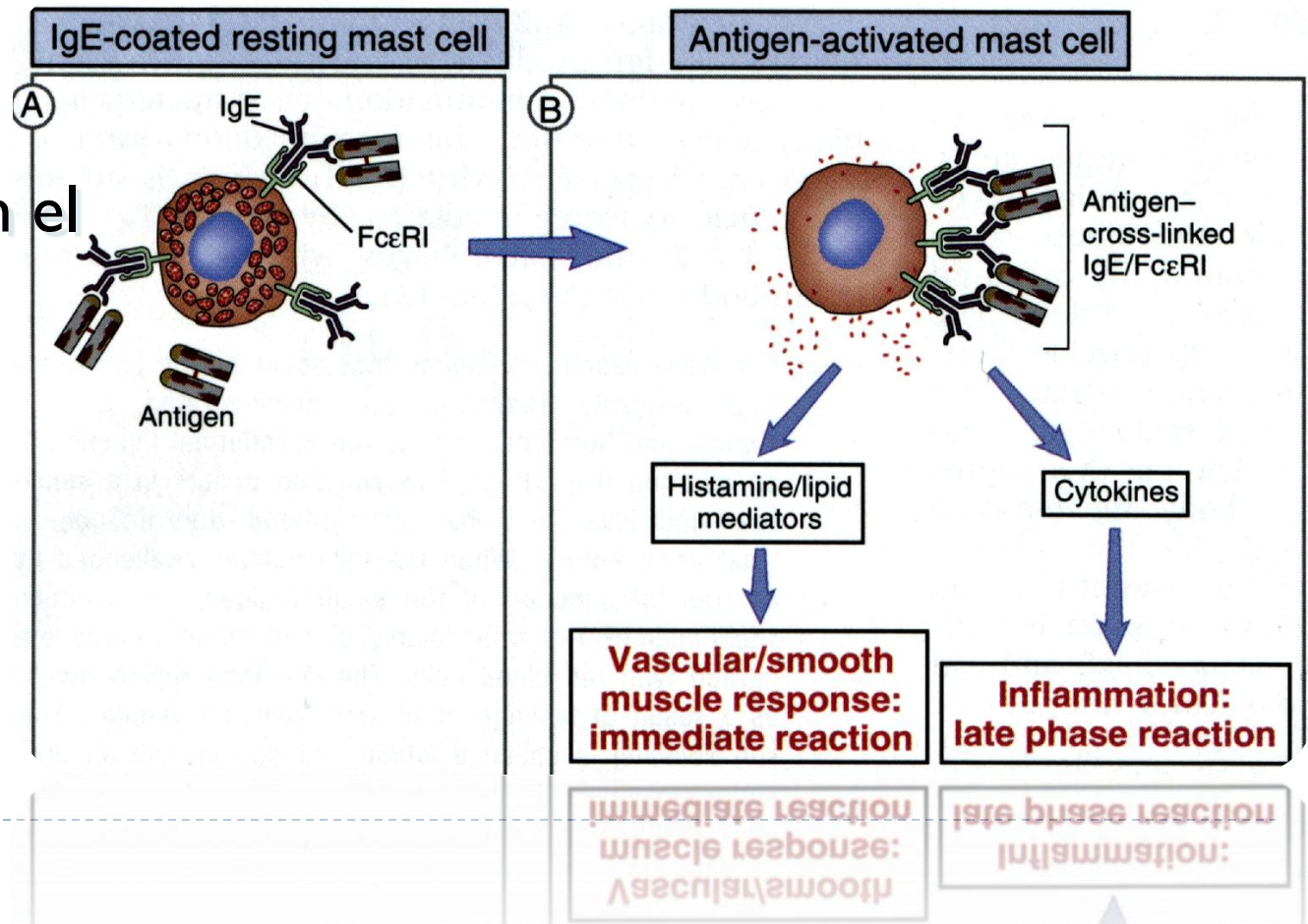
Mastocitos sensibilizados

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

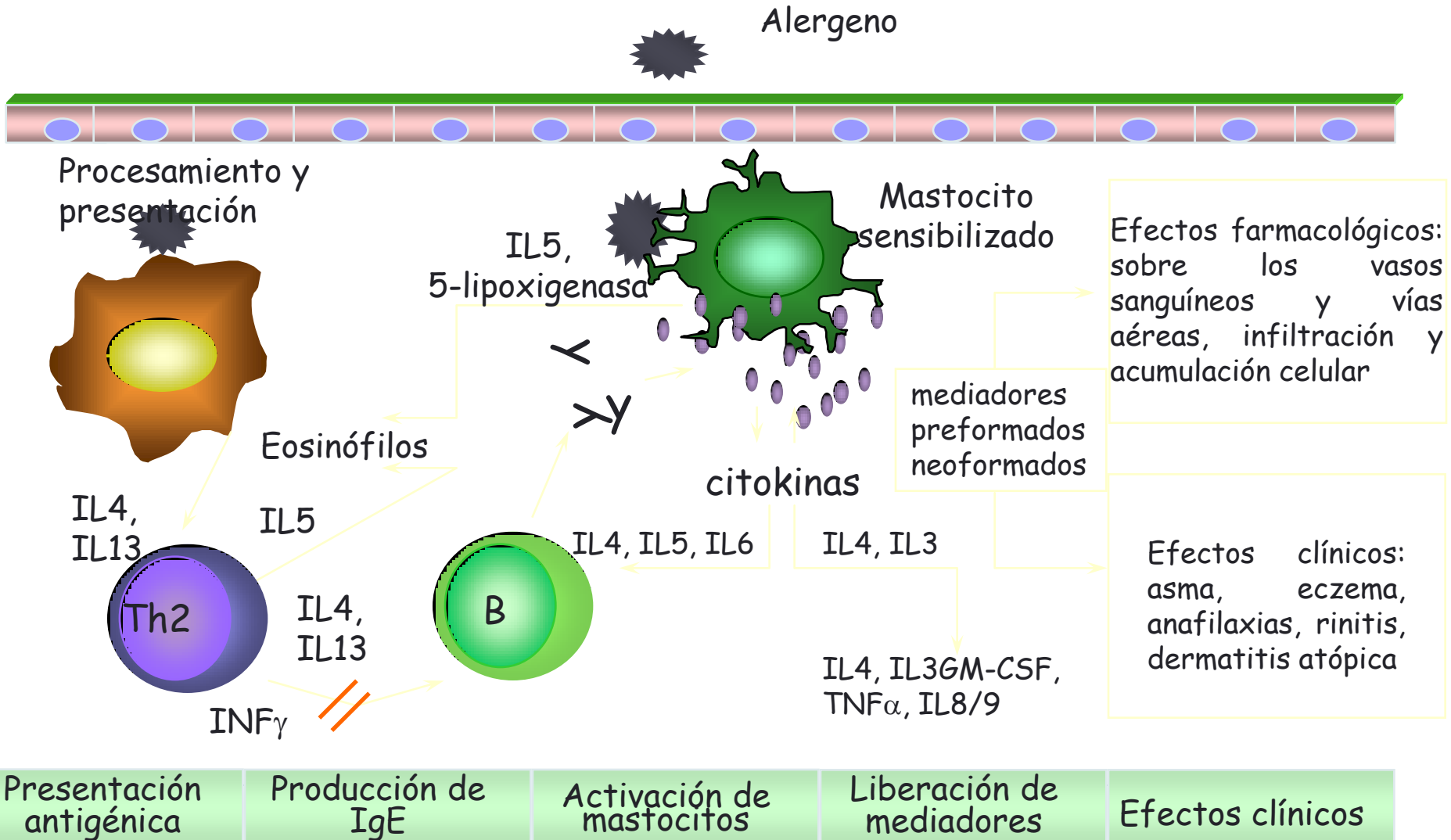


HIPERSENSIBILIDAD INMEDIATA: Inmunopatogenia del asma

- ▶ Segundo encuentro con el alérgeno



Inmunopatogenia del asma: RESPUESTA INFLAMATORIA



Presentación antigénica	Producción de IgE	Activación de mastocitos	Liberación de mediadores	Efectos clínicos
-------------------------	-------------------	--------------------------	--------------------------	------------------

Inmunopatogenia del asma: Participación de los Mastocitos

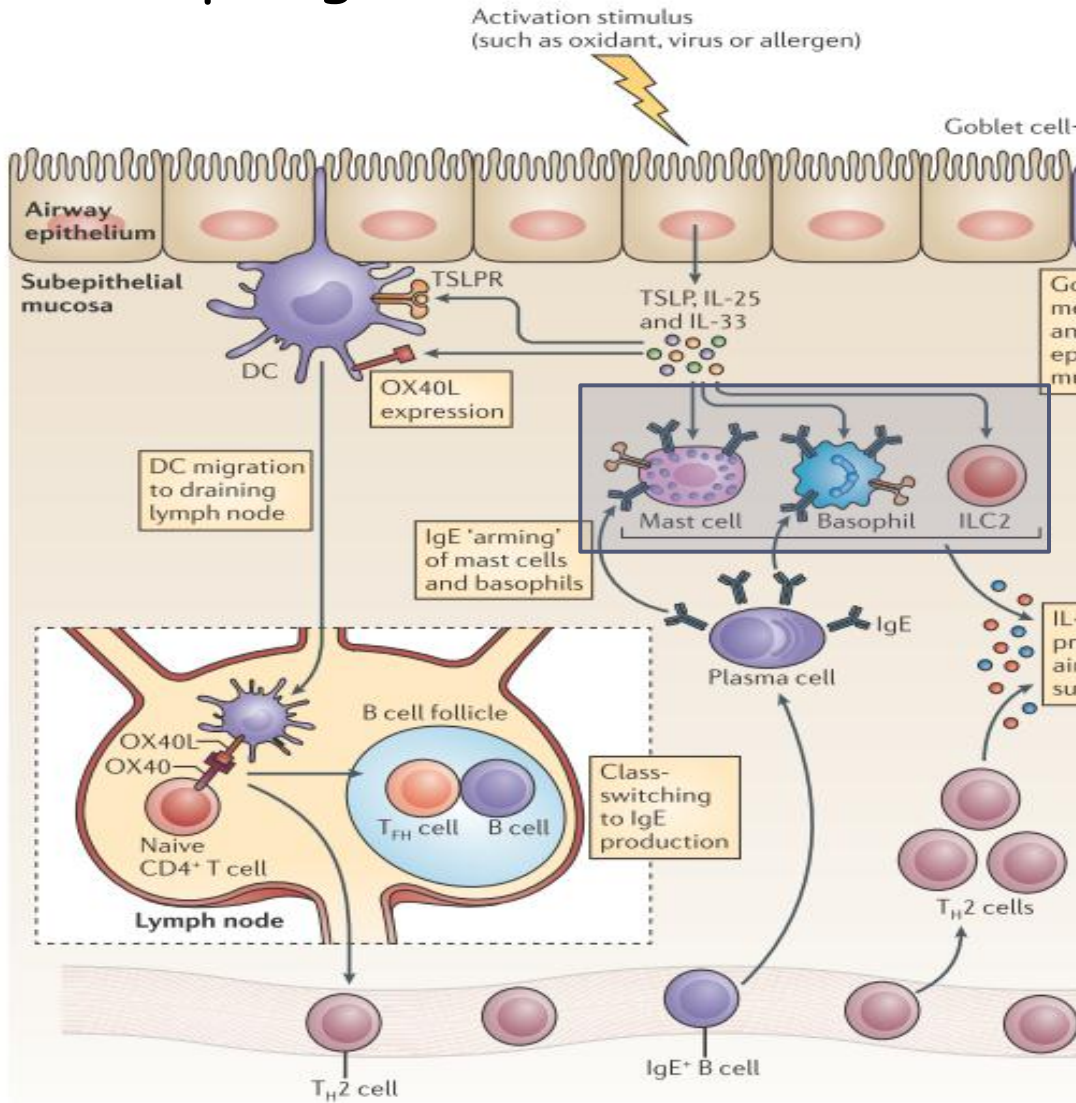
- ▶ Degranulación de mastocitos
 - ▶ Entrecruzamiento de receptores FcεRI
 - ▶ C3a
 - ▶ ACTH, codeína, morfina, sustancia P
- ▶ Mediadores preformados
- ▶ Mediadores neoformados



Inmunopatogenia del asma: Participación de los leukotrienos



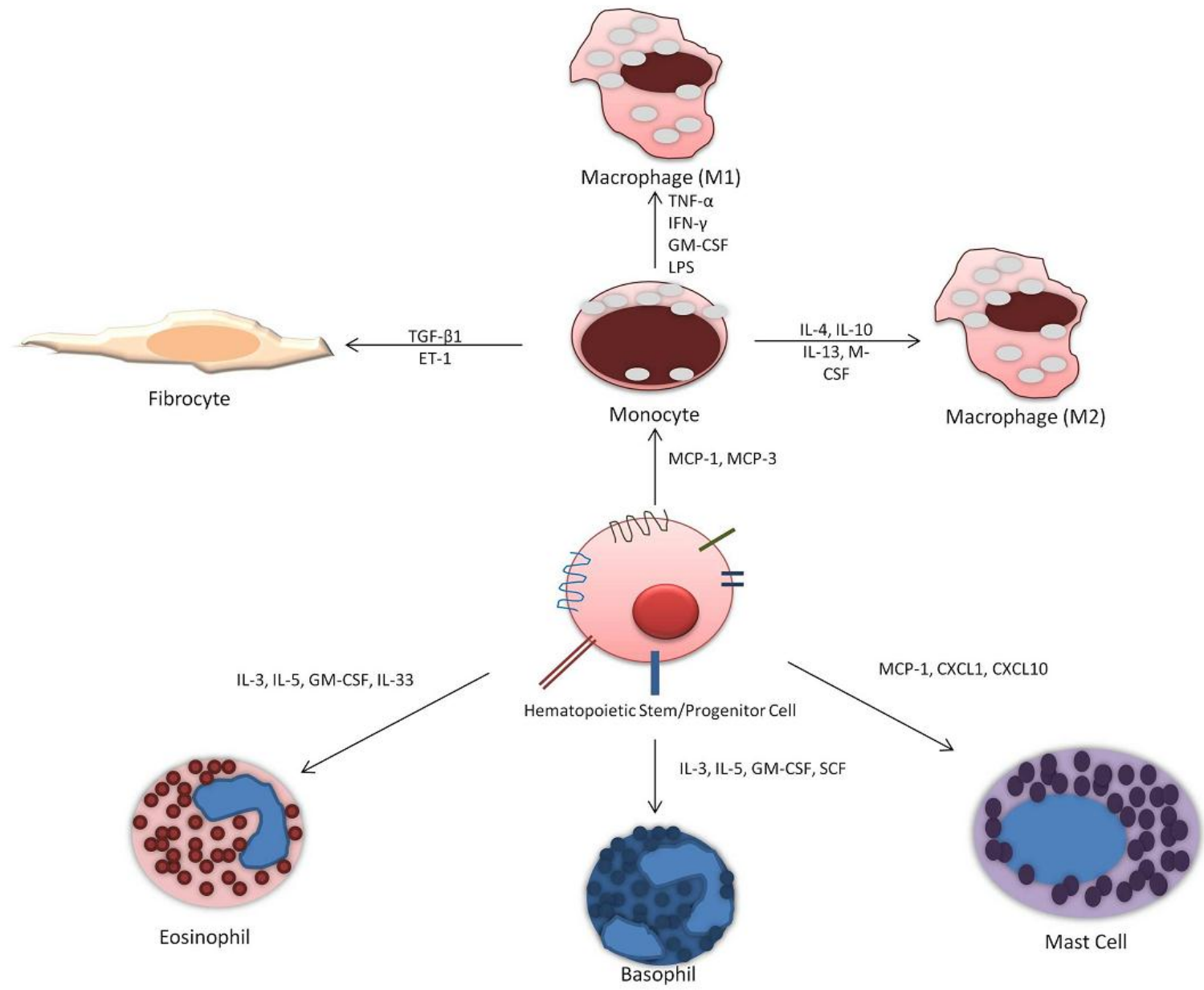
Presentacion antigenica y cambio de isotipo IgE



M
h

▶ HS
pul
SD
aur
CX

▶ CC
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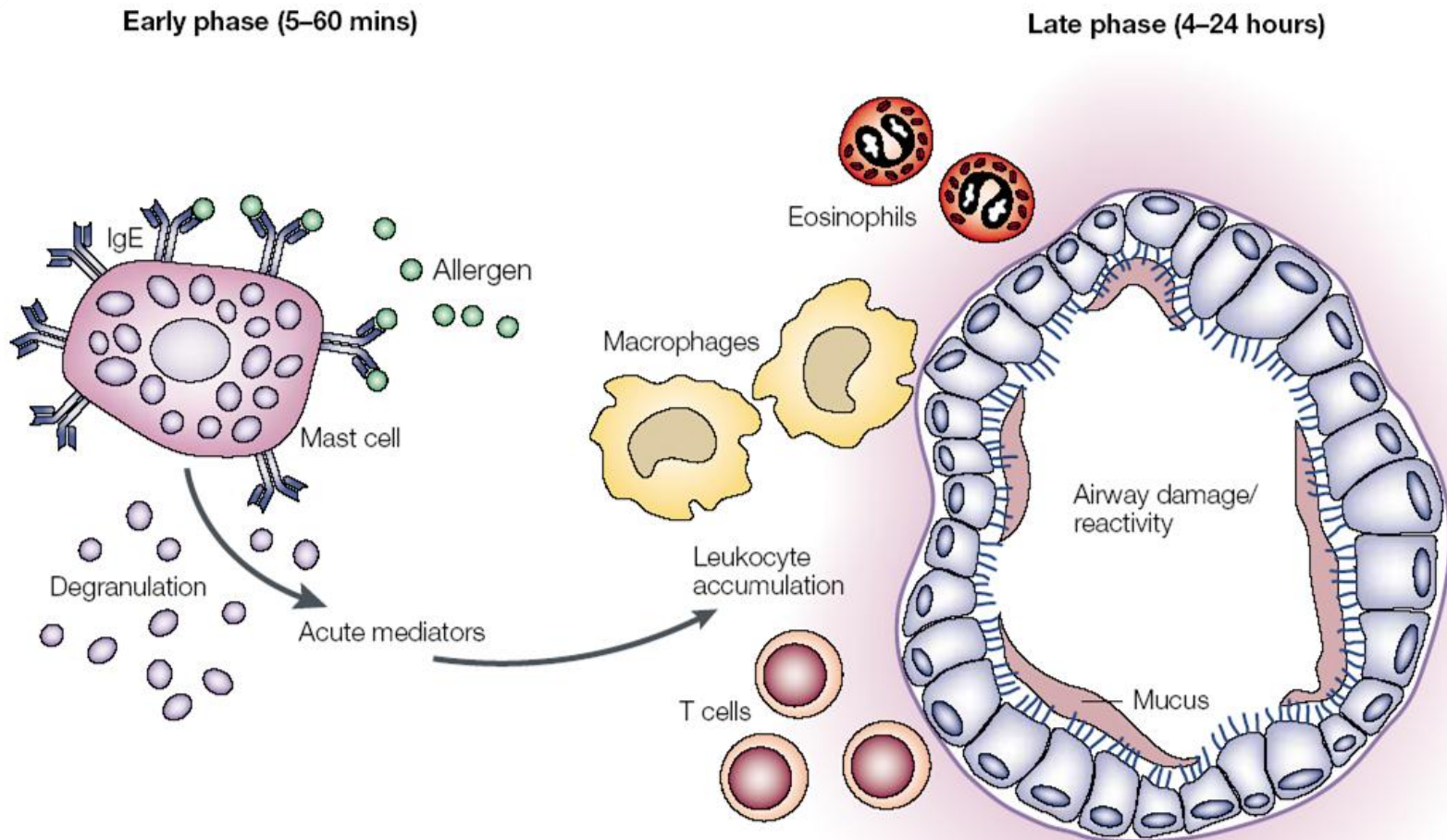


- Macrophage (M1)
- Macrophage (M2)
- Fibrocyte
- Monocyte
- Hematopoietic Stem/Progenitor Cell
- Eosinophil
- Basophil
- Mast Cell
- SDF-1 α
- Eotaxin
- SCF

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.

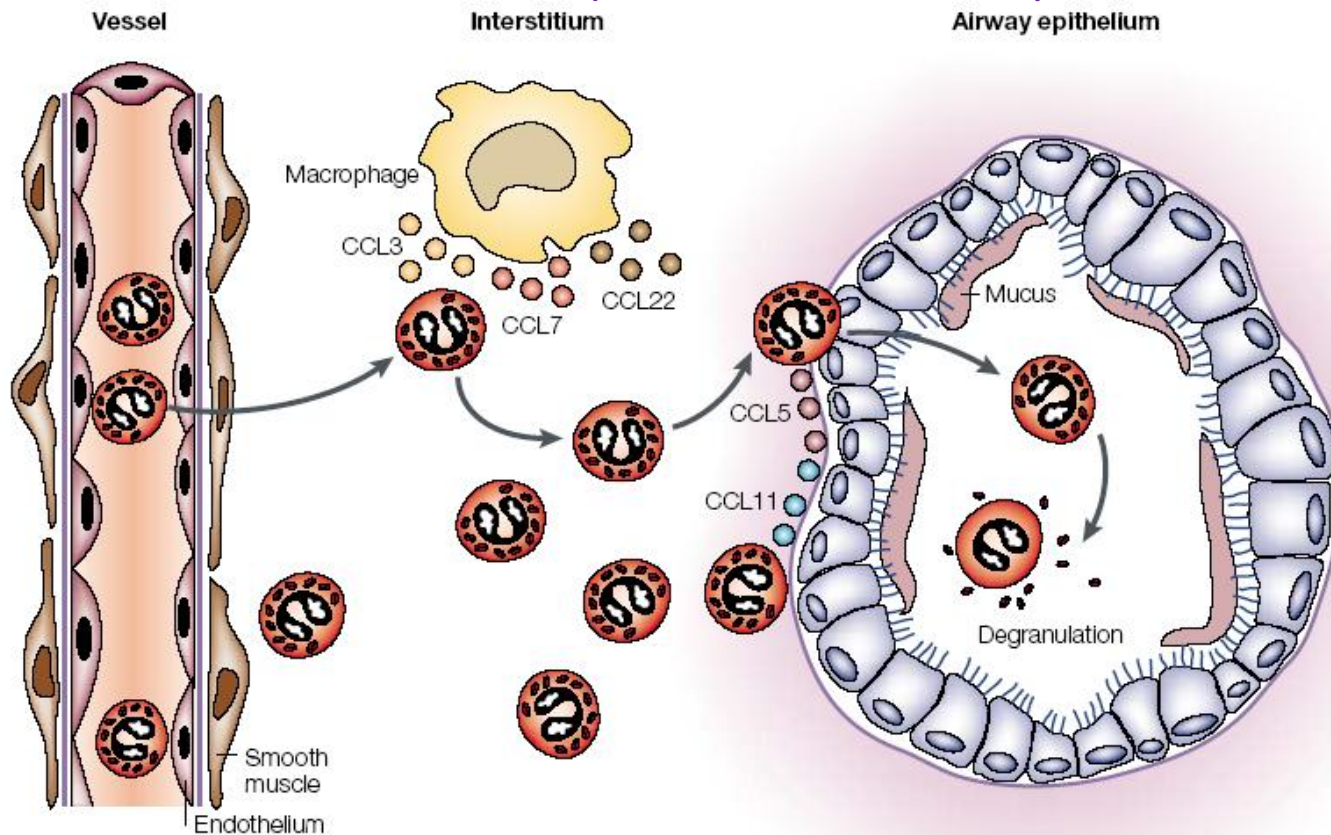
HIPERSENSIBILIDAD INMEDIATA:

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:

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

▶ Eosino

▶ Resp

▶ Atraí

CCL2

▶ IL-5 fa

y cito

▶ TSLP

expre

▶ Prote

facilita

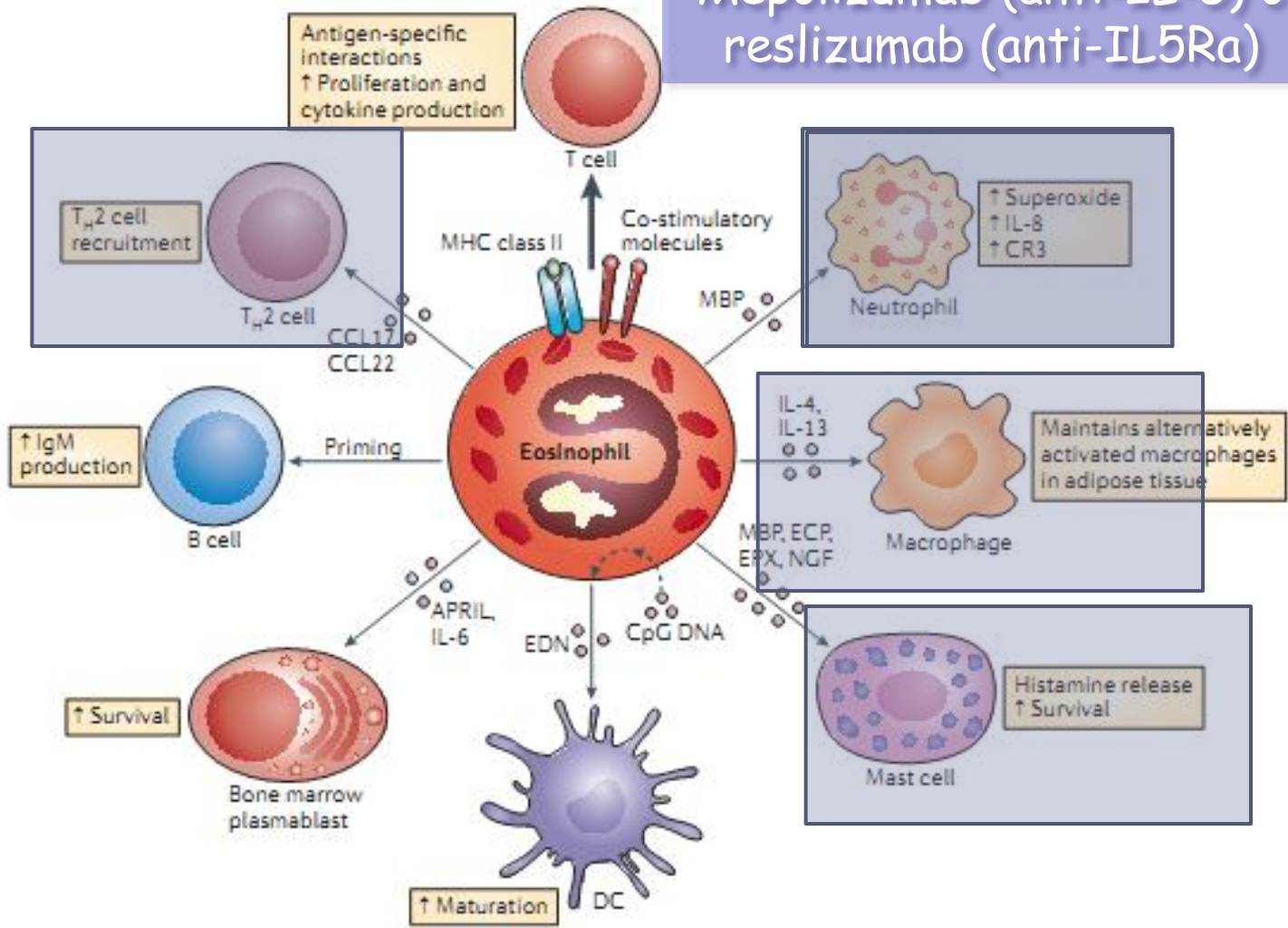
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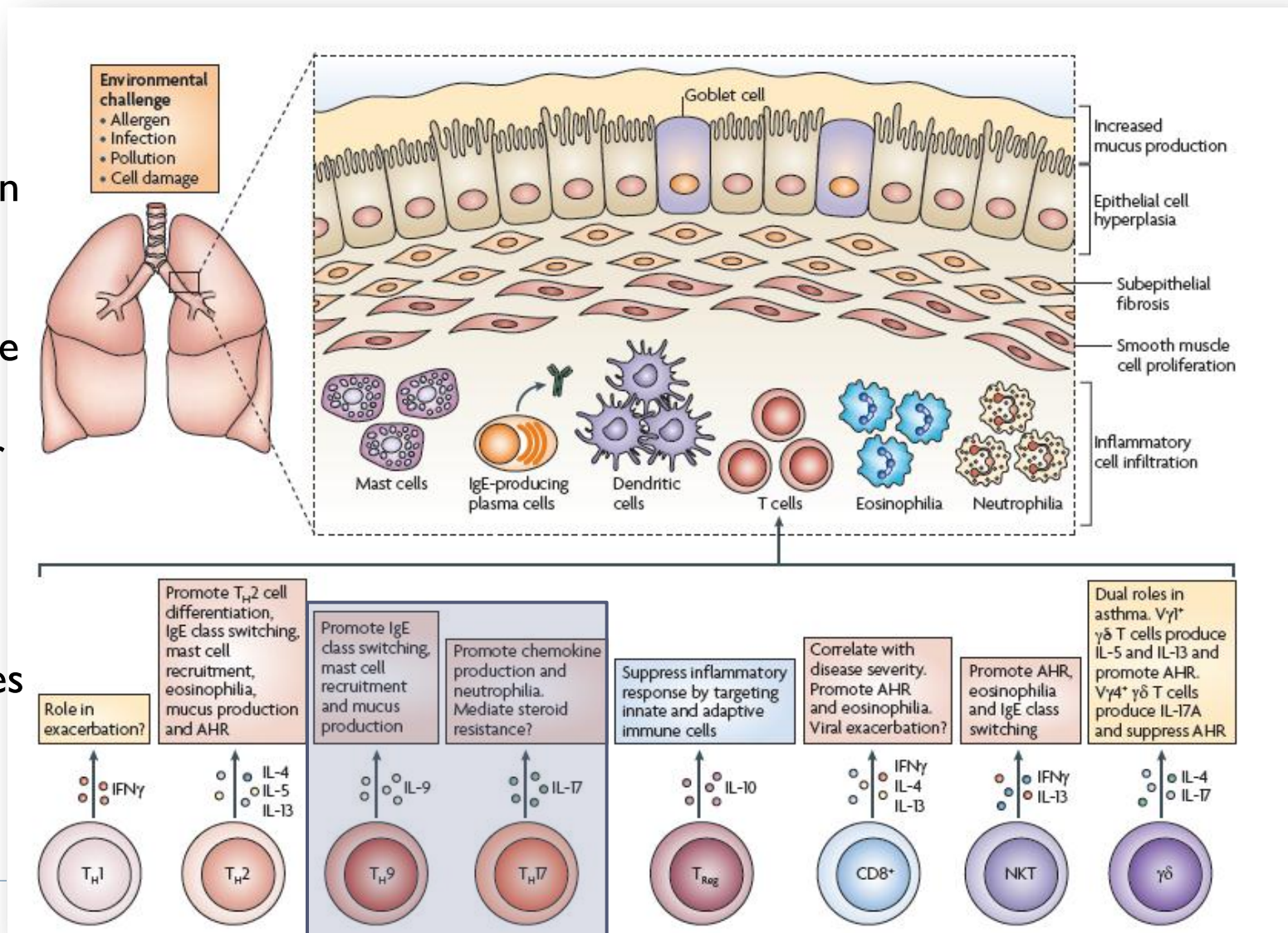
▶ Oxido

Mepolizumab (anti-IL-5) o
reslizumab (anti-IL5Ra)



Reclutamiento de células pro-inflamatorias

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



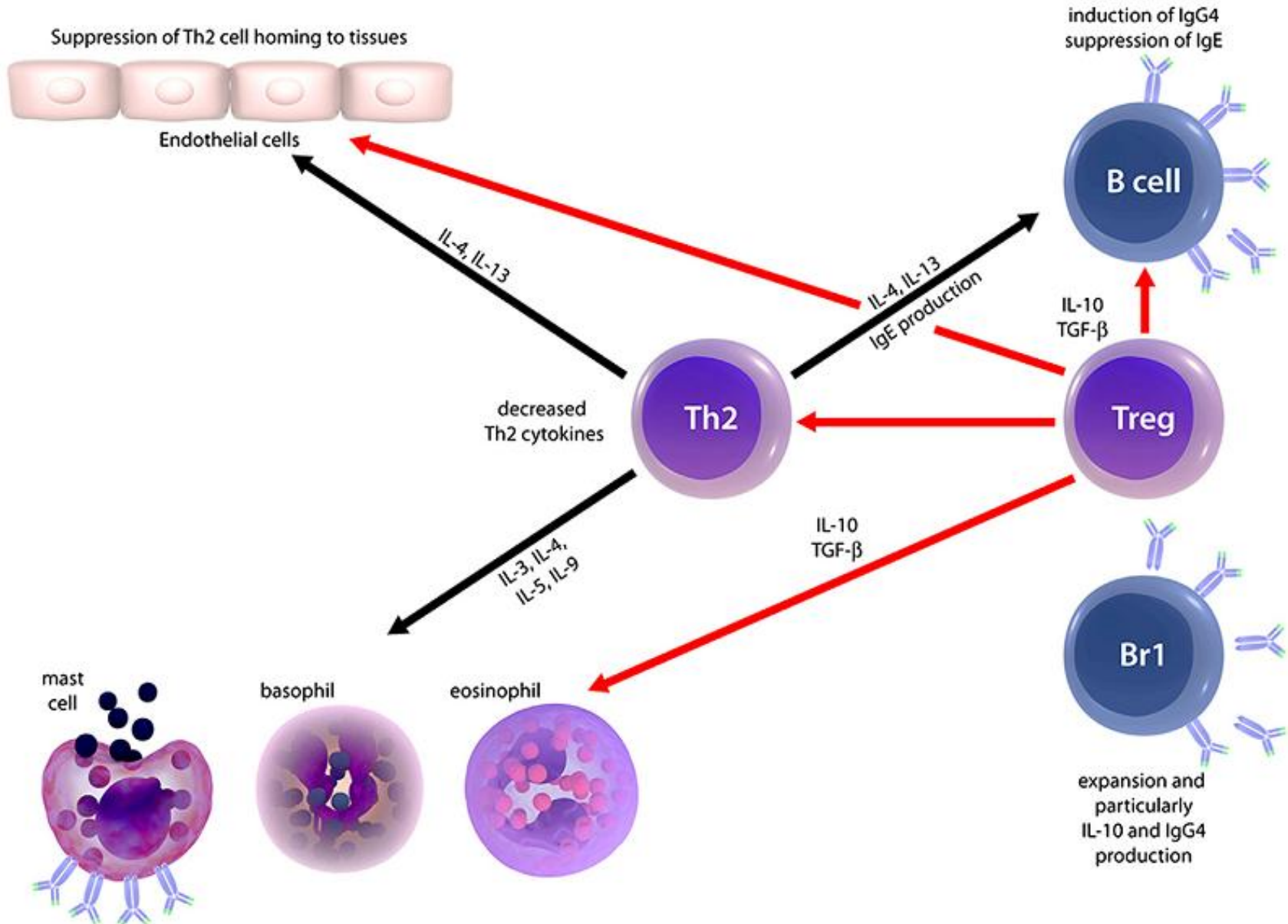
Terapia biológica e inmunoterapia

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 ⁷⁸	Decrease in asthma exacerbation rates and reductions in maintenance doses of oral corticosteroids ^{36,37} . 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 ²⁷⁻²⁹ .
Benralizumab (MedImmune/AstraZeneca)	Humanized IgG1	IL-5R α	NA	Decrease in asthma exacerbation rates when used to treat patients with asthma who have persistent eosinophilia despite corticosteroid treatment ⁴⁵ .
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 ⁴⁶ .
Lebrikizumab (Genentech/Roche)	Human IgG4	IL-13 (IL-4R α -binding epitope)	<10 pM ⁷⁹	No effect on FEV1 in steroid-naïve individuals with asthma ⁴⁷ . Improvements in FEV1 and asthma exacerbations in steroid-treated patients with moderate and severe asthma ⁴⁸ . Greatest effects in patients with high serum periostin levels.
GSK679586 (GlaxoSmithKline)	Human IgG1	IL-13R α 1 and IL-13R α 2	300–400 pM ⁸⁰	No improvement in FEV1 or exacerbations in patients with moderate to severe asthma.
Tralokinumab (MedImmune/AstraZeneca)	Human IgG4	IL-13R α 1 and IL-13R α 2	165 pM ⁸¹	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 α	NA	Maintenance of asthma control and FEV1 when corticosteroid dose is tapered in patients with moderate to severe asthma ³⁰ . 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 α , α -chain of the IL-5 receptor; NA, not applicable.

Papel de la inmunoterapia



Perspectivas futuras



Novel immunotherapy vaccine development

Marek Jutel^{a,b} and Cezmi A. Akdis^c

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

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Review

Vitamin E and D regulation of allergic asthma immunopathogenesis[☆]

Joan M. Cook-Mills^{*}, Pedro C. Avila

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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

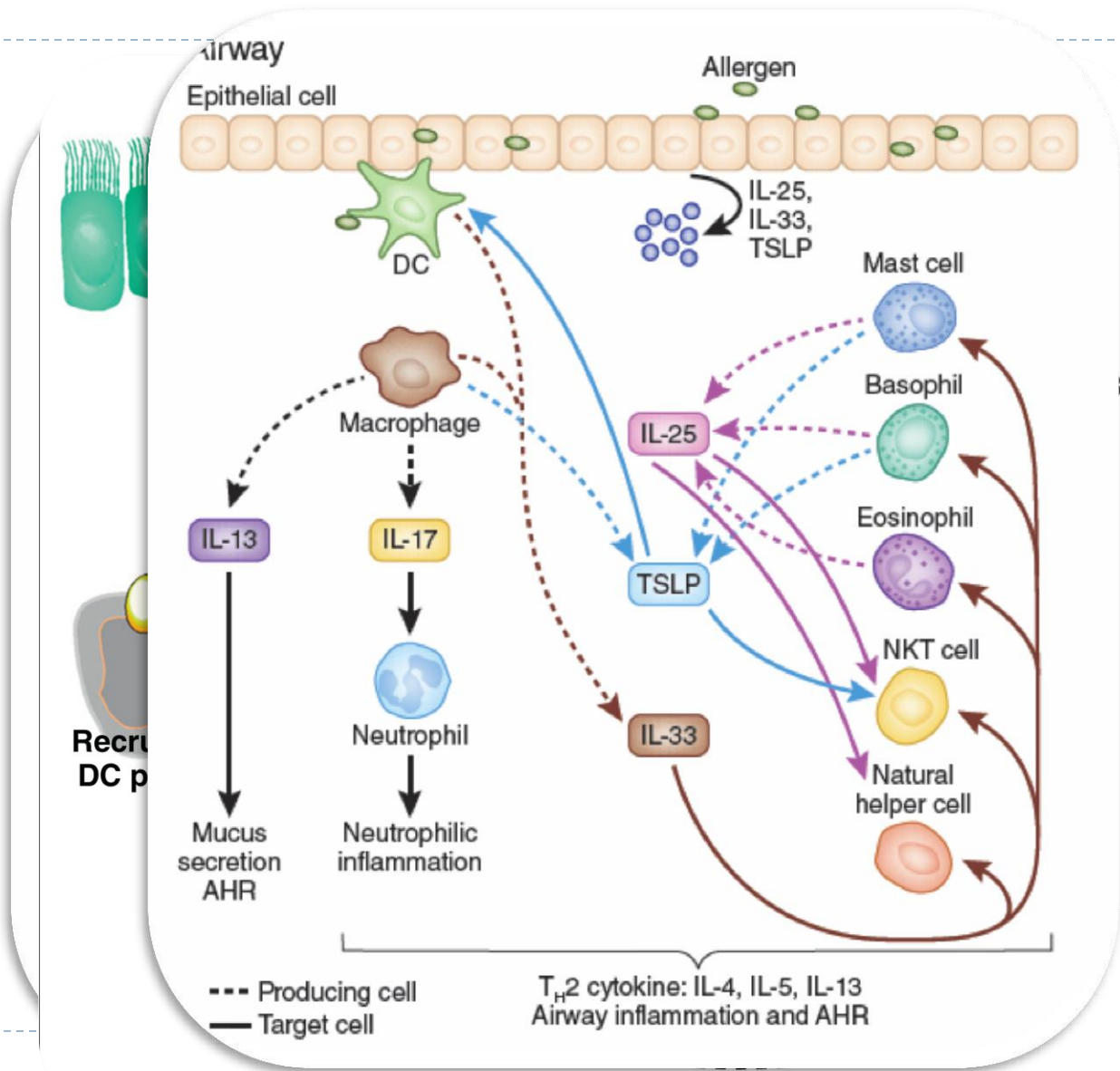
(J Allergy Clin Immunol 2014; nnn : nnn - nnn .)

Inmunopatogenia del asma: Resumen

- ▶ Individuo genéticamente predispuesto
- ▶ Alergenos
- ▶ Producción de IgE por el linfocito B durante el primer contacto
- ▶ Unión de la IgE a los receptores Fc ϵ 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

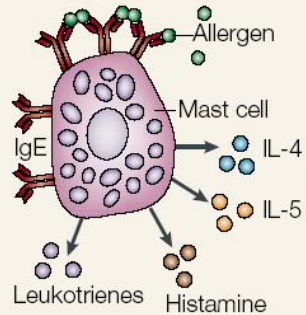


Inmunopatogenia del Asma: RESUMEN

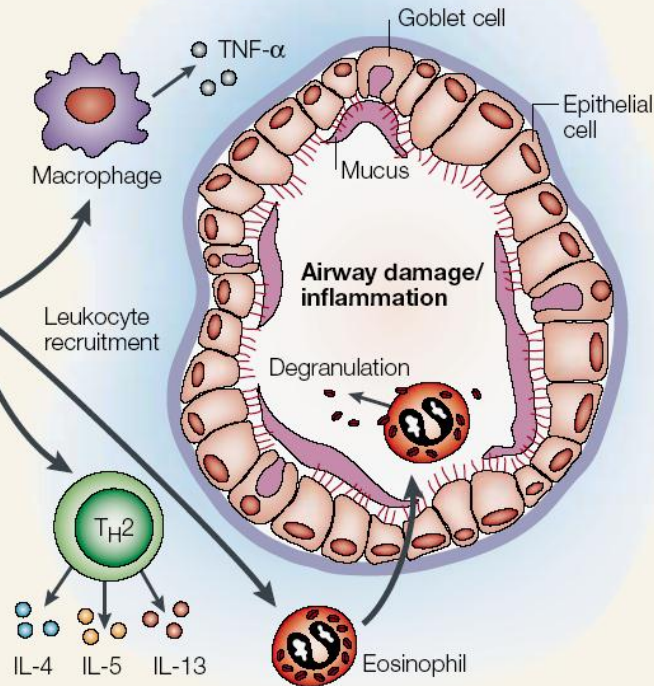


Inmunopatogenia del Asma: RESUMEN

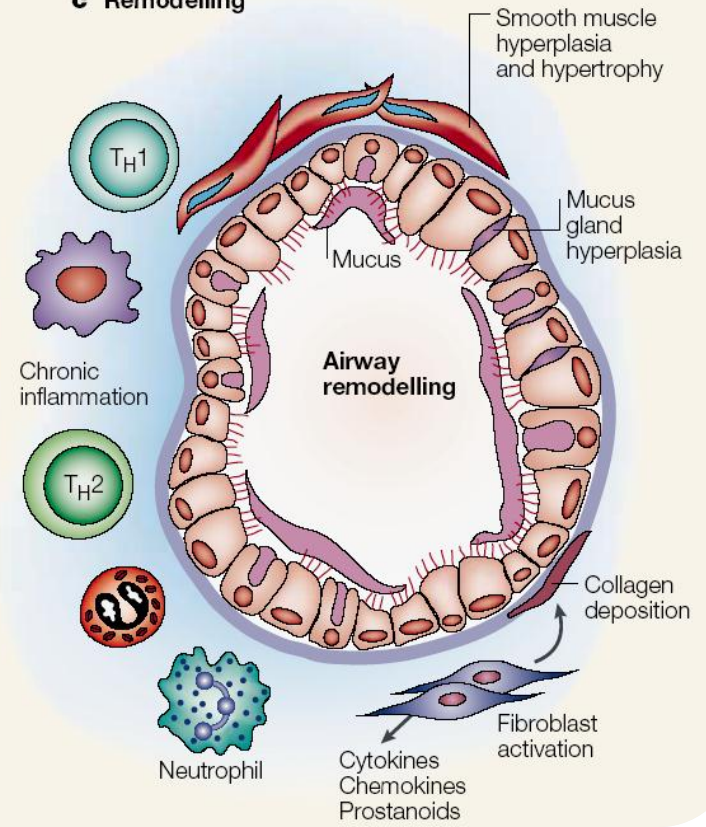
a Acute phase



b Chronic phase



c Remodelling



IL-4 IL-5 IL-13

Eosinophil

Neutrophil

Cytokines

activation