CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Nantes Université

CRTI UMR 1064 Centre de Recherche en Transplantation et Immunologie

Rôle de l'immunité innée dans la réponse allergique

Maladies Allergiques et Apparentées

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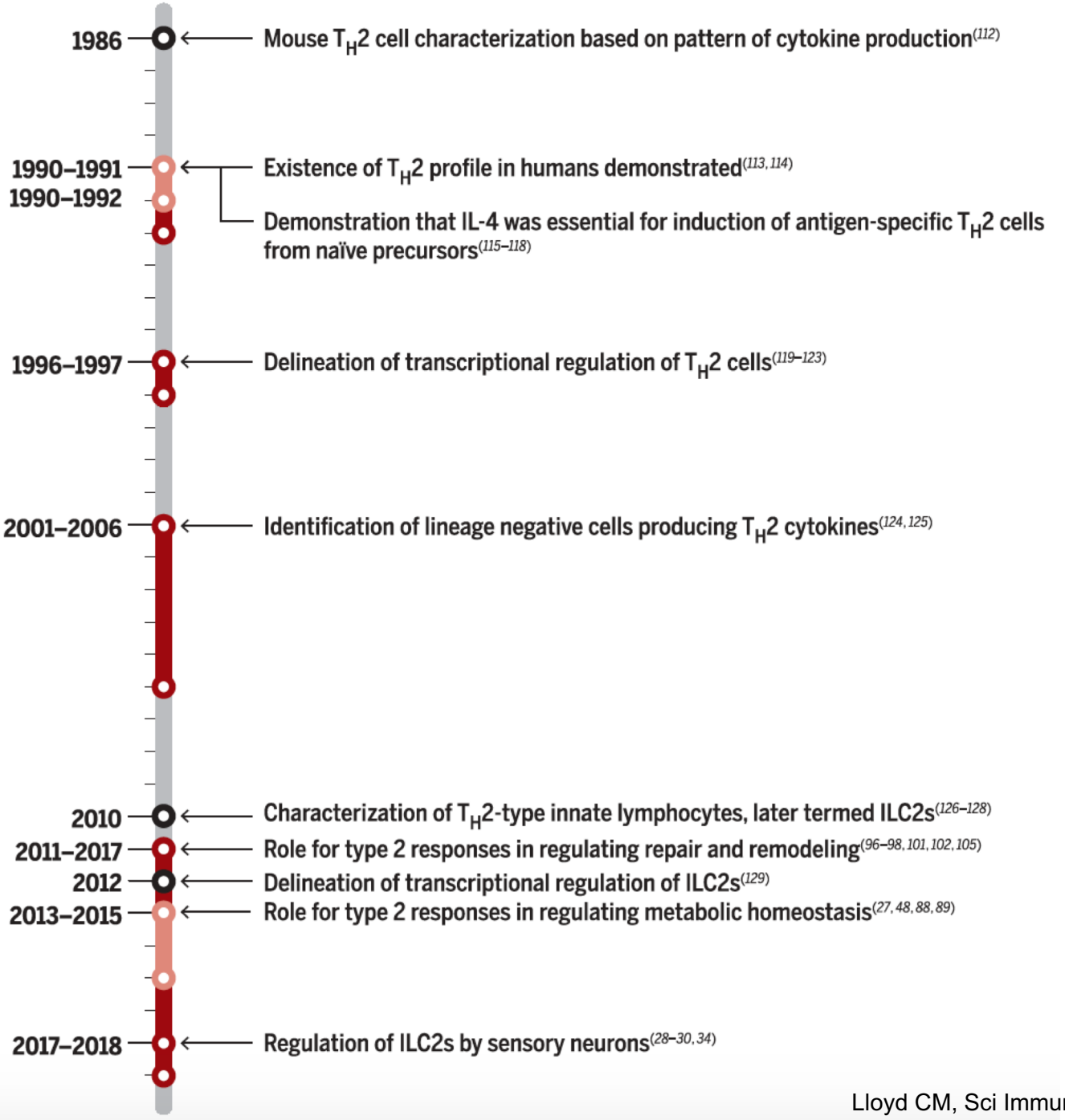
MASTER 1 Sciences et Santé + MASTER 1 Sciences du médicament

Chronologie des découvertes relatives aux réponses Th2

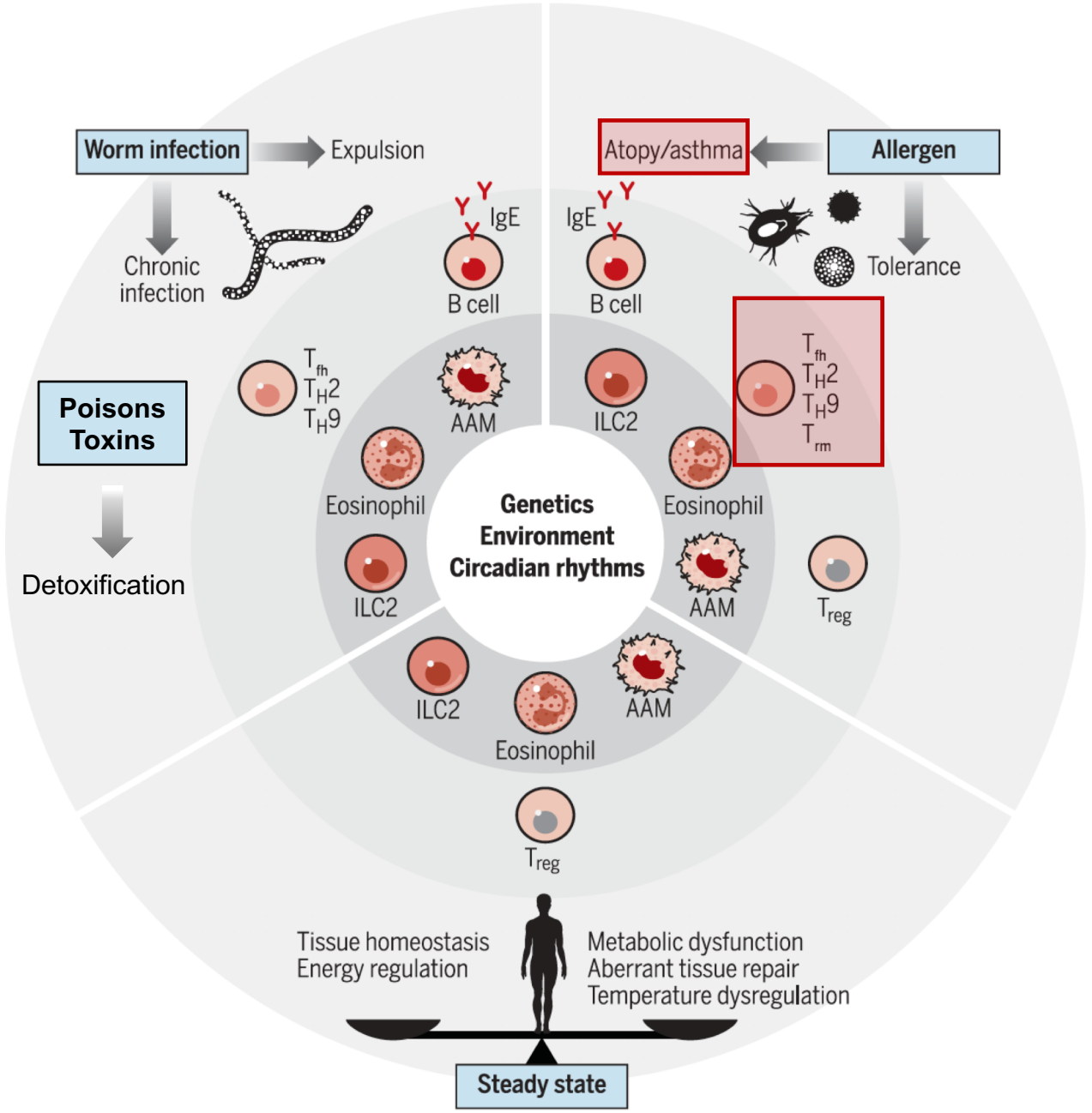


Lloyd CM, Sci Immunol, 2018

Contribution de l'Immunité de Type 2 aux processus homéostatiques et pathologiques

Immunité de type 2:

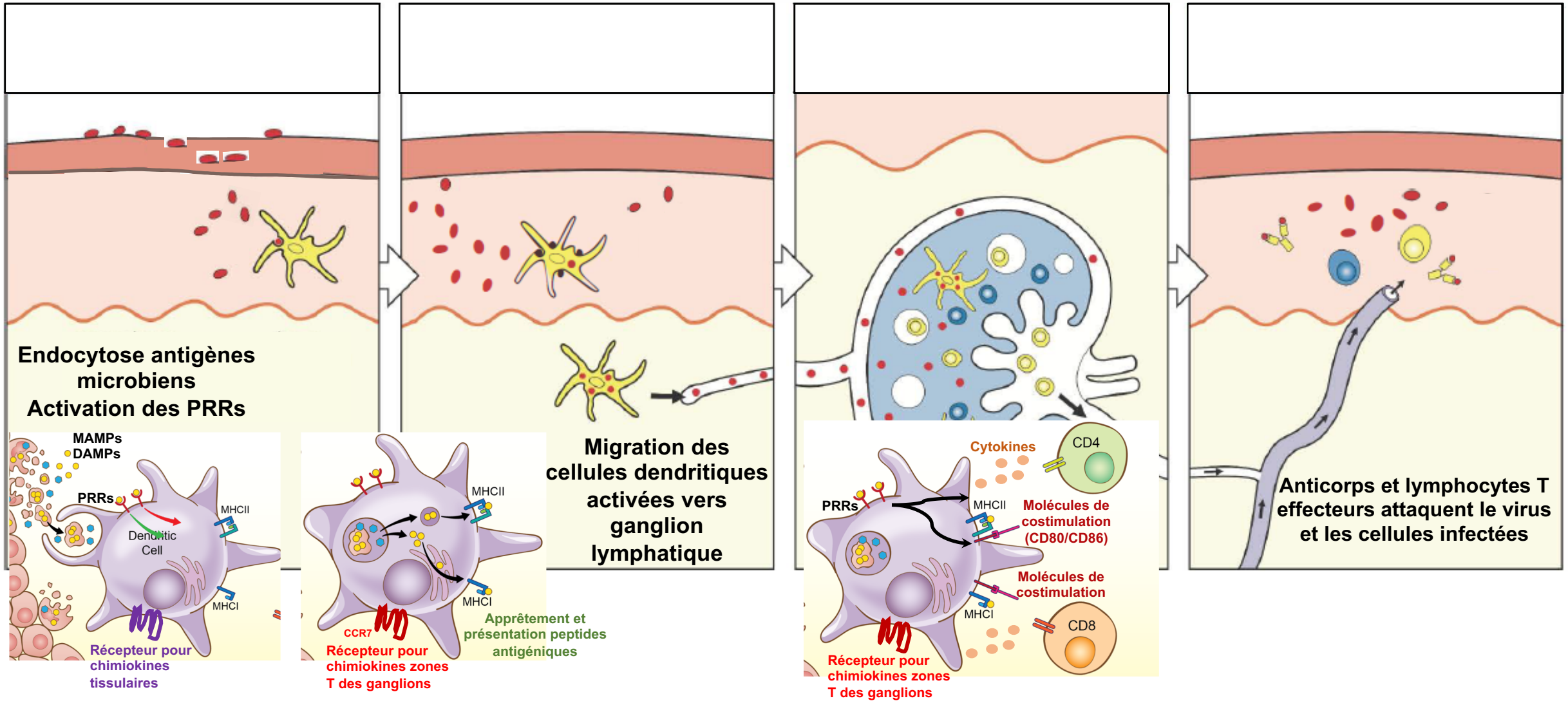
Réponses immunitaires caractérisées par la production des cytokines **IL-4, IL-5 et IL-13** par les lymphocytes T et innées



Lloyd CM, Sci Immunol, 2018

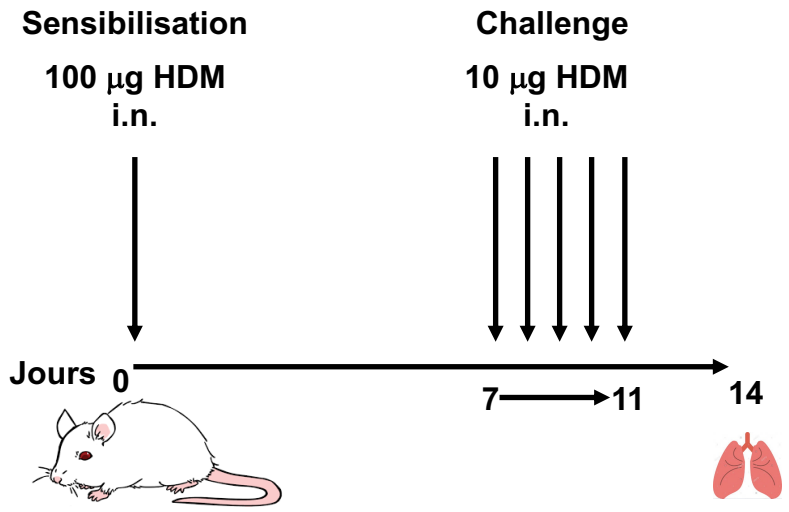
Induction des réponses adaptatives T

Qu'en est-il des réponses Th2 ??

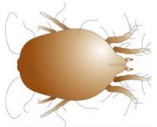


Les cellules dendritiques sont nécessaires et suffisantes à la réponse allergique

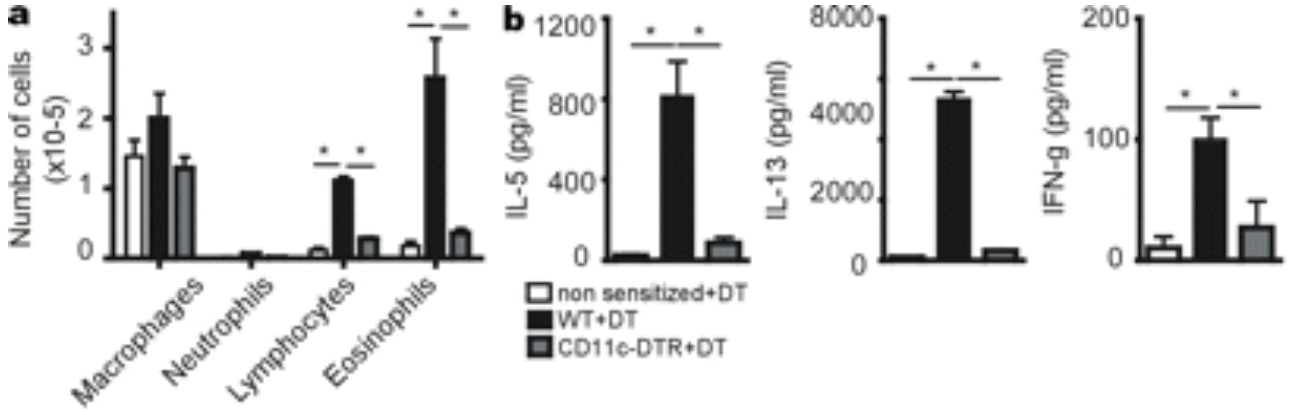
Modèle de réponse allergique pulmonaire



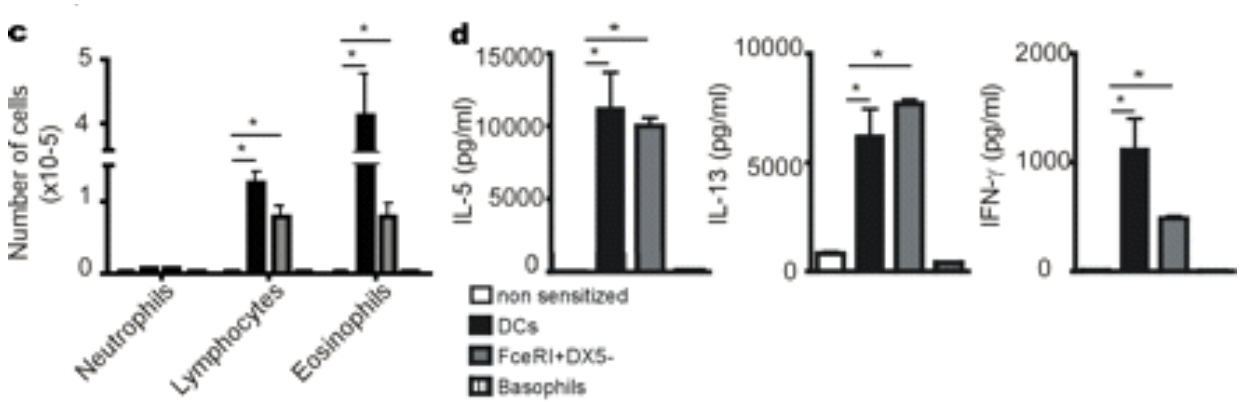
HDM: House dust mite



L'absence de cellules dendritiques prévient le développement de la réponse allergique



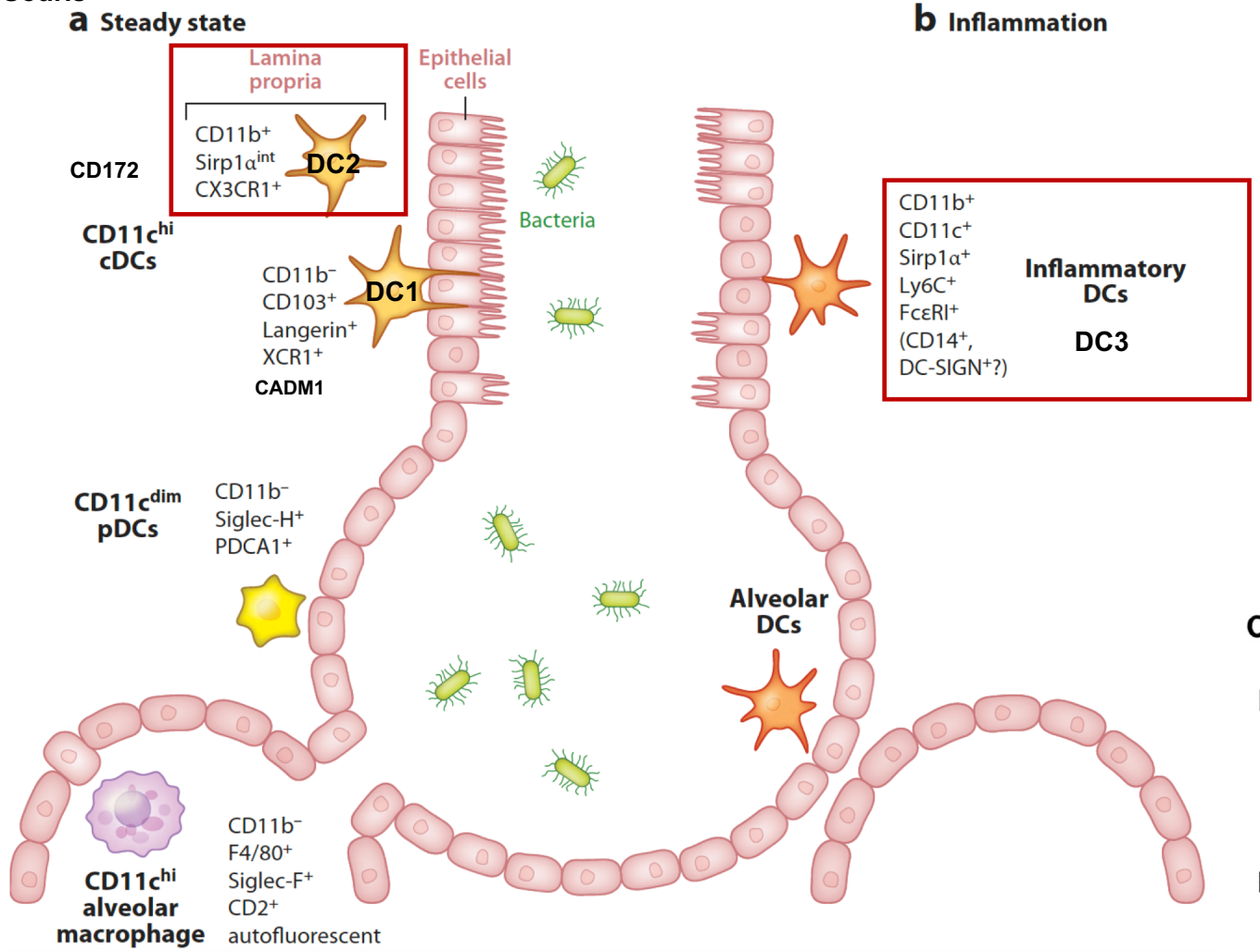
L'injection de cellules dendritiques issues de souris sensibilisées par HDM avant la sensibilisation induit une réponse allergique

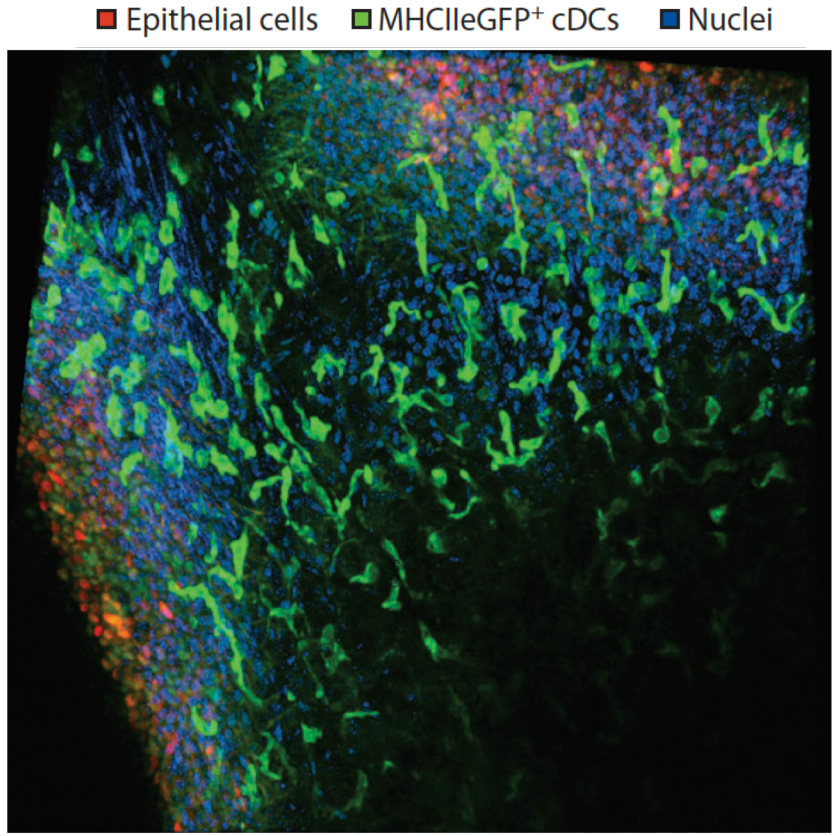


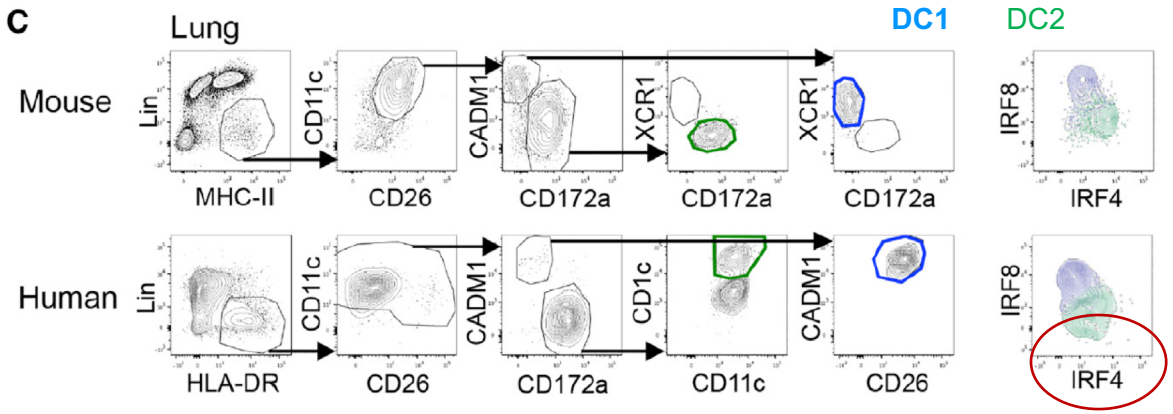
Hammad H, J Exp Med, 2010

Populations de cellules dendritiques dans le poumon

Souris





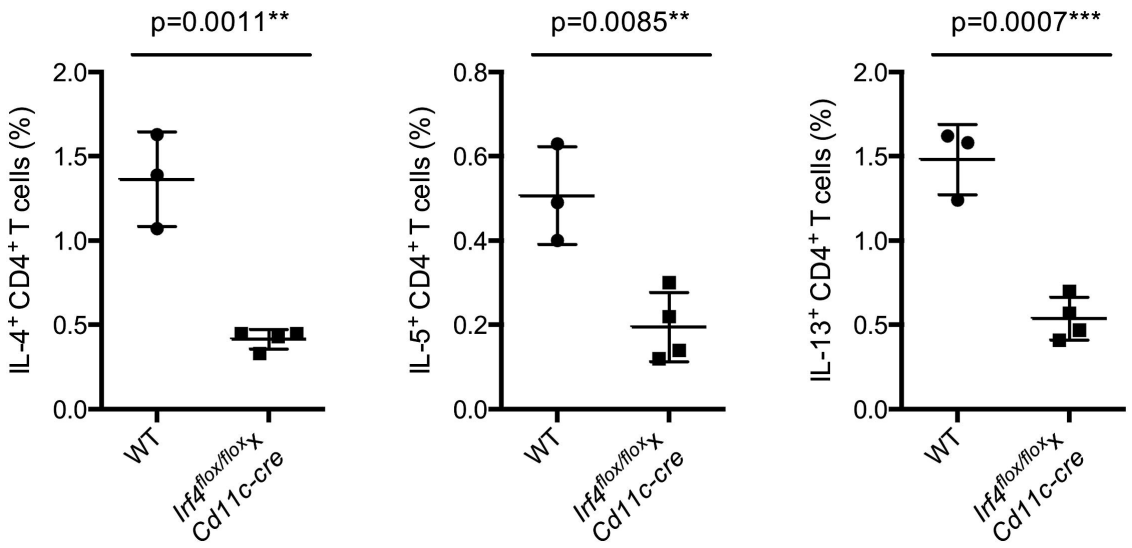


Lambrecht B, Ann Rev Immunol, 2012

Guilliams M, Immunity, 2016

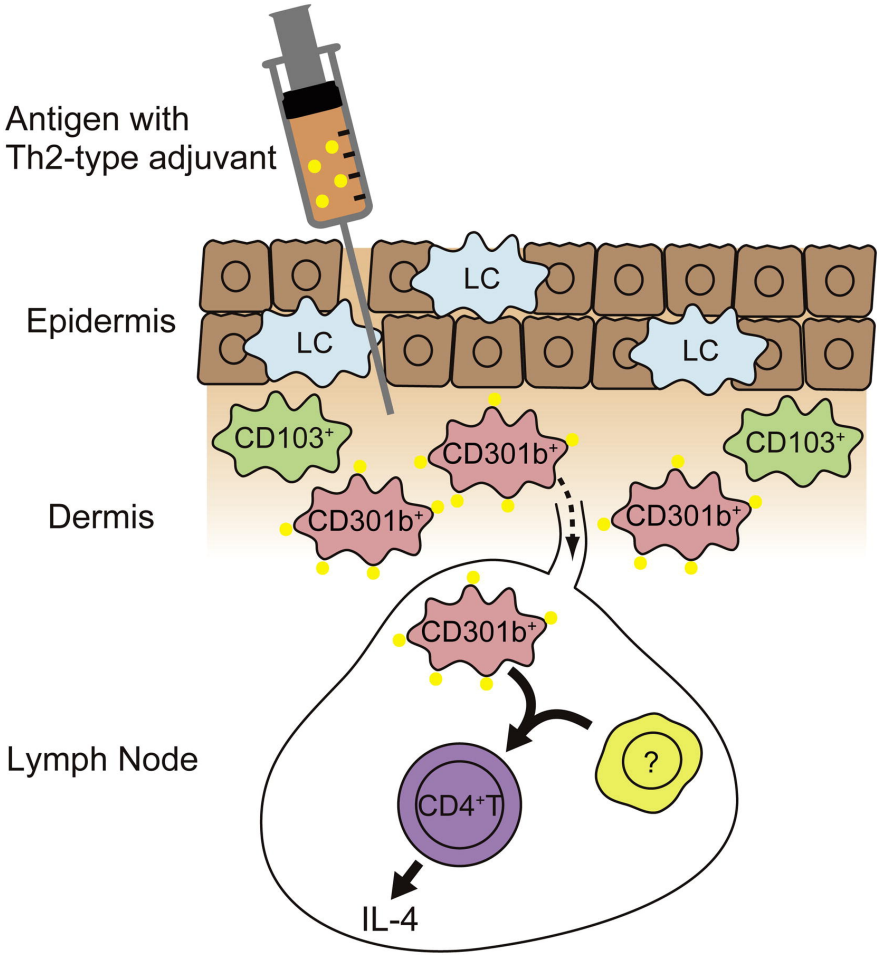
L'induction des réponses Th2 est assurée par les DC2

Perte de la réponse Th2 dans l'infection par *Nippostrongylus brasiliensis* en l'absence de DC2



Gao Y, Immunity, 2013

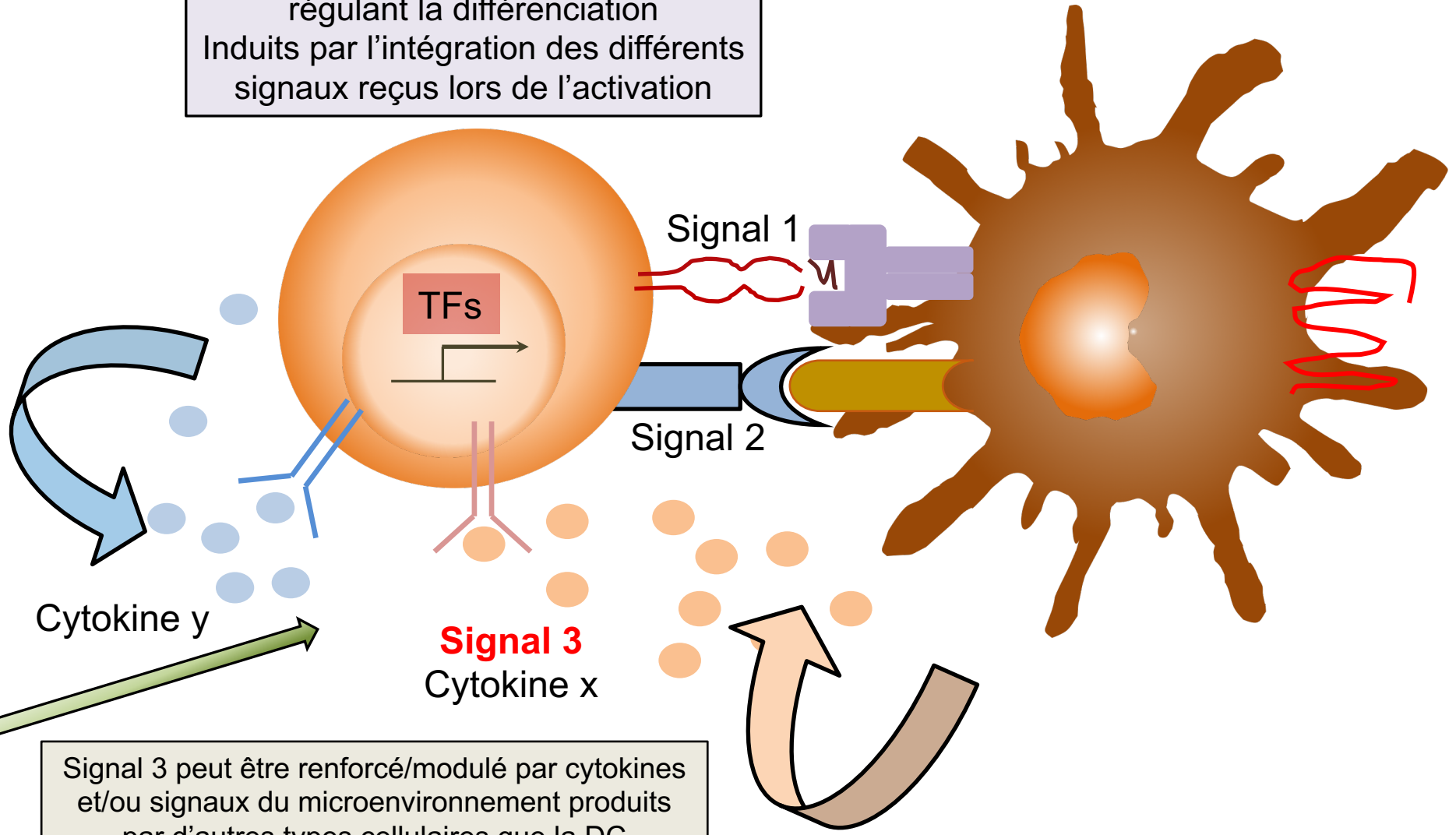
Les DC2 pro-Th2 expriment CD301b



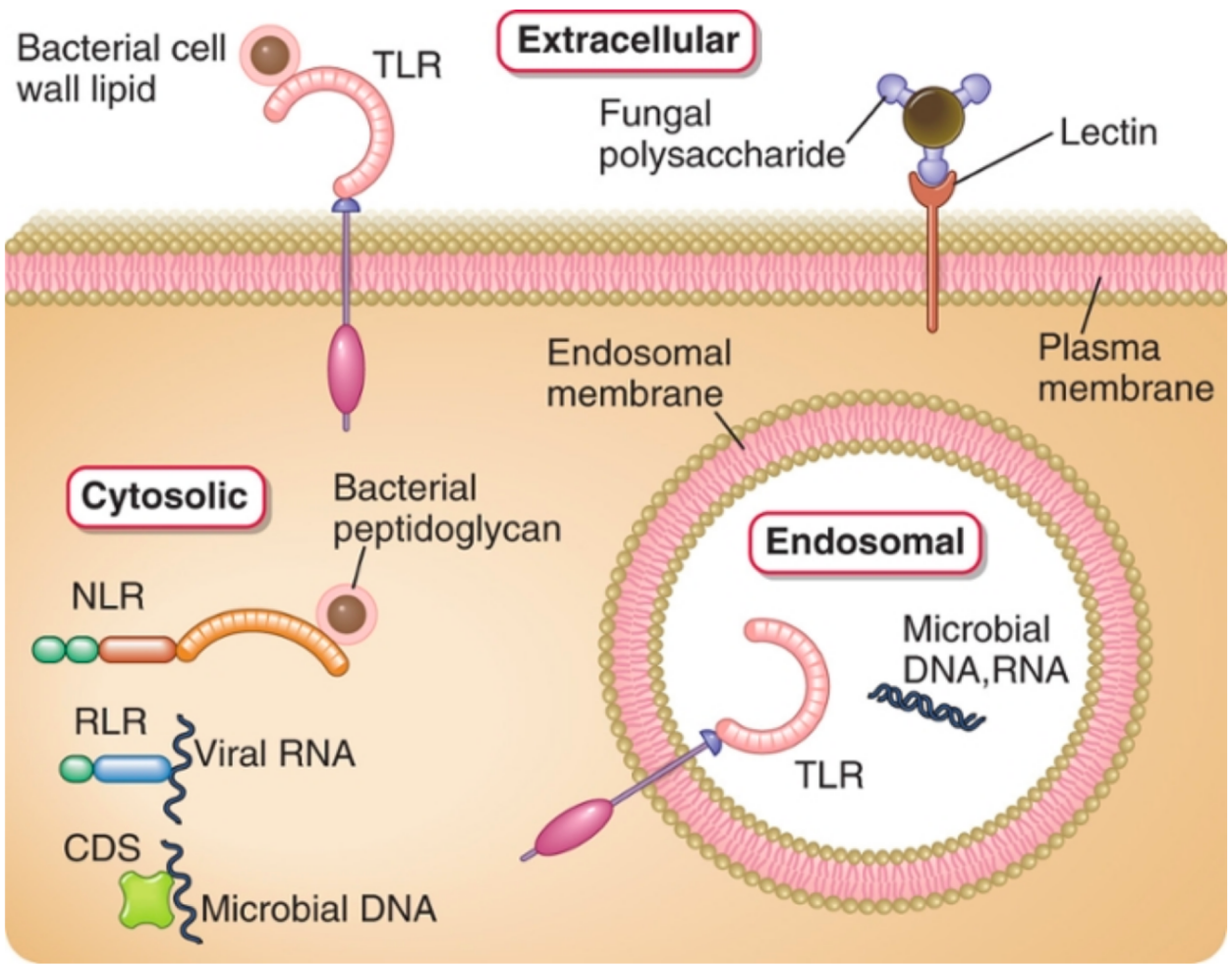
Kumamoto Y, Immunity, 2013

Principe général de la différenciation du lymphocyte T CD4+ en cellule effectrice

Facteurs de transcritpion majeurs régulant la différenciation
Induits par l'intégration des différents signaux reçus lors de l'activation



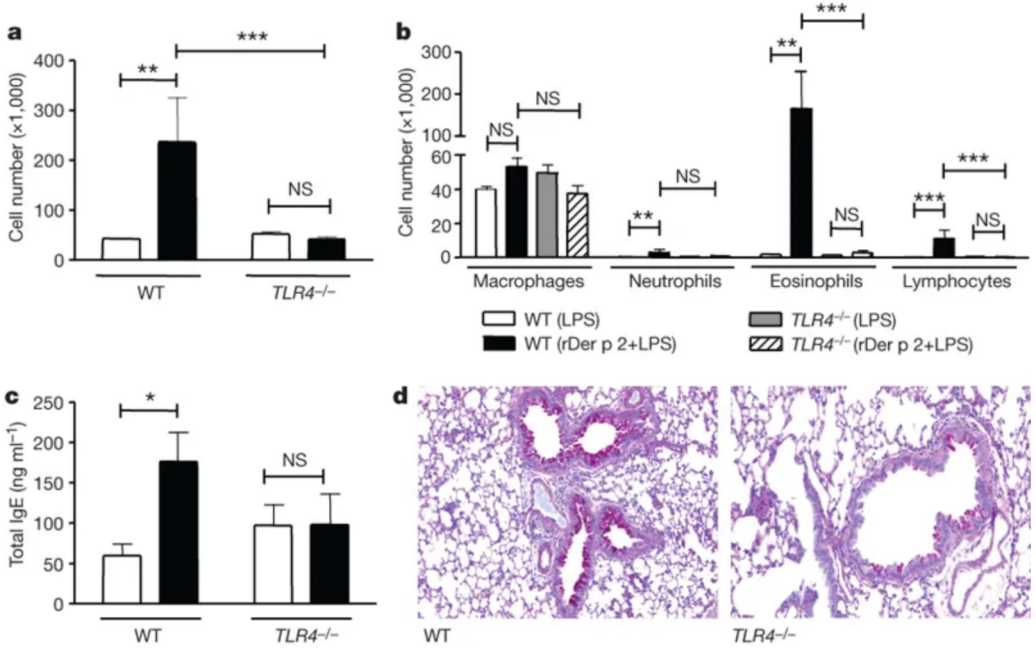
Pattern recognition receptors (PRR)



Les allergènes contiennent des motifs capables d'engager les PRR

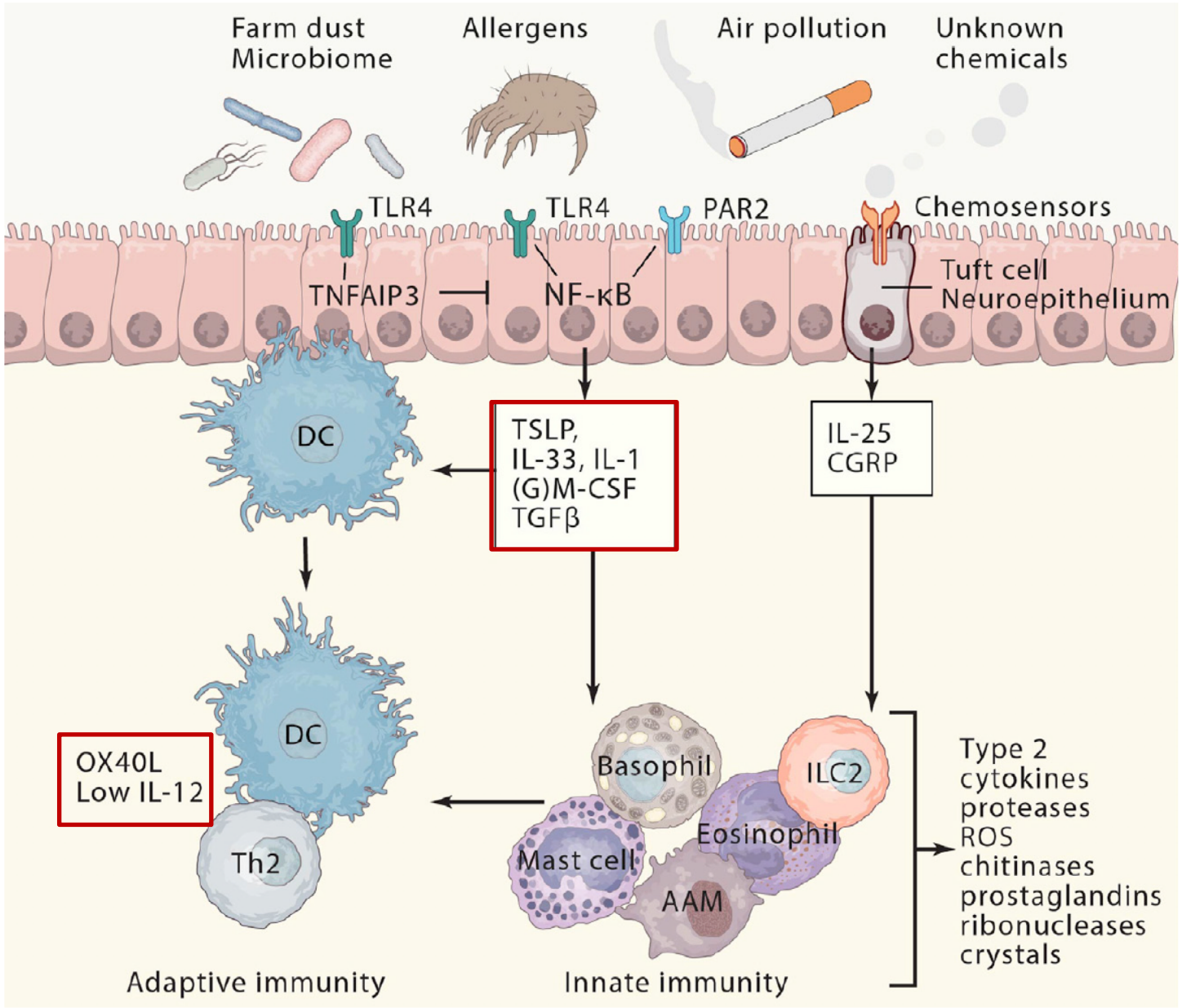
(Wills-Karp M, Curr Op Immunol, 2010)

Der p 2, l'allergène principal de HDM, se lie à TLR4 (non montré)
La réponse allergique à Der p 2 est perdue en l'absence de TLR4



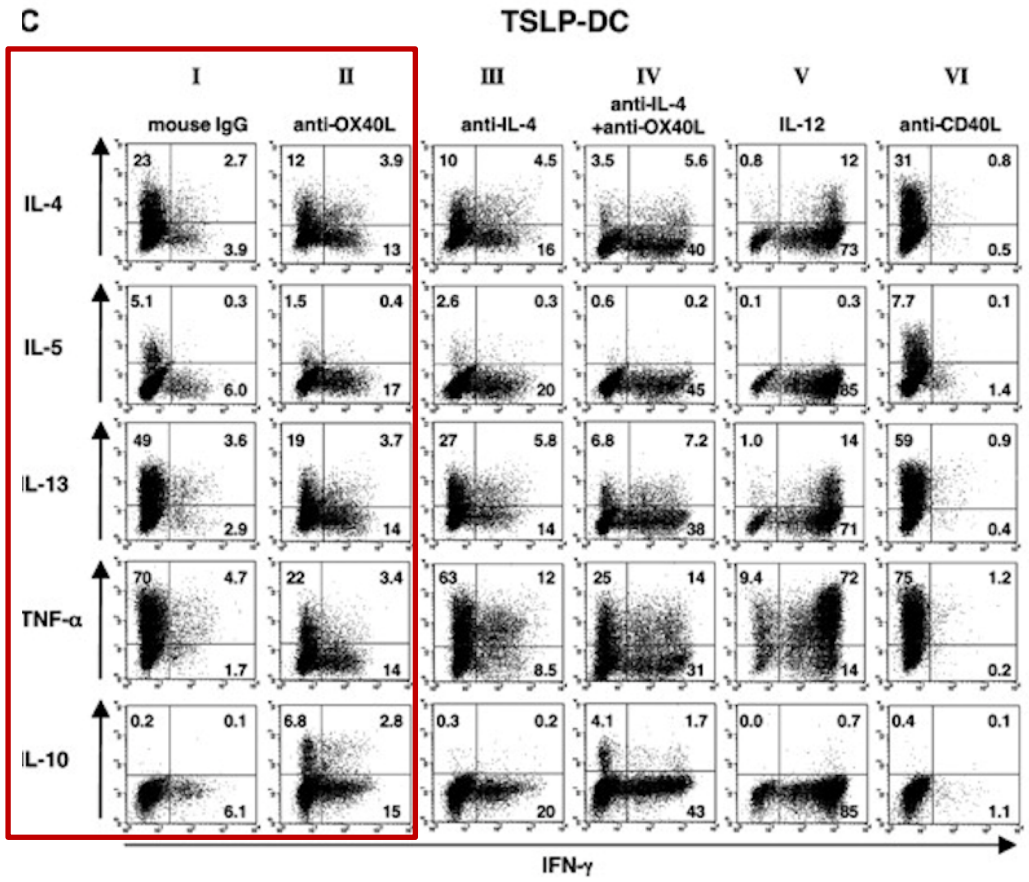
Trompette A, Nature, 2009

Les DC acquièrent la possibilité d'induire des réponses Th2 en réponse à des cytokines épithéliales



Lambrecht B, Immunity, 2019

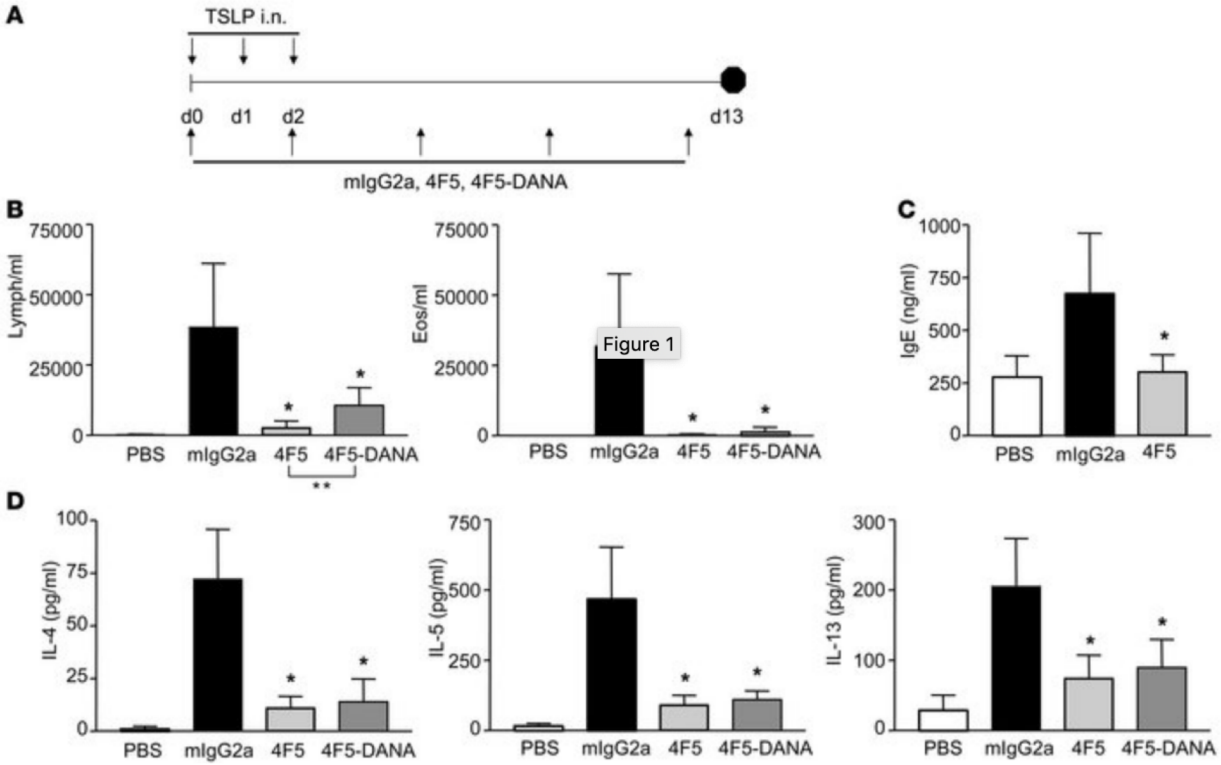
Co-culture de T CD4⁺ naïves en présence de DC activées par TSLP



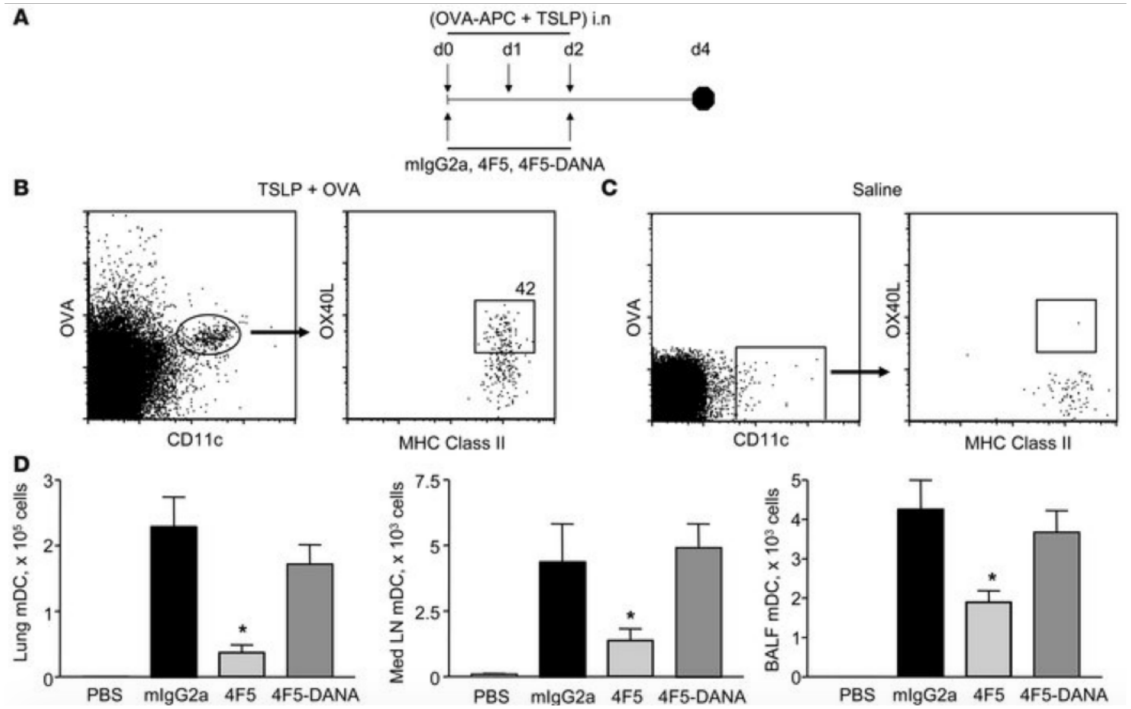
Ito T, J Exp Med, 2005

OX40L: signal de costimulation (signal 2) dans réponses allergiques de type 2

Blocage d'OX40L prévient les réponses inflammatoires induites par TSLP dans le poumon et la peau

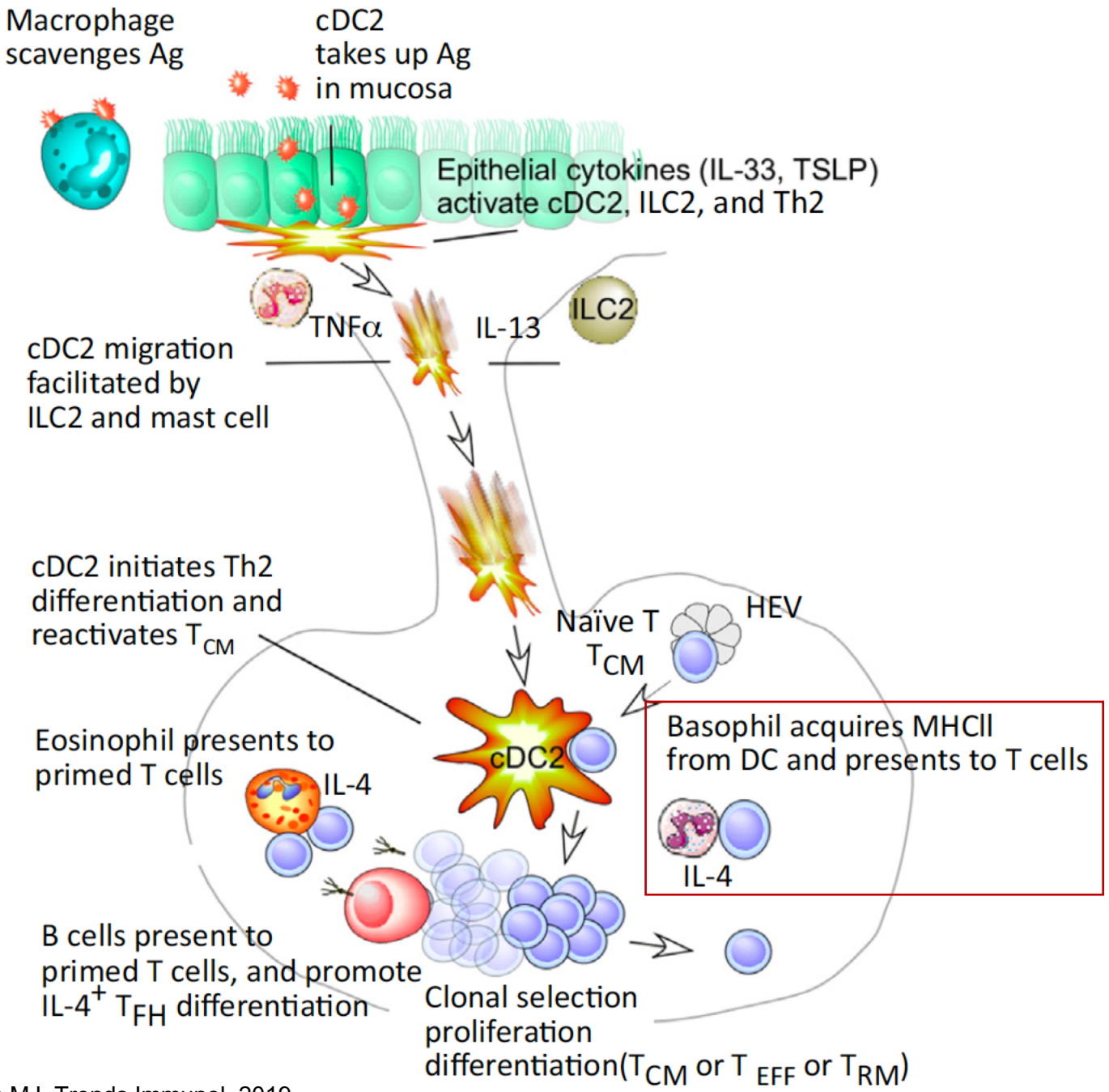


La protection induite par l'anti-OX40L dépend en partie de la déplétion des DC OX40L⁺



4F5: anti-OX40L
4F5-DANA: anti-OX40L sans region effectrice

Seshasayee D, J Clin invest, 2007



Schuijs MJ, Trends Immunol, 2019

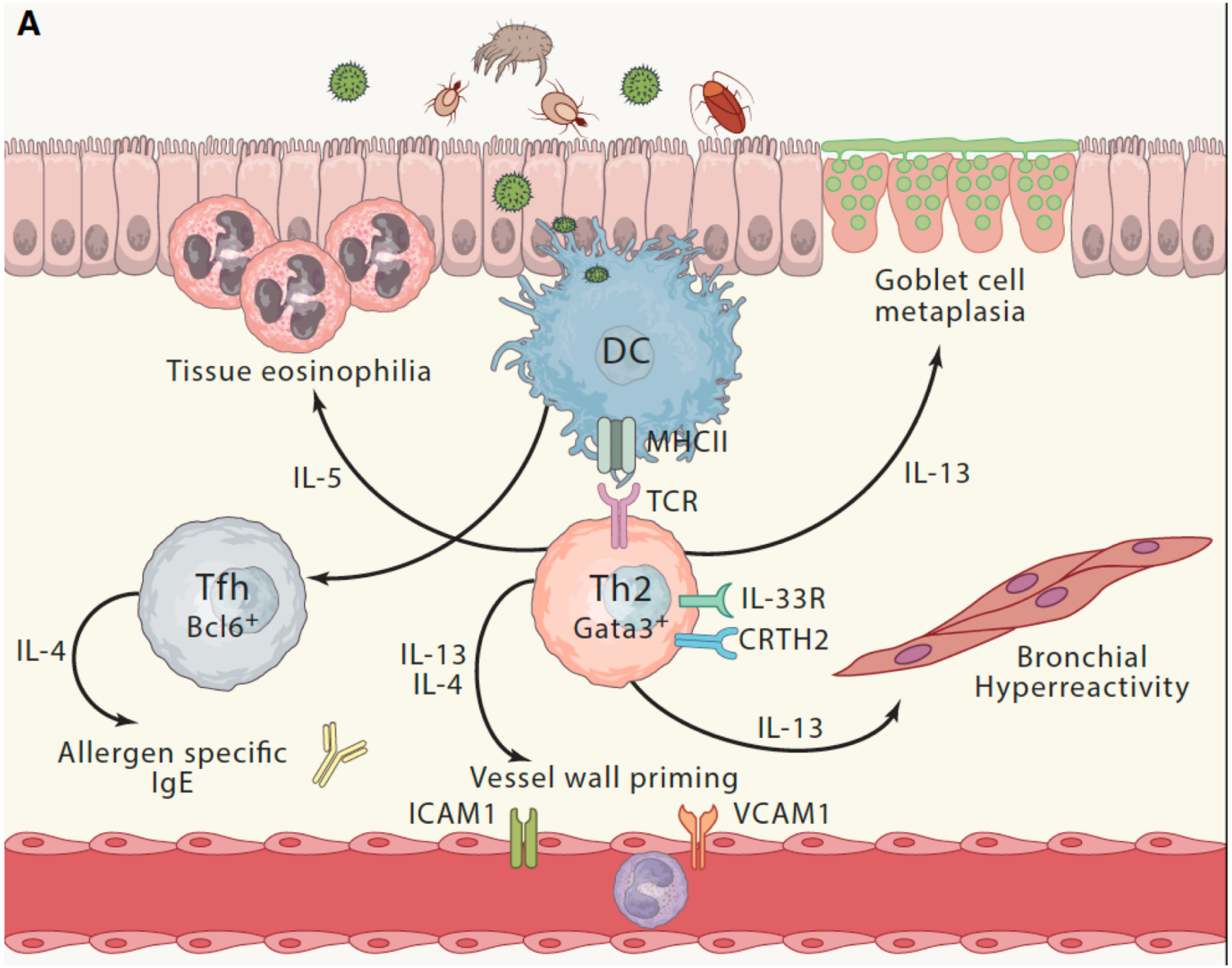
Signalisation STAT6 induite par IL-4 est essentielle aux réponses Th2

Shimoda K, Nature, 1996

Les DC ne produisent pas d'IL-4

Les basophiles **pourraient** représenter une source d'IL-4 contribuant à la polarisation Th2 (signal 3) dans les ganglions

Rôles des cytokines Th2 dans la réponse allergique



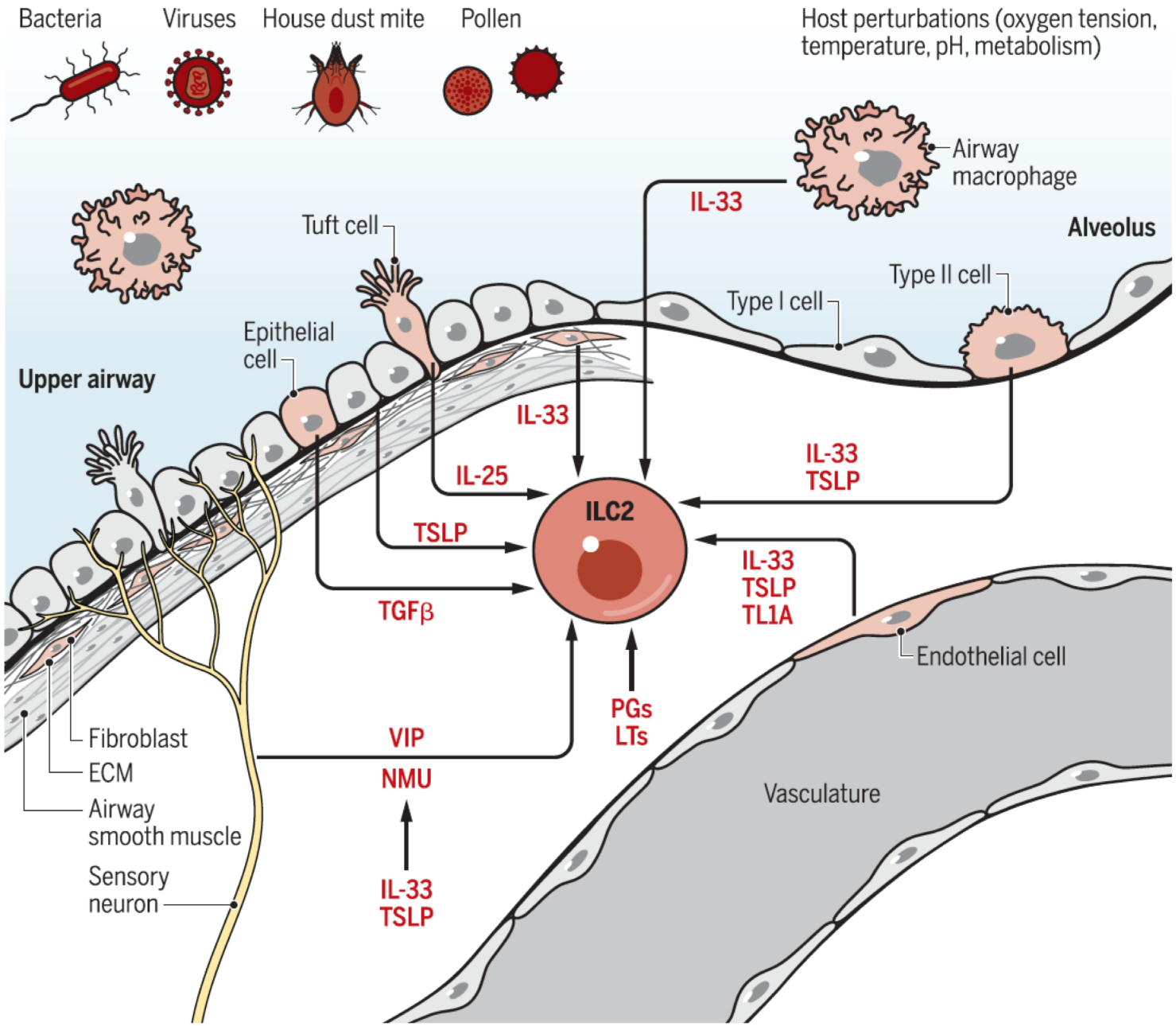
Lambrecht B, Immunity, 2019

Table 1. Summary of Data from Clinical Trials of Treatments Directed at Type 2 Cytokines in Asthma*

Drug	sotope	Targeted Epitope	Relative Affinity	Main Effects in Human Asthma Trials
Mepolizumab (GlaxoSmithKline)	Humanized IgG1	IL-5	N/A	Decrease in asthma exacerbation rates in patients with moderate and severe asthma selected for systemic eosinophilia. Small effects on FEV1 and asthma symptoms (Bel et al., 2014; Haldar et al., 2009).
Benralizumab (MedImmune/ AstraZeneca)	Humanized IgG1	IL-5Rα	N/A	Decrease in asthma exacerbation rates in patients with moderate and severe asthma selected for systemic eosinophilia. Small effects on FEV1 and asthma symptoms (Bleecker et al., 2016; FitzGerald et al., 2016; Nair et al., 2017).
Reslizumab (Teva Pharmaceuticals)	Humanized IgG4	IL-5	20 pM	Decrease in asthma exacerbation rates in patients with moderate and severe asthma selected for systemic eosinophilia. Small effects on FEV1 and asthma symptoms (Bjermer et al., 2016; Castro et al., 2015).
Lebrikizumab (Genentech/Roche)	Human IgG4	IL-13 (IL-4Rα-binding epitope)	<10 pM	Increase in FEV1 and decrease in asthma exacerbations in steroid-treated moderate and severe asthma in phase 2 studies with greatest effects in patients with high levels of serum periostin. Inconsistent and weaker effects on asthma exacerbations in phase 3 trials. This drug is not currently being studied further in clinical trials in asthma (Corren et al., 2011; Hanania et al., 2016).
GSK679586 (Glaxo Smith Kline)	Human IgG1	IL13Rα1 and IL13Rα2	300-400 pM	No improvement in FEV1 or exacerbations in moderate to severe asthma (De Boever et al., 2014).
Tralokinumab (MedImmune/Astra Zeneca)	Human IgG4	IL13Rα1, IL13Rα2	165 pM	Limited effects on FEV1 but was effective in reducing asthma exacerbations and had biggest effects in patients with high serum periostin levels. This drug is not currently being studied further in clinical trials in asthma (Panettieri et al., 2018; Russell et al., 2018).
Dupilumab (Regeneron Pharmaceuticals/ Sanofi)	Human IgG4	IL4Rα	N/A	Decrease in asthma exacerbation rates, decrease in maintenance dose of oral corticosteroids, decrease in symptoms, and increase in FEV1 in patients with moderate and severe asthma. These clinical effects were largest in the subgroup with systemic eosinophilia (Castro et al., 2018; Rabe et al., 2018).
Tezepelumab	Human IgG2	TSLP	N/A	Decrease in asthma exacerbation rates, decrease in maintenance dose of oral corticosteroids, decrease in symptoms, and increase in FEV1 in patients with moderate and severe asthma. These clinical effects were independent of baseline eosinophil counts (Corren et al., 2017).

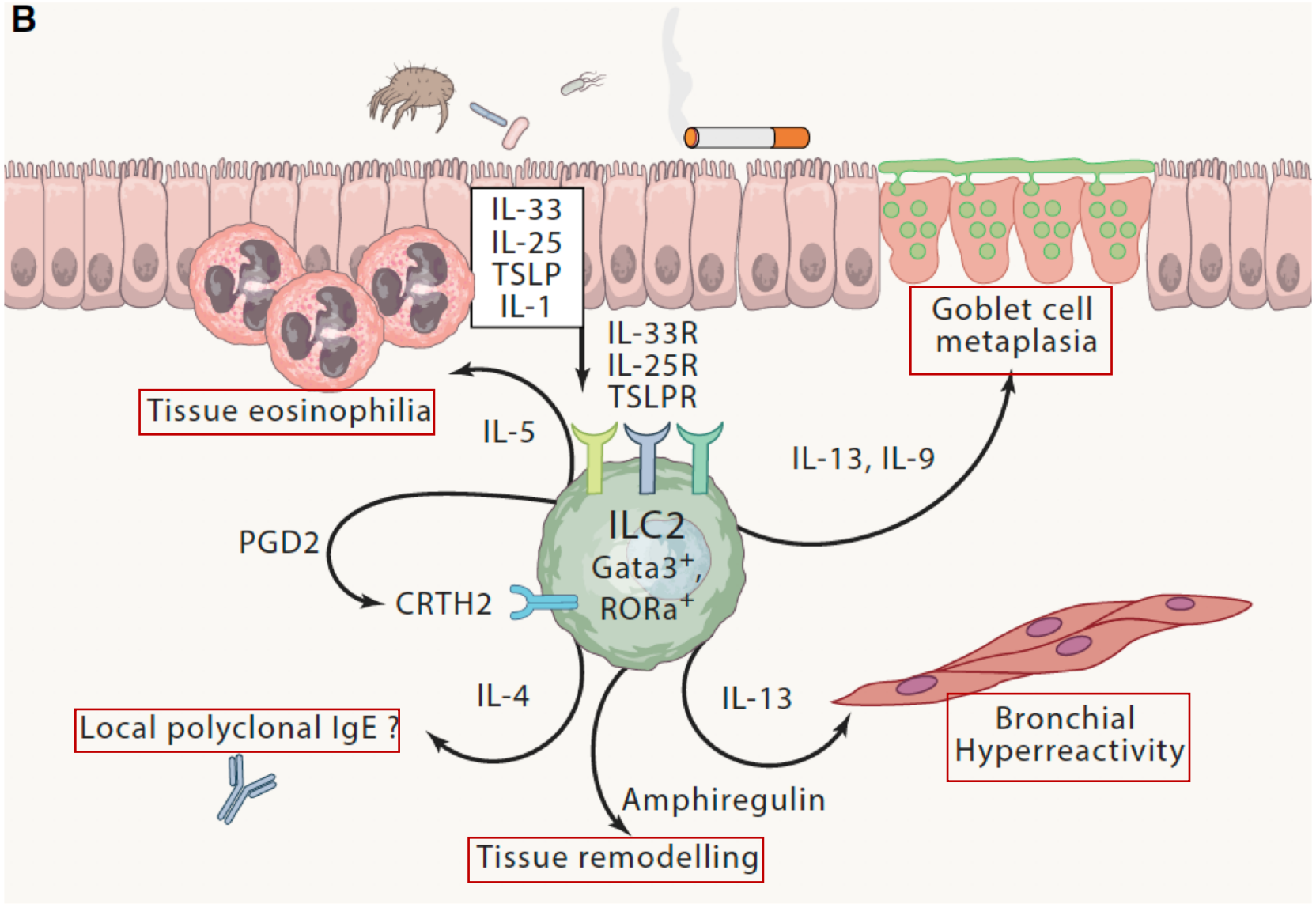
*The table is restricted to data from phase 2 and 3 trials, with emphasis on phase 3 data. Abbreviations are as follows: FEV1, forced expired volume in 1 s; IL, interleukin; IL-5Rα, α-chain of the IL-5 receptor; TSLP, thymic stromal lymphopoietin; N/A, not applicable.

Les cellules lymphoïdes innées de du groupe 2 (ILC2) répondent également aux cytokines pro-Th2



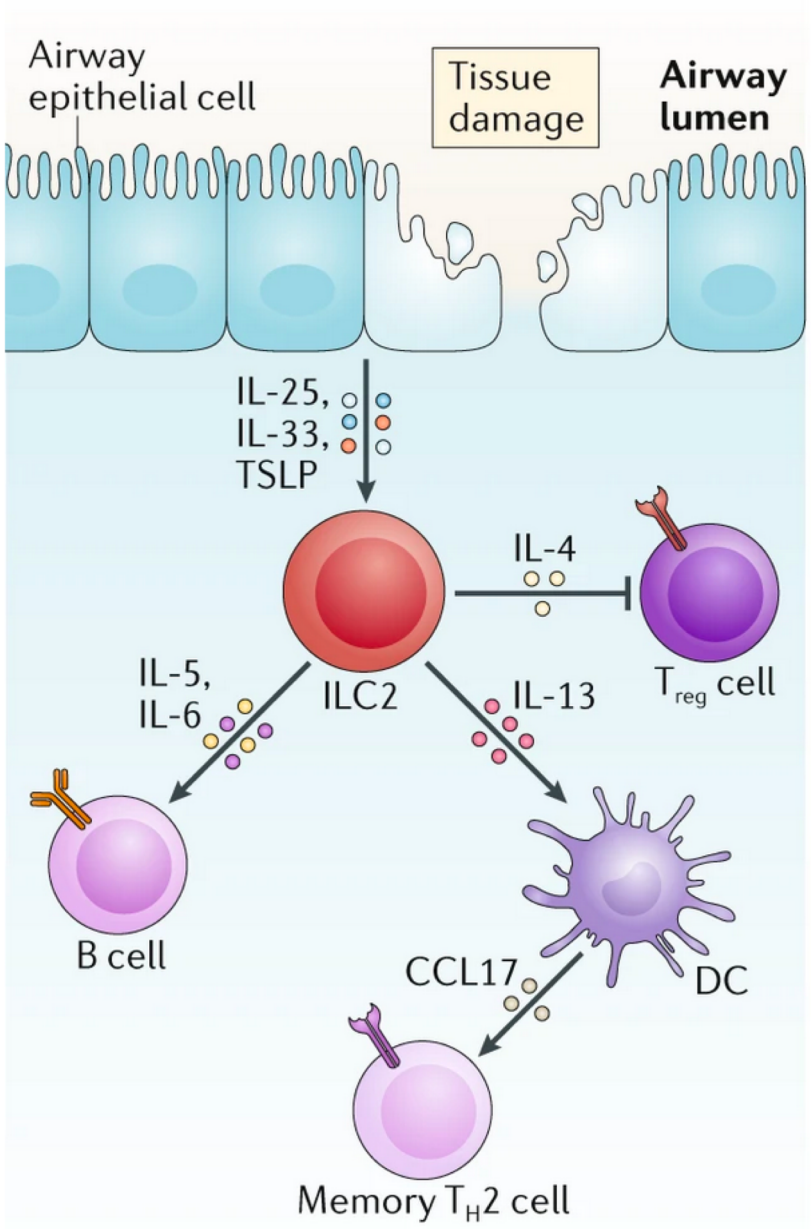
Lloyd CM, Sci Immunol, 2018

Rôles pathologiques des ILC2 au cours de la réponse allergique



Lambrecht B, Immunity, 2019

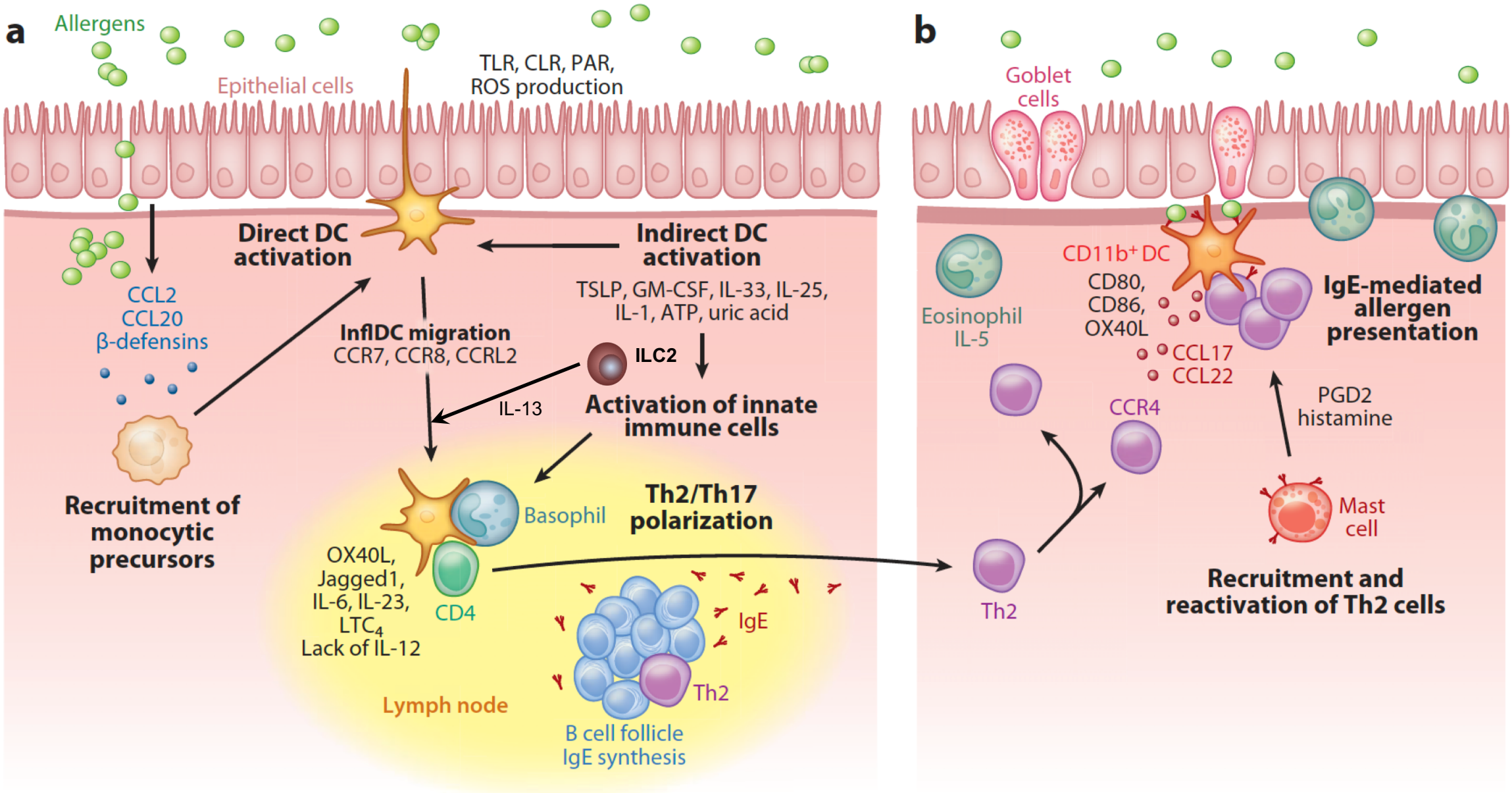
Rôles **possibles** des ILC2 dans l'organisation des réponses adaptives allergiques



1. Blocage de la différenciation de Tregs
2. Induction de la migration des DC activées dans les ganglions
3. Recrutement des Th2 mémoires dans le tissus
4. Réponses B?

Sonnenberg GF, Nat Rev Immunol, 2019

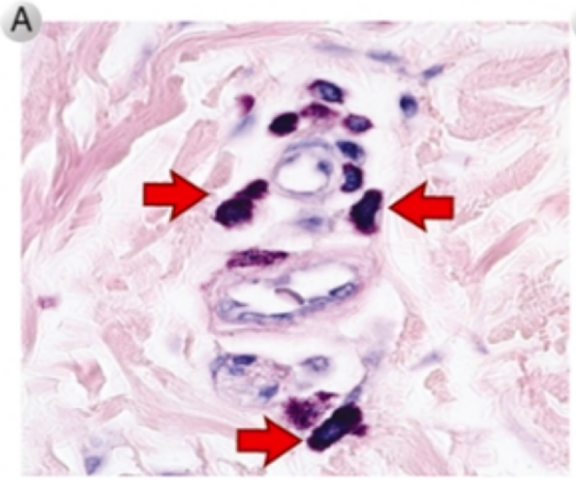
Rôle des DC dans l'induction et la phase d'état de la réponse allergique

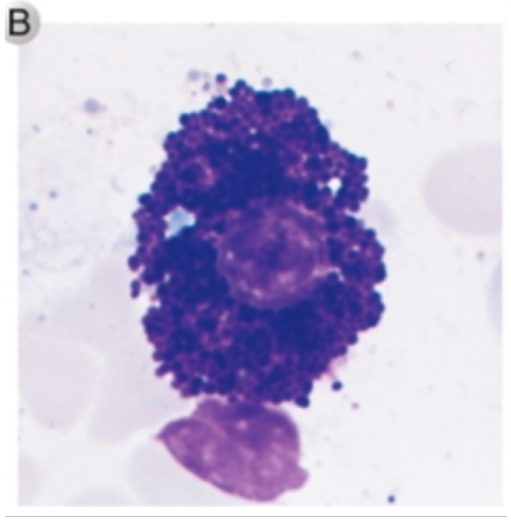


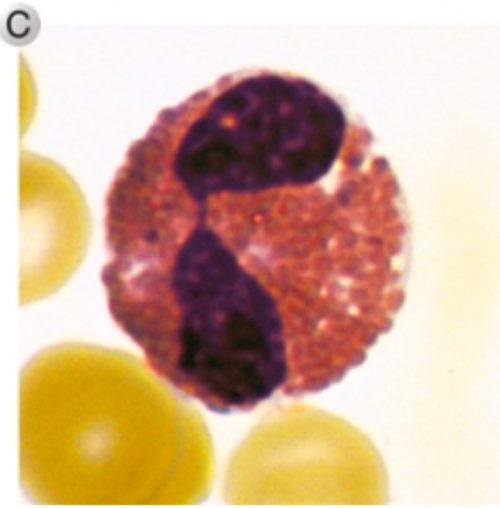
Lambrecht B, Ann Rev Immunol, 2012

Characteristic	Mast Cells	Basophils	Eosinophils
Major site of maturation	Bone marrow precursors mature in connective tissue and mucosal tissues	Bone marrow	Bone marrow
Location of cells	Connective tissue and mucosal tissues	Blood (~0.5% of blood leukocytes); recruited into tissues	Blood (~2% of blood leukocytes); recruited into tissues
Life span	Weeks to months	Days	Days to weeks
Major growth and differentiation factor (cytokines)	Stem cell factor, IL-3	IL-3	IL-5
Expression of FcεRI	High	High	Low
Major granule contents	Histamine, heparin and/or chondroitin sulfate, proteases	Histamine, chondroitin sulfate, protease	Major basic protein, eosinophil cationic protein, peroxidases, hydrolases, lysophospholipase

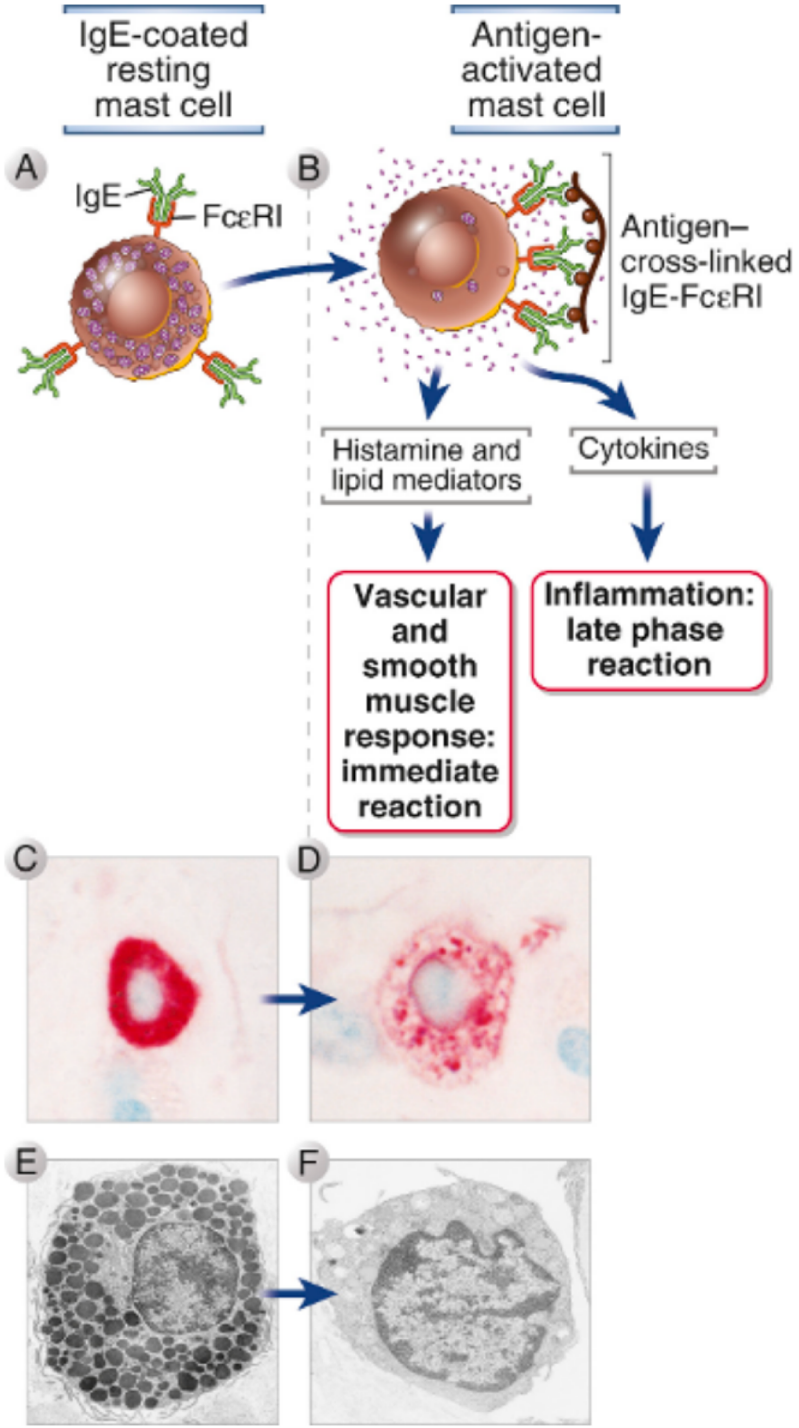
FcεRI, Fcε receptor type I; *IL,* interleukin.

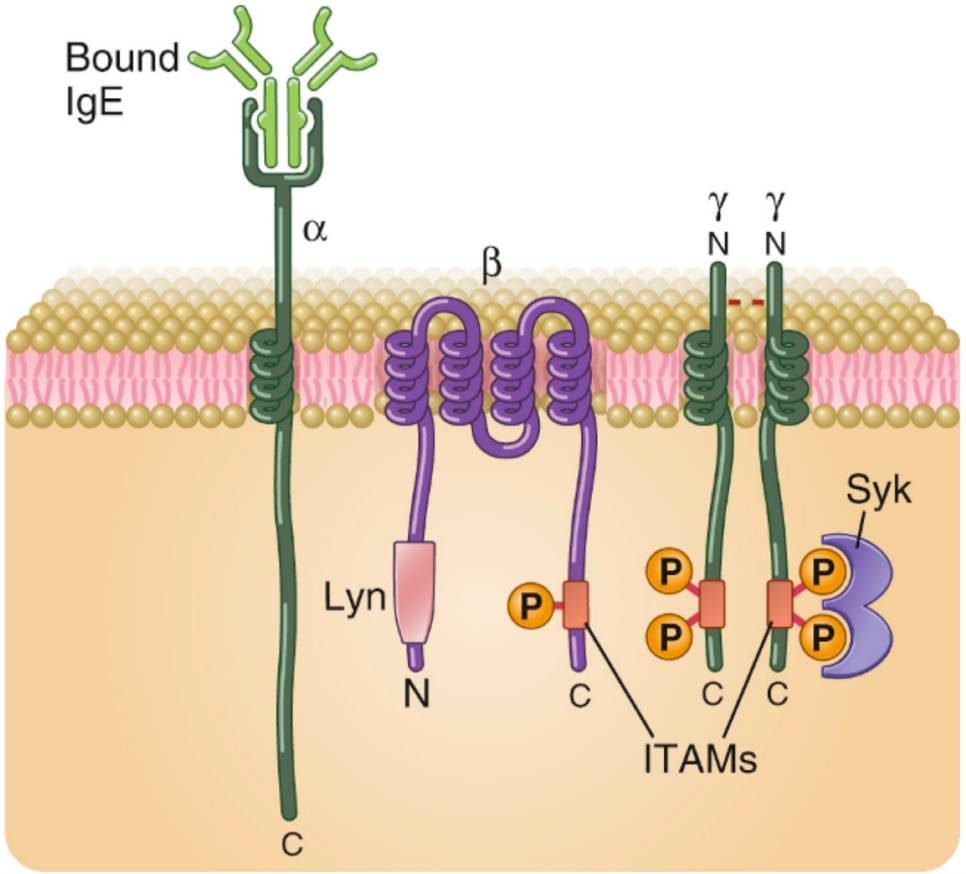




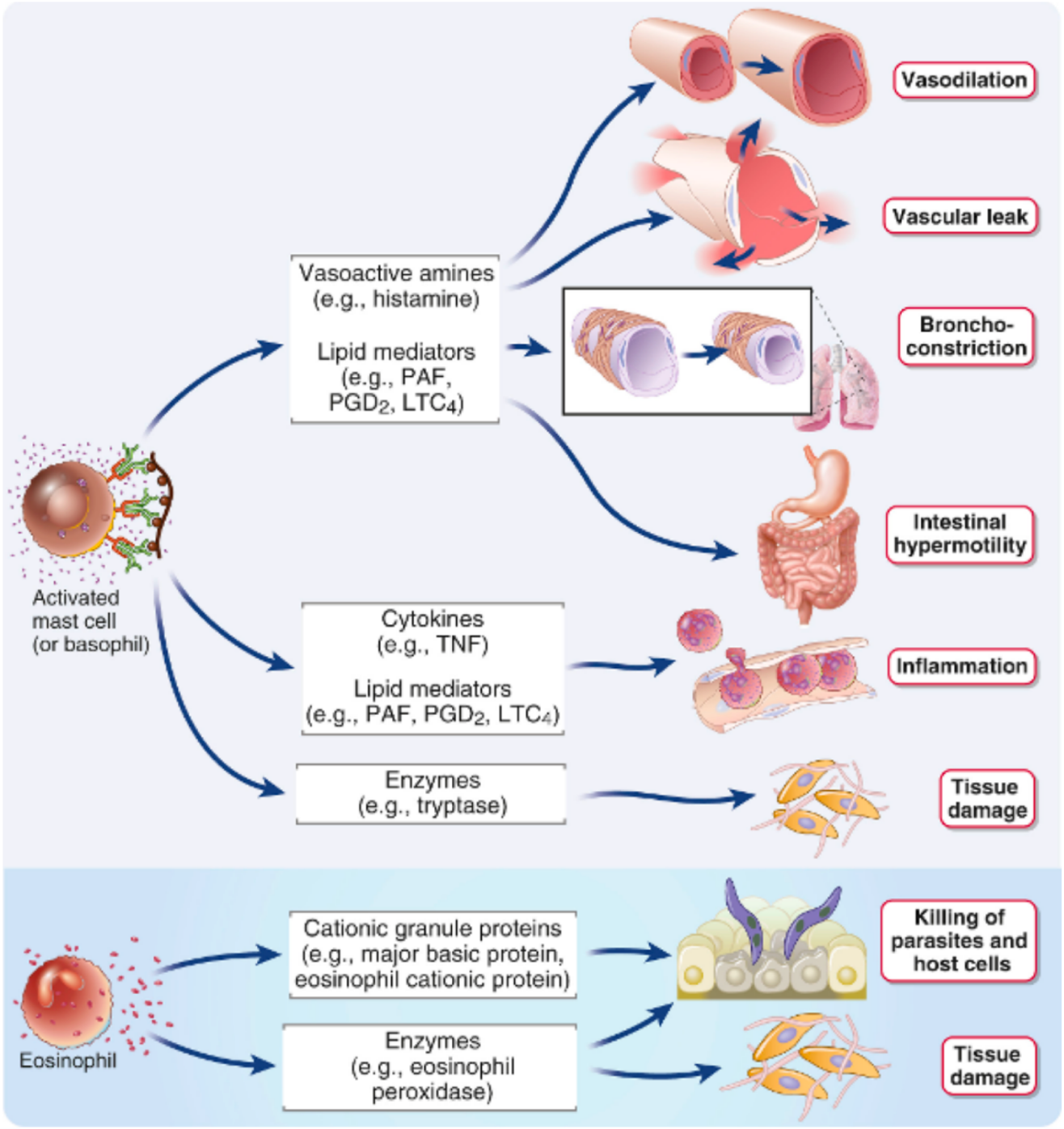


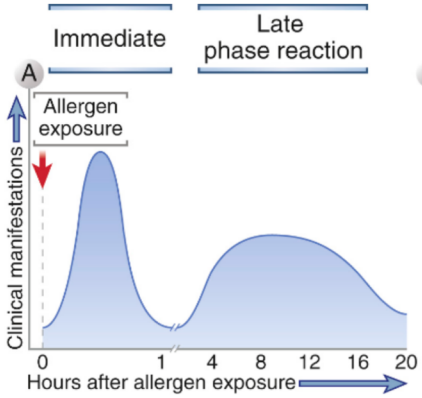
Activation des mastocytes

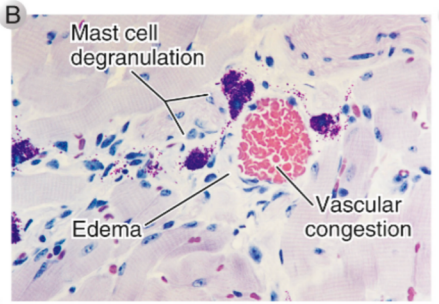


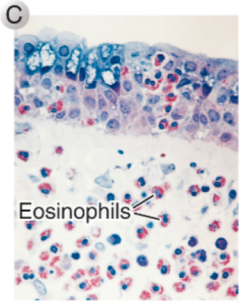


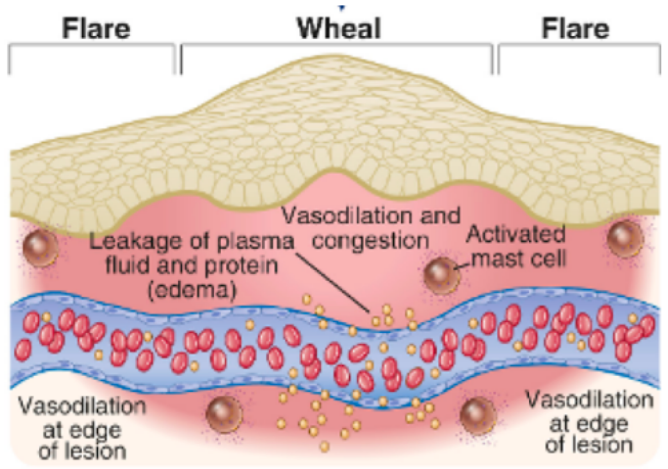
Effets biologiques des mastocytes et éosinophiles dans la réponse allergique











Cell Type	Mediator Category	Mediator	Function/Pathologic Effects
Mast Cells and Basophils			
	Stored preformed in cytoplasmic granules	Histamine	Increase vascular permeability; stimulate smooth muscle cell contraction
		Enzymes: neutral proteases (tryptase and/or chymase), acid hydrolases, cathepsin G, carboxypeptidase	Degradation of microbial structures; tissue damage/remodeling
	Major lipid mediators produced on activation	PGD_2	Vasodilation; bronchoconstriction; leukocyte chemotaxis
		Leukotrienes C_4, D_4, E_4	Prolonged bronchoconstriction; mucus secretion; increased vascular permeability
		PAF	Vasodilation; increased vascular permeability; leukocyte adhesion, chemotaxis, degranulation, oxidative burst
	Cytokines produced on activation	IL-3, TNF, MIP-1α	Mast cell proliferation; inflammation (late-phase reaction)
		IL-4, IL-13	IgE production; mucus secretion
		IL-5	Eosinophil production and activation
Eosinophils			
	Stored preformed in cytoplasmic granules	Major basic protein, eosinophil cationic protein	Toxic to helminths, bacteria, host cells
		Eosinophil peroxidase, lysosomal hydrolases, lysophospholipase	Degradation of helminthic and protozoan cell walls; tissue damage/remodeling
	Major lipid mediators produced on activation	Leukotrienes C_4, D_4, E_4	Prolonged bronchoconstriction; mucus secretion; increased vascular permeability
	Cytokines produced on activation	IL-3, IL-5, GM-CSF	Eosinophil production and activation
		IL-8, IL-10, RANTES, MIP-1α, eotaxin	Chemotaxis of leukocytes

FcεRI, Fcε receptor type I; *GM-CSF,* granulocyte-monocyte colony-stimulating factor; *MIP-1α,* monocyte inflammatory protein 1α; *PAF,* platelet-activating factor; *PGD_2,* prostaglandin D2; *RANTES,* regulated by activation, normal T cell expressed and secreted; *TNF,* tumor necrosis factor.