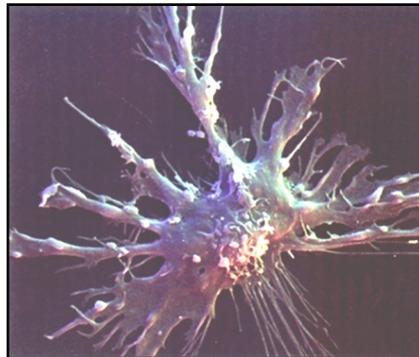


# Cellules présentatrices d'antigène et lymphocytes T



# Cellules présentatrices d'antigènes et allergie : phénotype, propriétés, fonctions

- ✓ Antigen Presenting Cell = APC en Anglais
- ✓ Présentation de l'antigène aux Lymphocytes T

# La Cellule Dendritique est un lien essentiel entre Immunité Innée et Immunité Adaptative

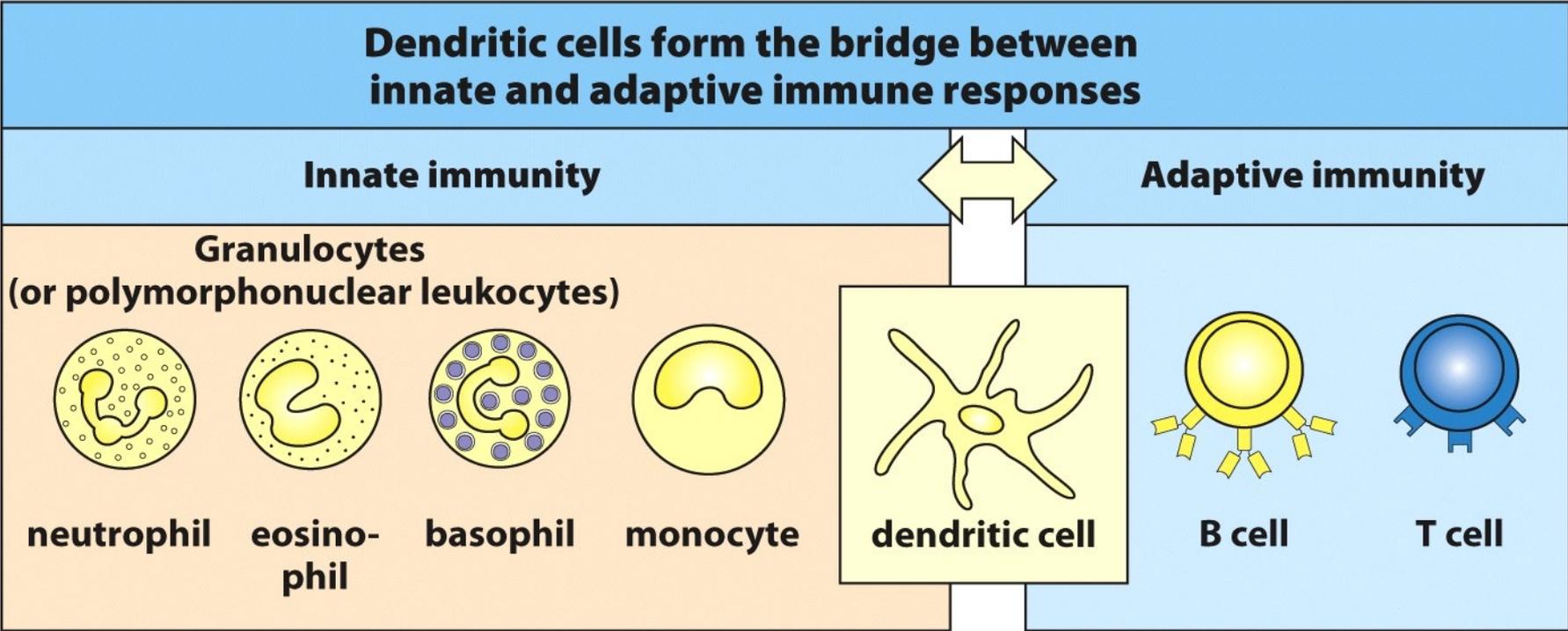


Figure 1.5 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

# Cellules présentatrices d'antigènes et allergie : phénotype, propriétés, fonctions

## POPULATION HÉTÉROGÈNE

- ✓ Fonction commune: Présenter les peptides étrangers ( Antigènes ou allergènes)
- ✓ Avec le complexe majeur d'histocompatibilité (CMH-I et CMH-II)
- ✓ Aux lymphocytes T
- ✓ Reconnaissance d'un antigène étranger ( Glycoprotéines, Lipides,..) = Detection du "danger"
- ✓ Phagocytose
- ✓ Maintien du signal d'alarme de la réponse immune primaire

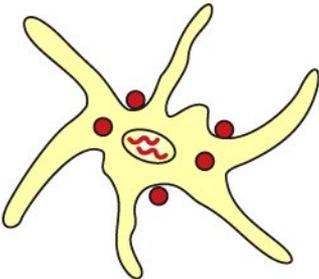
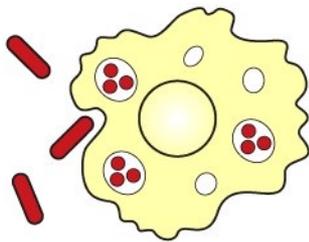
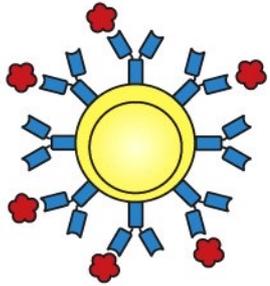
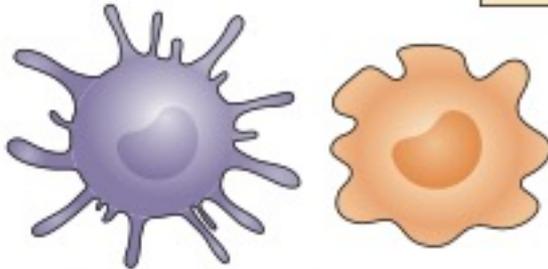
	<b>Dendritic cells</b>	<b>Macrophages</b>	<b>B cells</b>
			
<b>Antigen uptake</b>	+++ Macropinocytosis and phagocytosis by tissue dendritic cells	+++ Macropinocytosis +++ Phagocytosis	Antigen-specific receptor (Ig) ++++
<b>MHC expression</b>	Low on immature dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines - to +++	Constitutive Increases on activation +++ to ++++
<b>Co-stimulation delivery</b>	Constitutive by mature, nonphagocytic lymphoid dendritic cells ++++	Inducible - to +++	Inducible - to +++
<b>Location</b>	Ubiquitous throughout the body	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood
<b>Effect</b>	Results in activation of naive T cells	Results in activation of macrophages	Results in delivery of help to B cell

Figure 9.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

## Professional APCs



DCs and macrophages



B cells

### Key features

- Phagocytic
- Express receptors for apoptotic cells, DAMPs and PAMPs
- Localize to tissues
- Localize to T cell zone of lymph nodes following activation (DCs)
- Constitutively express high levels of MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

### Key features

- Internalize antigens via BCRs
- Constitutively express MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

# La Cellule Dendritique est un lien essentiel entre Immunité Innée et Immunité Adaptative

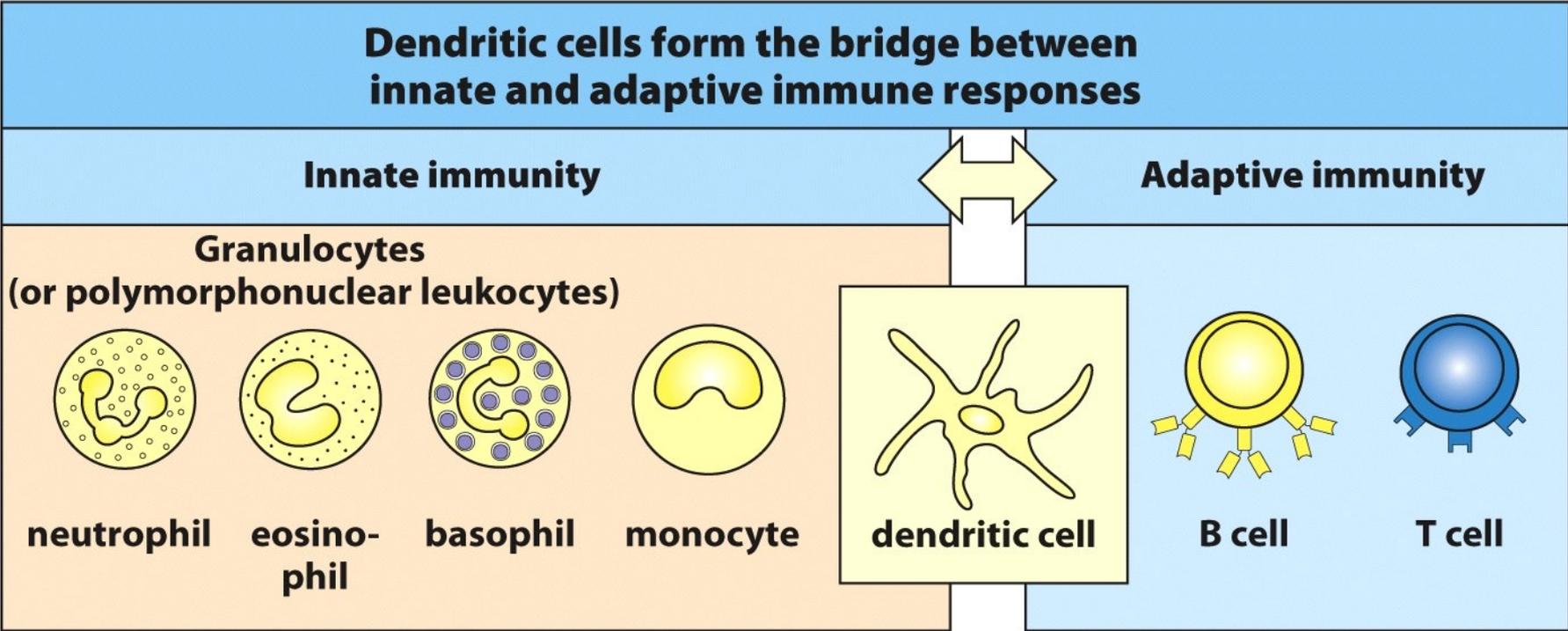
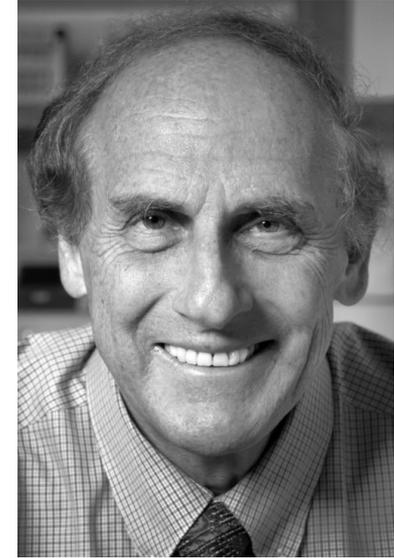
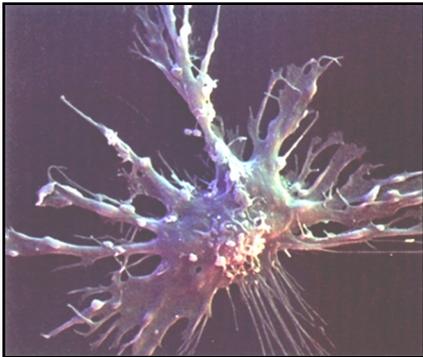


Figure 1.5 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

# Caractéristiques des cellules dendritiques conventionnelles (cDCs)

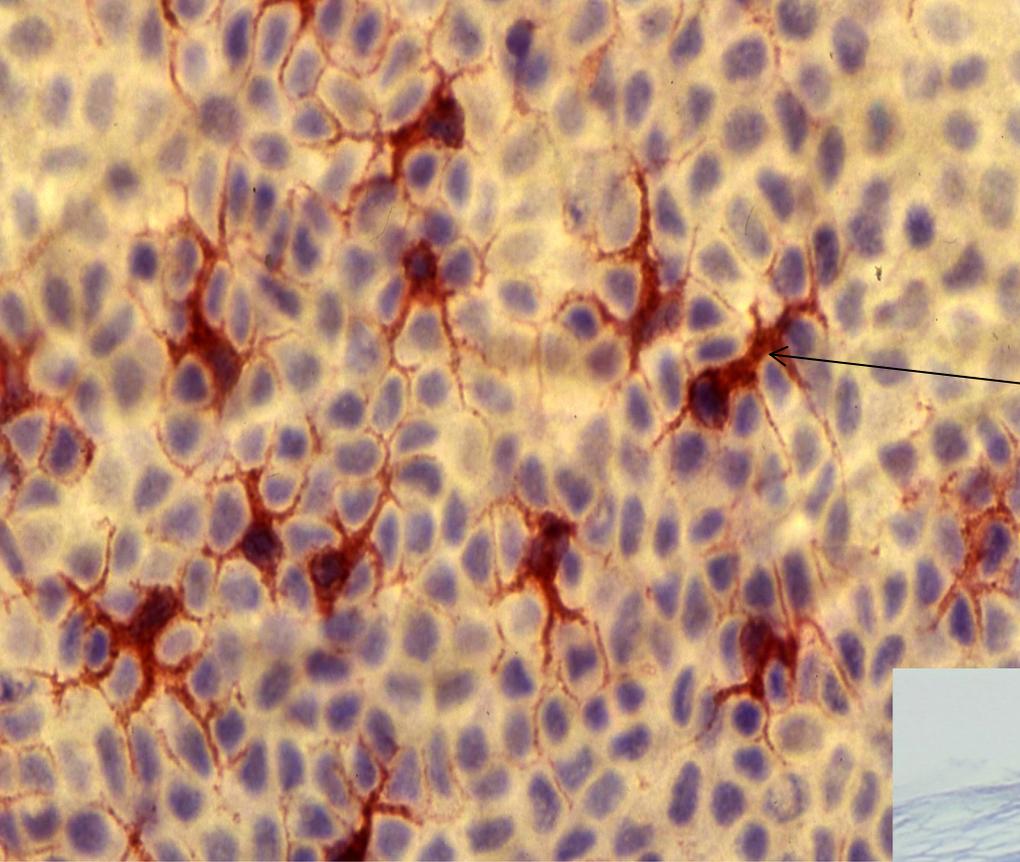
- ✓ Identifiée par R. Steinman
- ✓ Morphologie spécifique avec la présence de dendrites
- ✓ Expression du CMH classe II
- ✓ Capacité à activer les lymphocytes T naïfs



Nobel Prize in Physiology or  
Medicine 2011

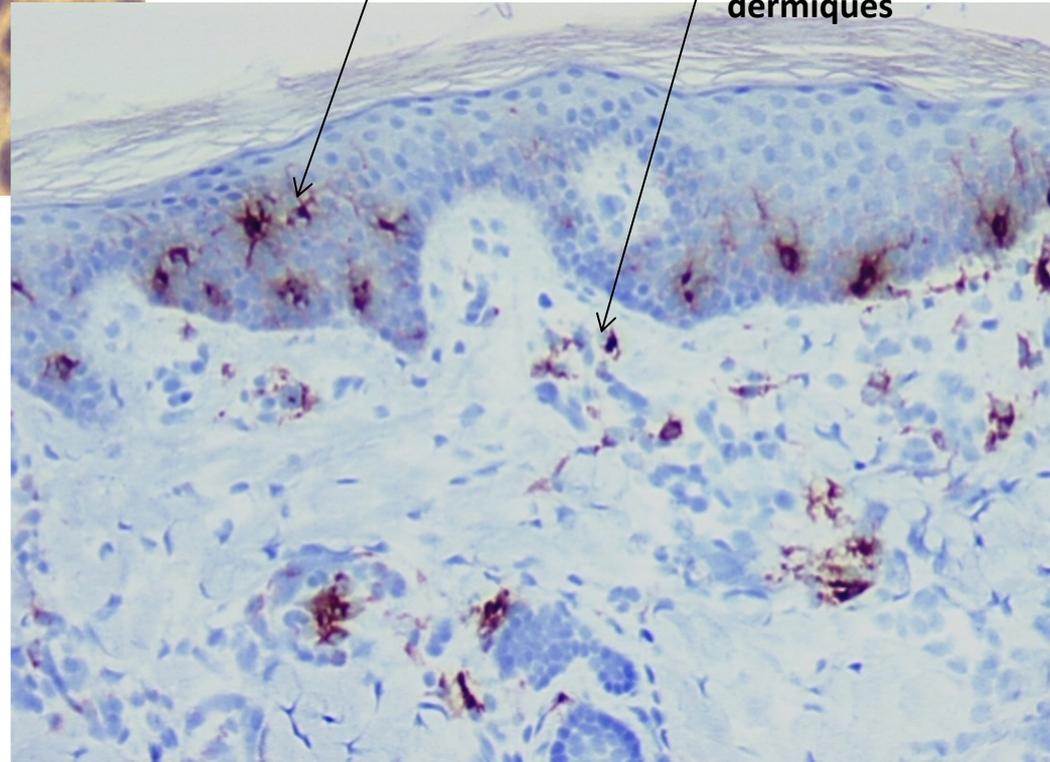
- Présentes dans les tissus à l'état basal = cellules sentinelles
- Population hétérogène

# Cellules dendritiques cutanées



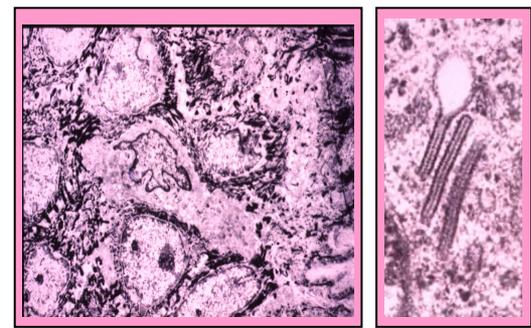
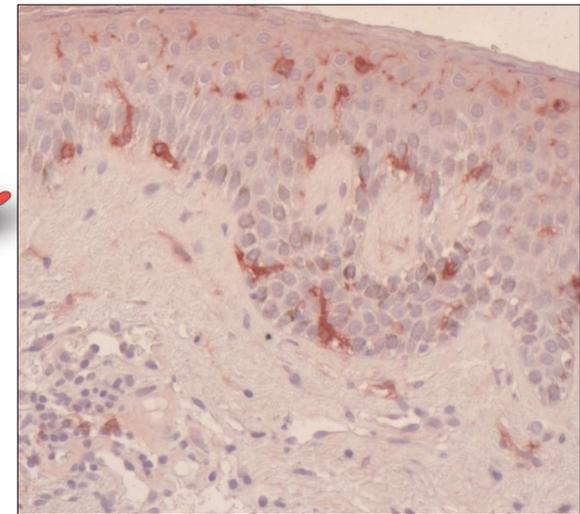
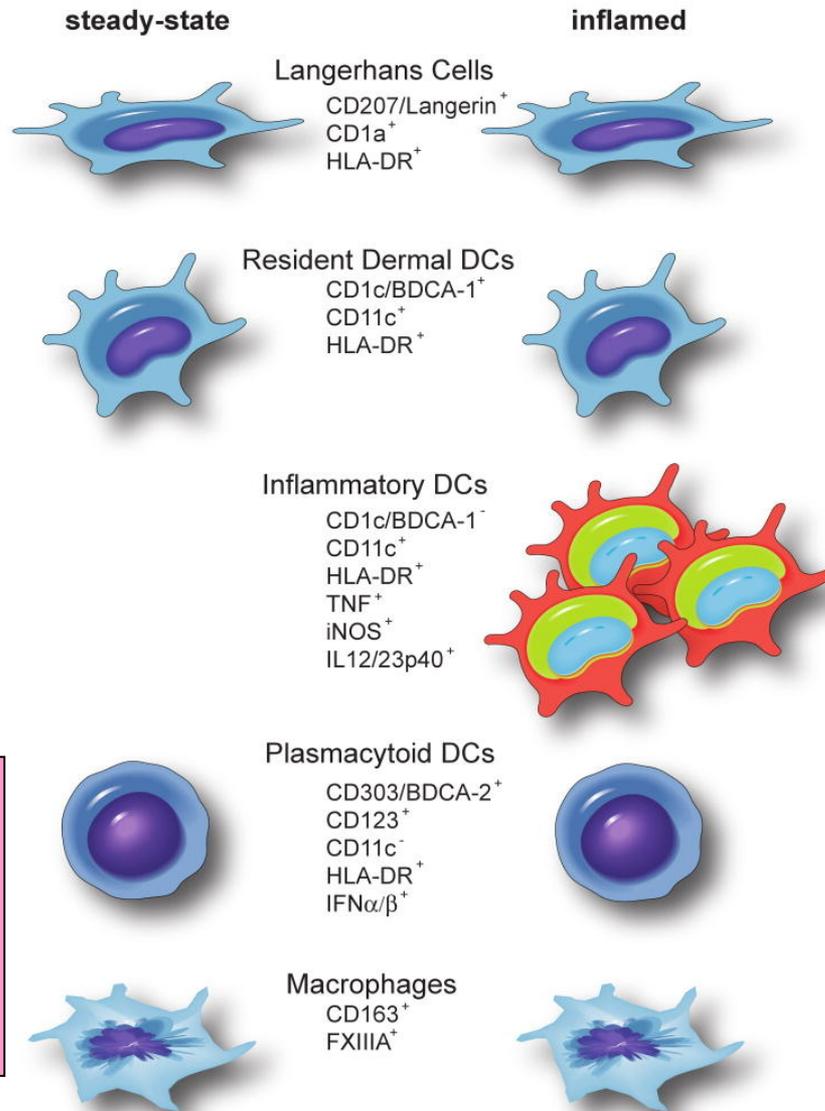
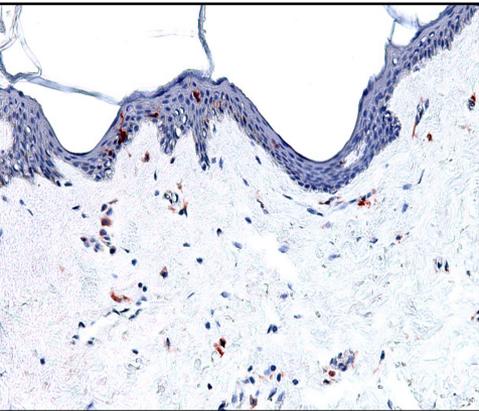
cellules de  
Langerhans

Cellules  
dendritiques  
dermiques



# Cellules présentatrices d'antigènes et allergie :

## phénotype, propriétés, fonctions



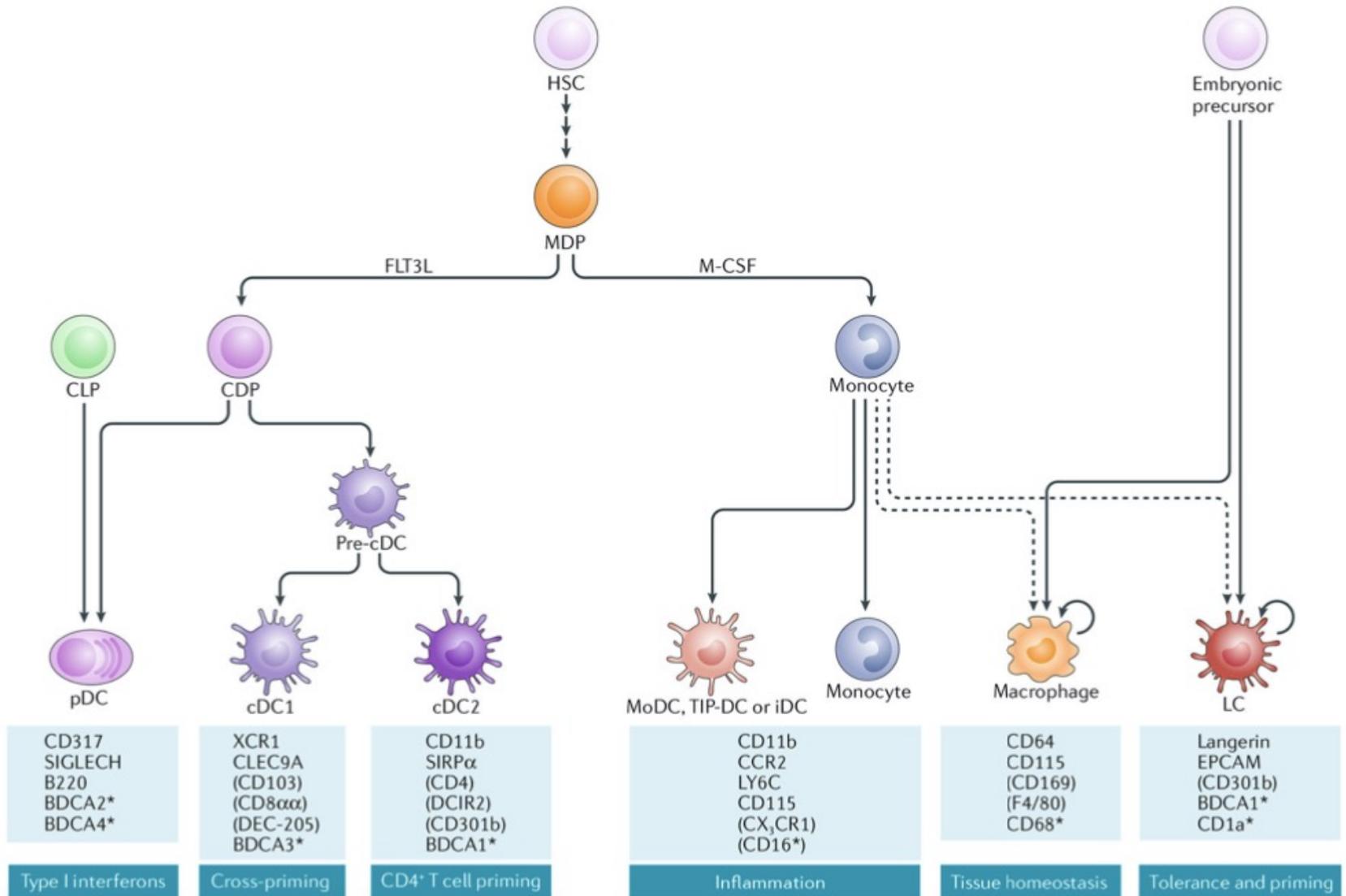
**Cellules de Langerhans / Granules de Birbeck**

Klechevsky et al, Immunity, 2008  
 Haniffa et al. J Exp Med, 2009  
 Zaba et al, J Invest Dermatol. 2009

# Différentes sous-populations de cellules dendritiques

<p><b>Blood</b></p>	<div style="border: 1px dashed black; padding: 5px;">  <p><b>DC1</b> CD11c<sup>low</sup> BDCA3<sup>high</sup> CD11b<sup>-</sup> XCR1<sup>+</sup> Clec9A<sup>+</sup></p>  <p><b>DC2</b> CD11c<sup>+</sup> BDCA1<sup>+</sup> CD11b<sup>+</sup></p> </div>	 <p><b>Plasmacytoid DC</b> CD11c<sup>-</sup> BDCA2<sup>+</sup> CD123<sup>+</sup></p>
<p><b>Tissues</b></p>	<div style="border: 1px dashed black; padding: 5px;">  <p><b>DC1</b> CD11c<sup>low</sup> BDCA3<sup>high</sup> XCR1<sup>+</sup> Clec9A<sup>+</sup></p>  <p><b>DC2</b> CD11c<sup>+</sup> BDCA1<sup>+</sup> CD11b<sup>+</sup></p> </div>	 <p><b>Langerhans cells</b> CD11c<sup>low</sup> CD11b<sup>-</sup> CD1a<sup>high</sup> CD207<sup>+</sup> EpCAM<sup>high</sup></p>
<p><b>Inflammation sites</b></p>	 <p><b>Inflammatory DC</b> CD11c<sup>+</sup> CD11b<sup>+</sup> SIRPα<sup>+</sup> FcεR1<sup>+</sup> BDCA1<sup>+</sup></p>	 <p><b>pDC</b> CD11c<sup>-</sup> BDCA2<sup>+</sup> CD123<sup>+</sup></p>

# Origine(s) des différentes sous-populations de cellules dendritiques



# Cellules dendritiques : fonctions

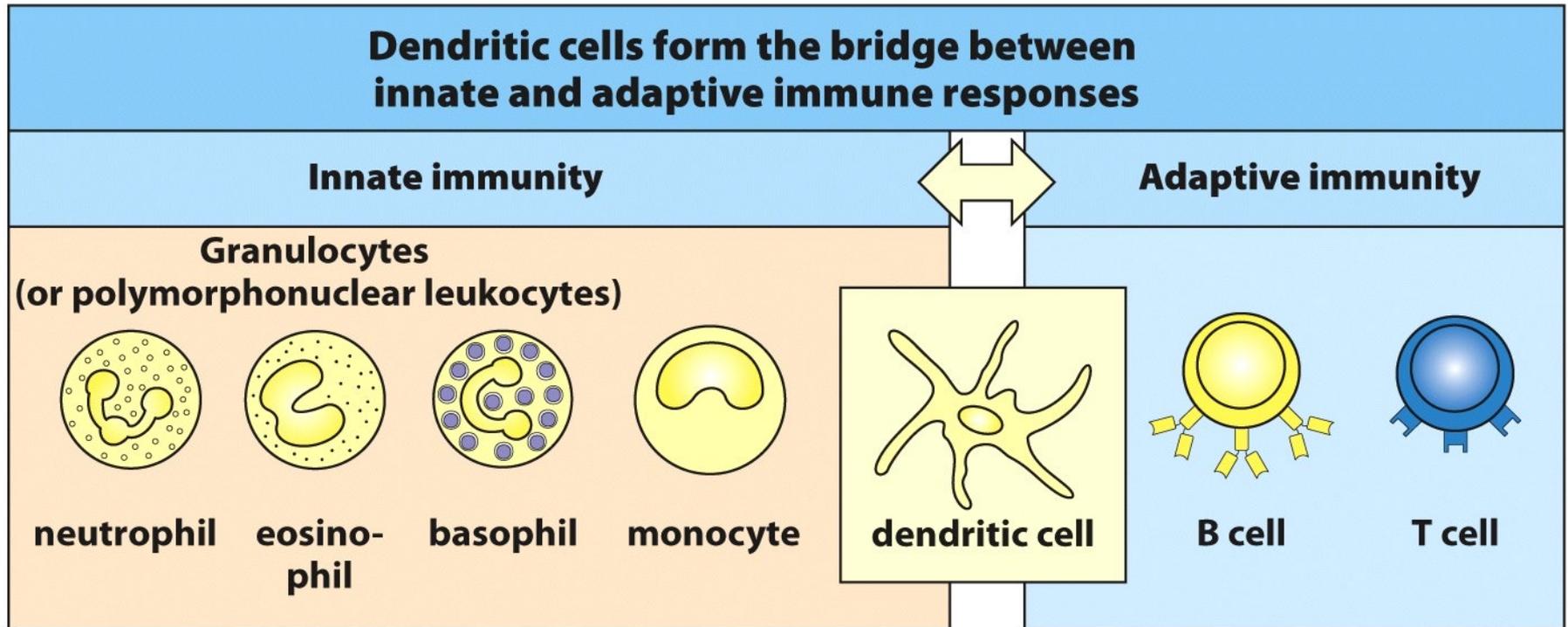
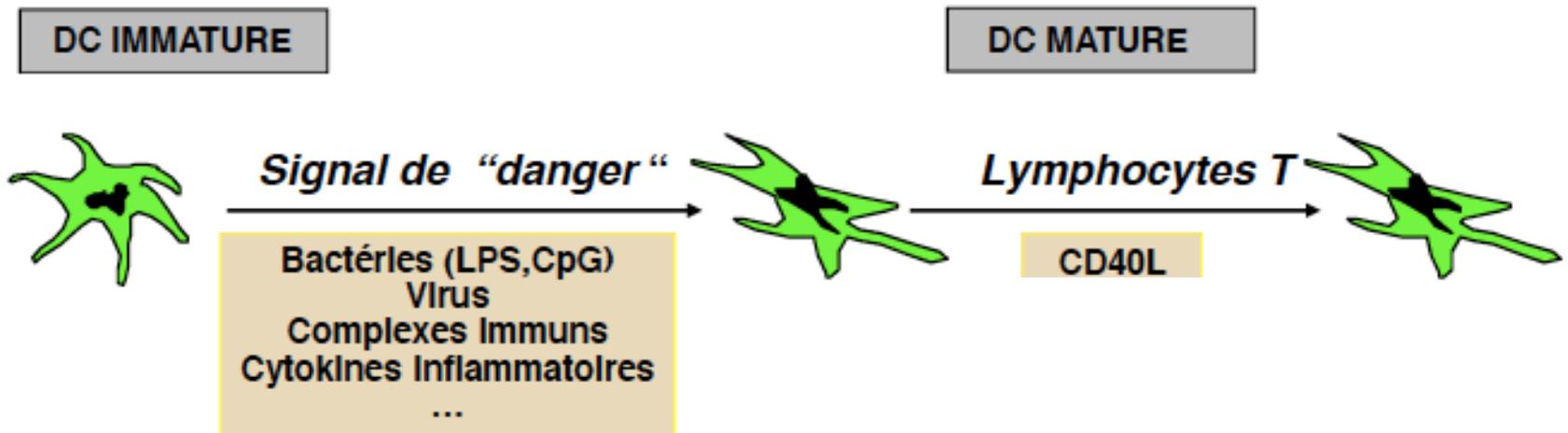


Figure 1.5 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Immature dendritic cell → Mature dendritic cell

# Cellules dendritiques : maturation

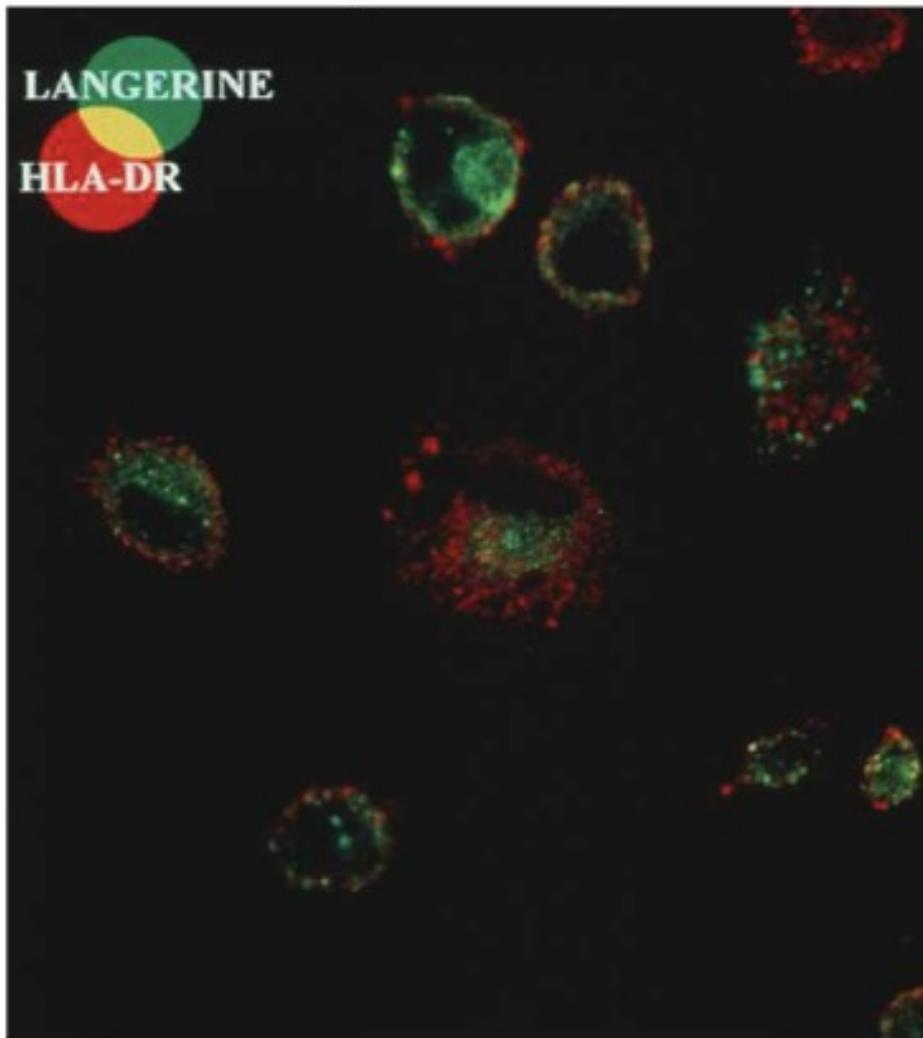


Faible costimulation des LT  
CMH de classe II Intracellulaire

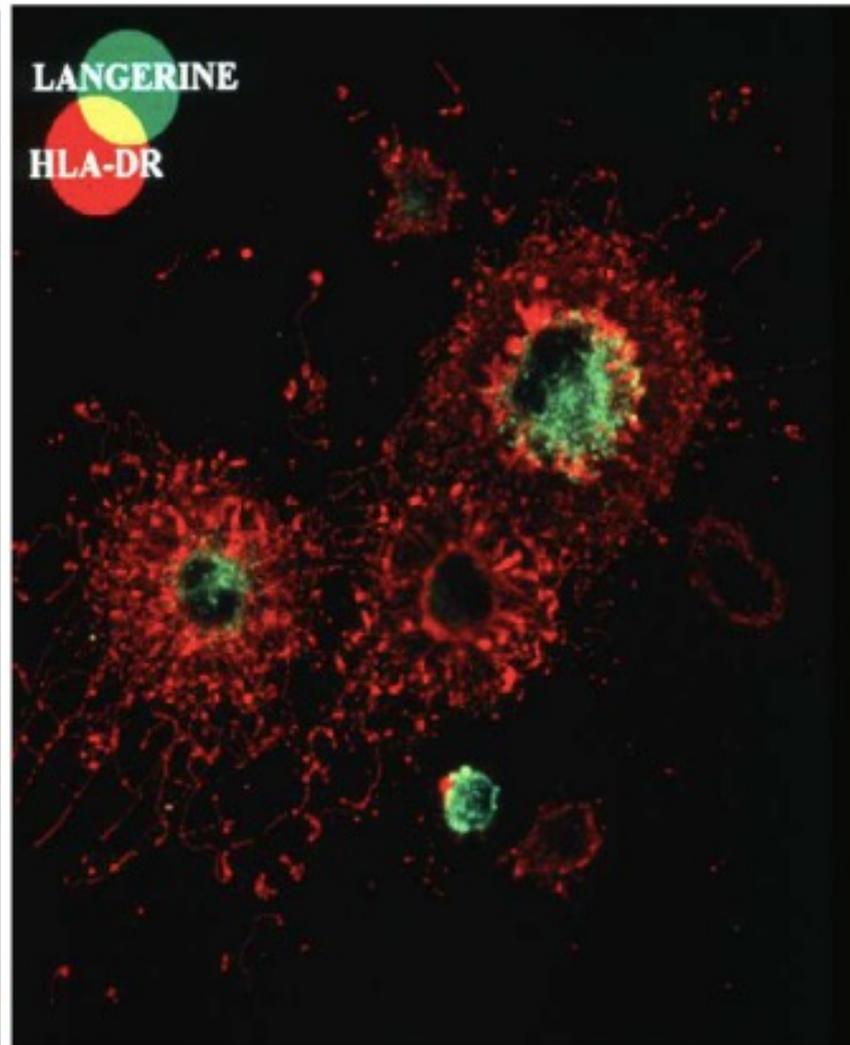
FORTE costimulation des lymphocytes T  
CMH de classe II en surface

# Cellules dendritiques : maturation

Cellules de Langerhans immatures



Cellules de Langerhans matures



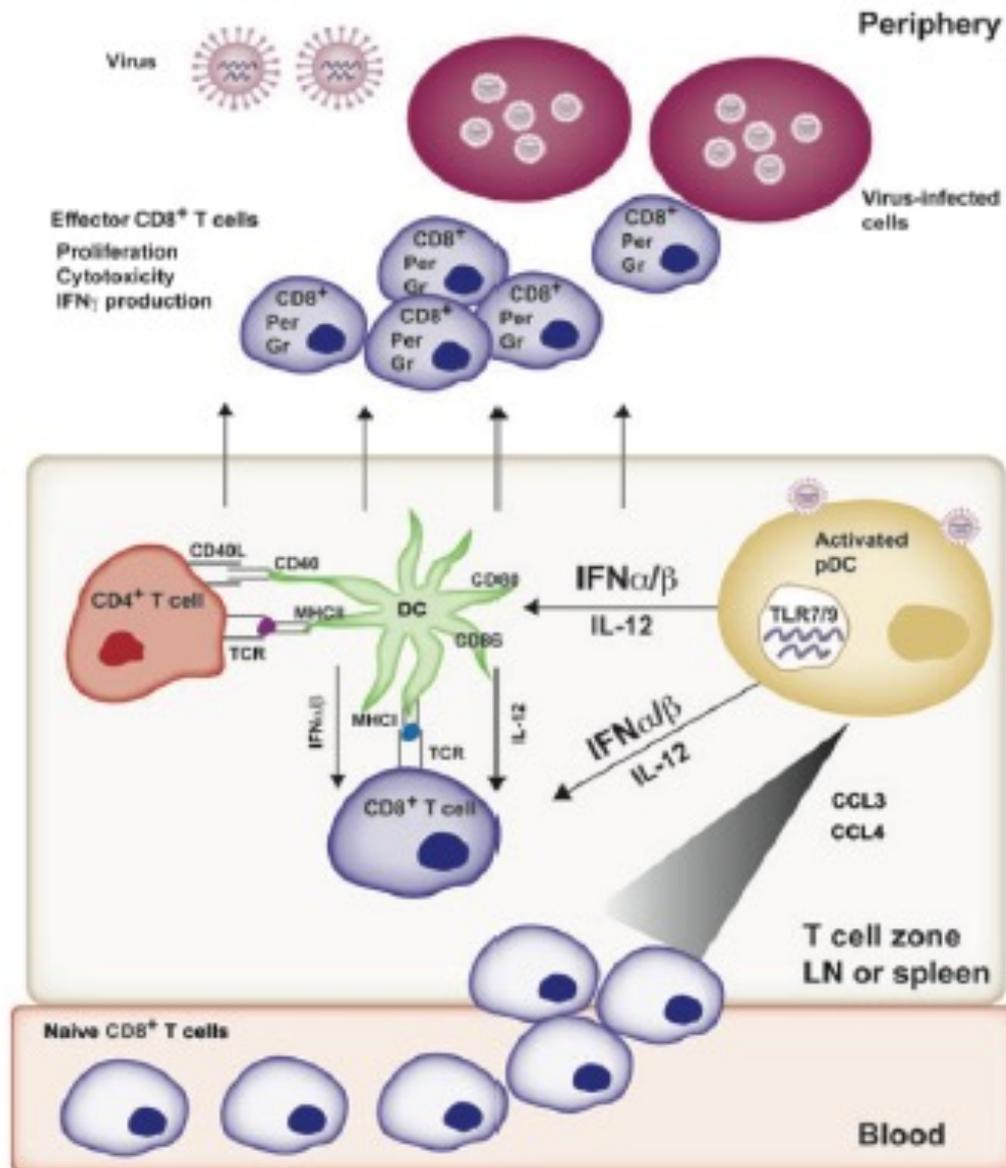
# Différentes sous-population de cellules dendritiques

<p><b>Blood</b></p>	<div style="border: 1px dashed black; padding: 5px;">  <p><b>DC1</b> CD11c<sup>low</sup> BDCA3<sup>high</sup> CD11b<sup>-</sup> XCR1<sup>+</sup> Clec9A<sup>+</sup></p>  <p><b>DC2</b> CD11c<sup>+</sup> BDCA1<sup>+</sup> CD11b<sup>+</sup></p> </div>	 <p><b>Plasmacytoid DC</b> CD11c<sup>-</sup> BDCA2<sup>+</sup> CD123<sup>+</sup></p>
<p><b>Tissues</b></p>	<div style="border: 1px dashed black; padding: 5px;">  <p><b>DC1</b> CD11c<sup>low</sup> BDCA3<sup>high</sup> XCR1<sup>+</sup> Clec9A<sup>+</sup></p>  <p><b>DC2</b> CD11c<sup>+</sup> BDCA1<sup>+</sup> CD11b<sup>+</sup></p> </div>	 <p><b>Langerhans cells</b> CD11c<sup>low</sup> CD11b<sup>-</sup> CD1a<sup>high</sup> CD207<sup>+</sup> EpCAM<sup>high</sup></p>
<p><b>Inflammation sites</b></p>	 <p><b>Inflammatory DC</b> CD11c<sup>+</sup> CD11b<sup>+</sup> SIRPα<sup>+</sup> FcεR1<sup>+</sup> BDCA1<sup>+</sup></p>	 <p><b>pDC</b> CD11c<sup>-</sup> BDCA2<sup>+</sup> CD123<sup>+</sup></p>

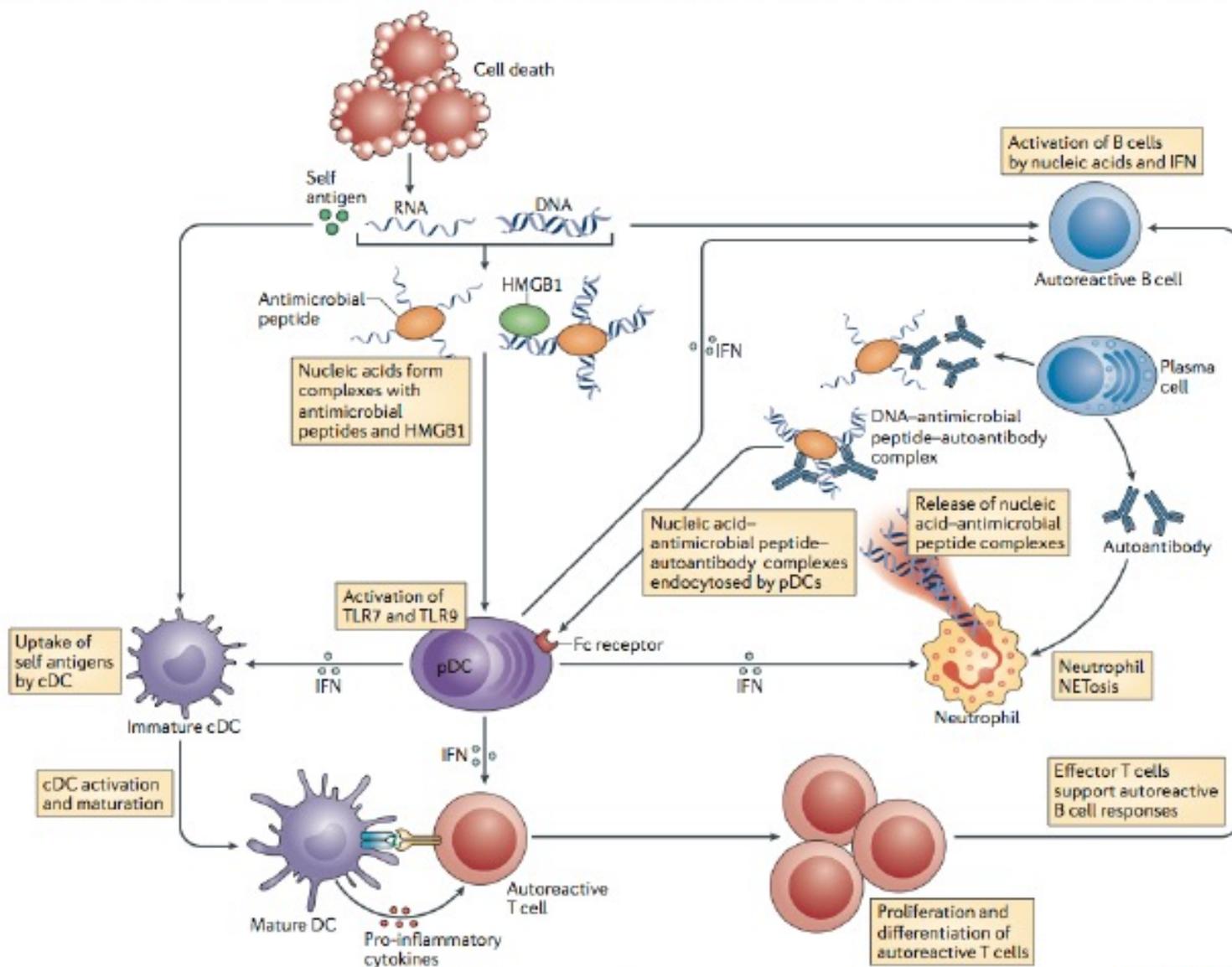
## Cellules dendritiques plasmacytoïdes

- ✓ Identifiée en 1999 comme des cellules sécrétrices d'IFN de type 1 (IFN $\alpha/\beta$ )
- ✓ Morphologie de cellules plasmacytoïdes
- ✓ Faible niveau d'expression du CMH II
- ✓ Sécrète du TNF $\alpha$  et IL-12

# pDC viral infection



# pDC autoimmunity



# La Cellule Dendritique est un lien essentiel entre Immunité Innée et Immunité Adaptative

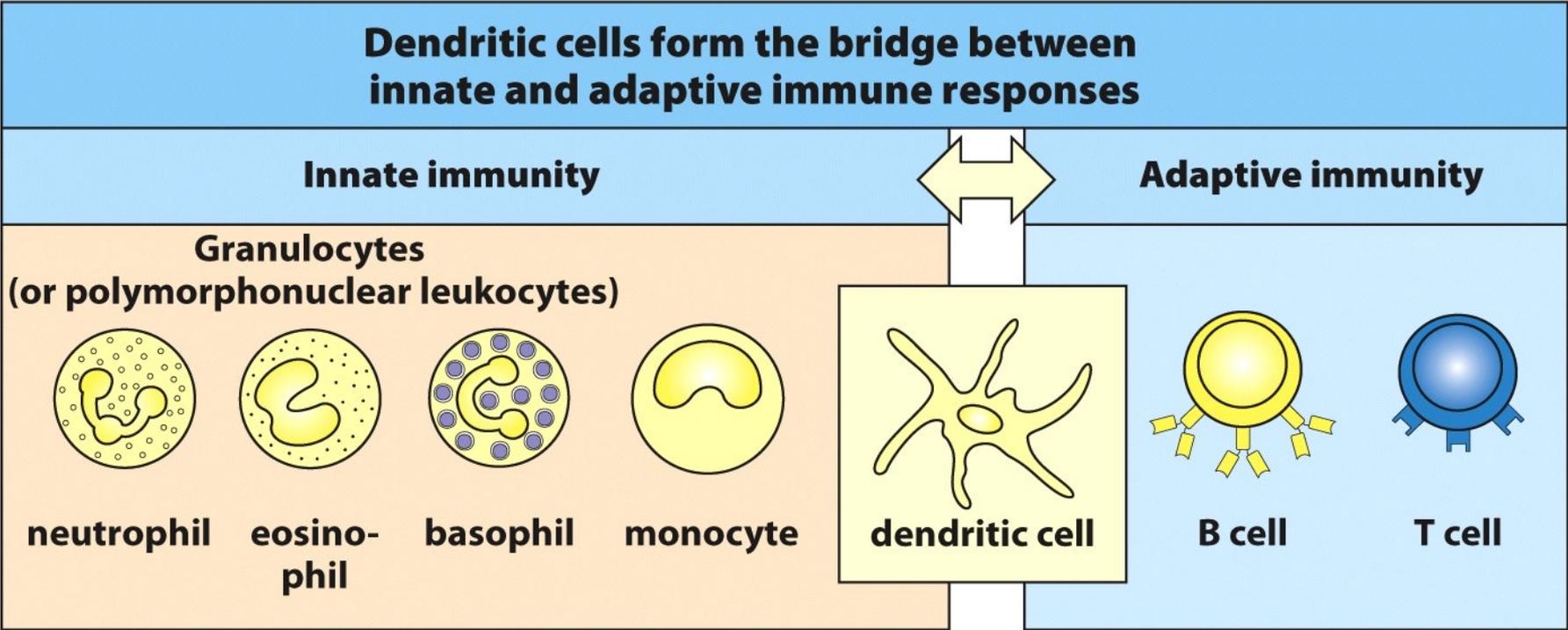
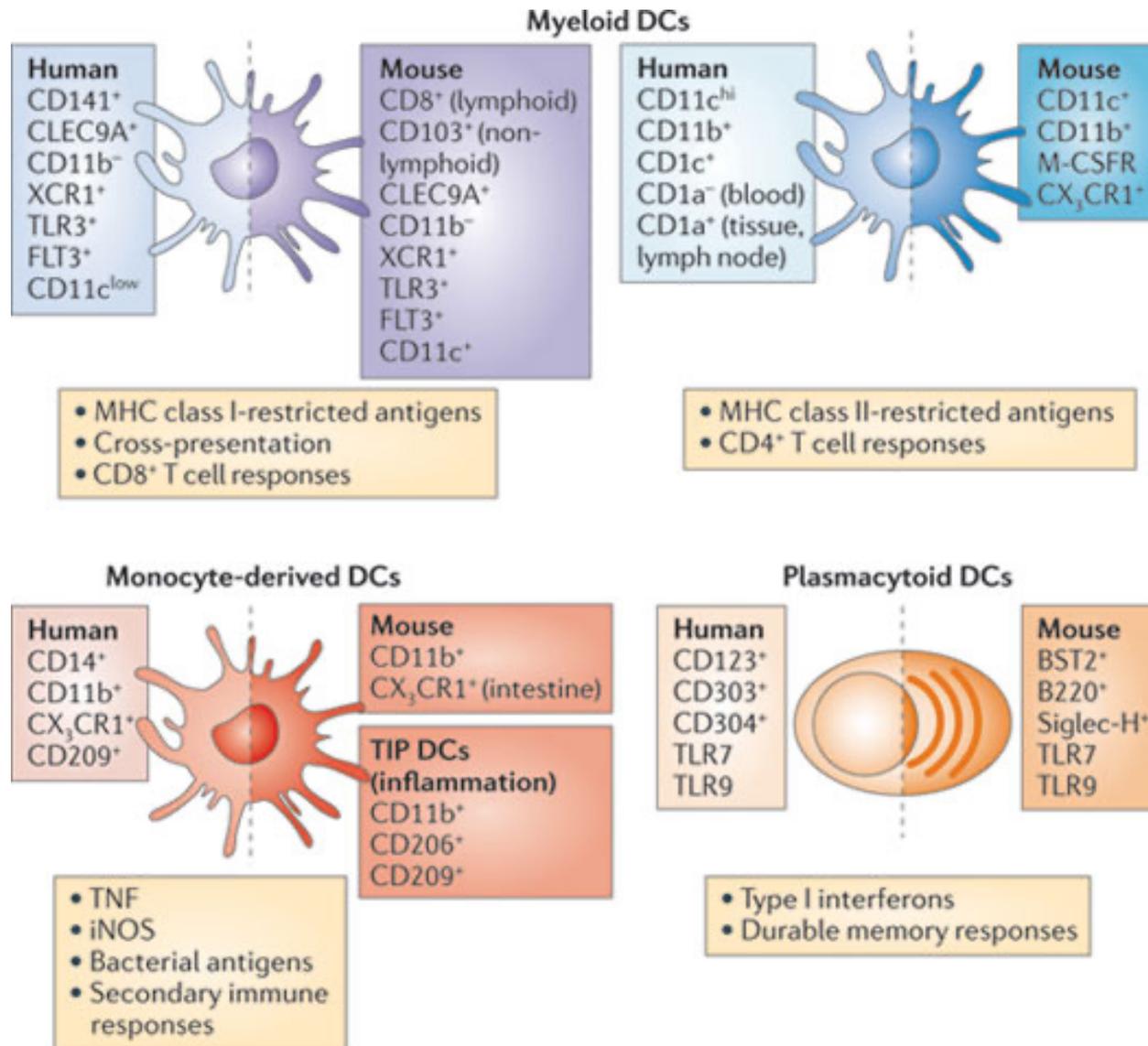


Figure 1.5 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Immature dendritic cell → Mature dendritic cell

# Cellules présentatrices d'antigènes et allergie :

## phénotype, propriétés, fonctions



# Cellules dendritiques - Sous populations

cDC1	cDC2	pDC	moDC
HLA-DR <sup>+</sup>	HLA-DR <sup>+</sup>	HLA-DR <sup>+</sup>	HLA-DR <sup>+</sup>
CD11c <sup>low</sup>	CD11c <sup>+</sup>	CD14 <sup>+</sup>	CD14 <sup>+</sup>
BTLA <sup>int/low</sup>	BTLA <sup>low</sup>	CD303/Clec4c <sup>+</sup>	CD11c <sup>+</sup>
CD1c <sup>-/low</sup>	CD1c <sup>+</sup>	CD304/NRP1 <sup>+</sup>	CD206 <sup>+</sup>
SIRPα/CD72a <sup>-</sup>	SIRPα/CD72a <sup>+</sup>		CD64 <sup>+</sup>
CD141 <sup>++</sup>	CD11b <sup>+</sup>		SIRPα/CD72a <sup>+</sup>
CADM1 <sup>+</sup>	CD141 <sup>-</sup>		CD1a <sup>+</sup>
Clec9a <sup>+</sup>	CD1a <sup>+</sup>		DC-SIGN/CD209 <sup>+</sup>
XCR1 <sup>+</sup>	Clec4a/DCIR <sup>+</sup>		
CD26 <sup>+</sup>	CD103 <sup>+</sup> (intestine)		
CXCR3 <sup>+</sup>			
CD103 <sup>+</sup>			

**TABLE 1** Phenotype maker of human dendritic cell (DC) subpopulations<sup>41,42</sup>

Table 1 | Major subsets of DCs in humans and mice\*

DC subset	Phenotype		Specific transcription factors	Specific mediators produced upon activation	Specific antigen-presentation capacities	Location	Tissue condition
	Mice	Humans					
Plasmacytoid DC	CD11c <sup>int</sup> , MHC class II <sup>int</sup> , B220, BST2 and SIGLEC-H	CD11c <sup>-</sup> , MHC class II <sup>int</sup> , CD123, BDCA2 and BDCA4	TCF4 (also known as E2-2)	Type 1 IFN	Present and cross-present peptides only after activation	Lymphoid organs	Steady state
CD11b <sup>+</sup> ESAM <sup>hi</sup> cDC	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , CD11b, CX <sub>3</sub> CR1 <sup>low</sup> and ESAM <sup>hi</sup>	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , CD11b and BDCA1	Notch 2	ND	Present peptides on MHC class II molecules to CD4 <sup>+</sup> T cells	Lymphoid organs	Steady state
CD11b <sup>+</sup> ESAM <sup>low</sup> cDC <sup>‡</sup>	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , CD11b, CX <sub>3</sub> CR1 <sup>hi</sup> and ESAM <sup>low</sup>	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , CD11b, CD16 and CD14	ND	TNF and IL-12	ND	Lymphoid organs	Steady state
CD8α <sup>+</sup> cDC	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , XCR1, CLEC9A and CD8α	CD11c <sup>int</sup> , MHC class II <sup>hi</sup> , XCR1, CLEC9A and BDCA3	BATF3	IL-12	Cross-present peptides on MHC class I molecules to CD8 <sup>+</sup> T cells	Lymphoid organs	Steady state
CD103 <sup>+</sup> cDC	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , CD103, XCR1 and CLEC9A	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , XCR1, CLEC9A and BDCA3	BATF3	ND	Cross-present peptides on MHC class I molecules to CD8 <sup>+</sup> T cells	Peripheral tissues	Steady state
CD11b <sup>+</sup> cDC	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , CD103 <sup>§</sup> , CD11b and CD24	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , CD11b, SIRPα <sup>§</sup> and BDCA1 <sup>  </sup>	IRF4 and Notch 2 <sup>‡</sup>	IL-6 and IL-23	Present peptides on MHC class II molecules to CD4 <sup>+</sup> T cells	Lungs and gut	Steady state
Interstitial cDC	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , CX <sub>3</sub> CR1 and CD11b	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , CD11b, CD16 and CD14	ND	TNF and IL-12	ND	Peripheral tissues	Steady state
Langerhans cell	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , Langerin and CD205	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , CD1a, Langerin and CD205	ND	ND	ND	Epidermis	Steady state
Monocyte-derived DC	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> , CD11b, CX <sub>3</sub> CR1 and CD209	CD11c <sup>hi</sup> , MHC class II <sup>hi</sup> and CD11b	ND	TNF and iNOS	Present peptides on MHC class II molecules to CD4 <sup>+</sup> T cells	Inflamed lymph nodes and tissues	Inflamed

BATF3, basic leucine zipper transcription factor ATF-like 3; BDCA, blood dendritic cell antigen; BST2, bone marrow stromal antigen 2; cDC, classical dendritic cell; CLEC9A, C-type lectin domain family 9 member A; CX<sub>3</sub>CR1, CX<sub>3</sub>C-chemokine receptor 1; ESAM, endothelial cell-selective adhesion molecule; IFN, interferon; IL-12, interleukin-12; iNOS, inducible nitric oxide synthase; IRF4, interferon-regulatory factor 4; ND, not described; SIGLEC, salic acid-binding immunoglobulin-like lectin; SIRPα, signal-regulatory protein-α; TCF4, transcription factor 4; TNF, tumour necrosis factor; XCR1, XC-chemokine receptor 1. \*The table (which is by no means all-inclusive) shows the main cell surface markers, subset-specific transcription factors and predominant functional features of the putative orthologous human and mouse dendritic cell subsets<sup>3-5,116,117</sup>. <sup>‡</sup>It is unclear whether the human and mouse subsets of these DCs are orthologous. <sup>§</sup>Expression has been reported in the gut. <sup>||</sup>Expression has been reported in the lungs. <sup>‡</sup>The expression of Notch 2 is ubiquitous; however, its function is only required in this DC subset in the gut and not in the lungs.

# Déterminants antigéniques reconnus par les récepteurs de l'immunité innée (PRR)

- **PRRs**

- Faibles diversités
- Récepteurs reconnaissent des structures moléculaires très conservées présents sur les grands groupes de pathogènes (PAMPs)

- **PAMPs** présentent 3 caractéristiques communes

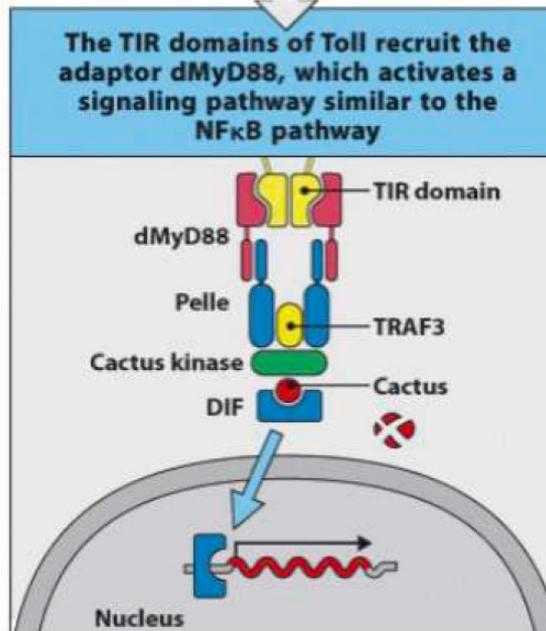
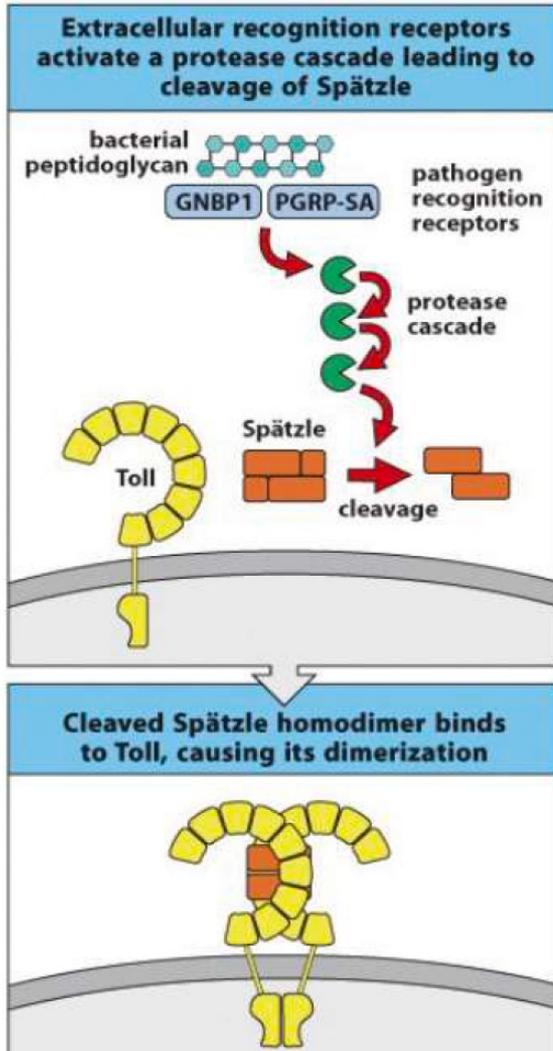
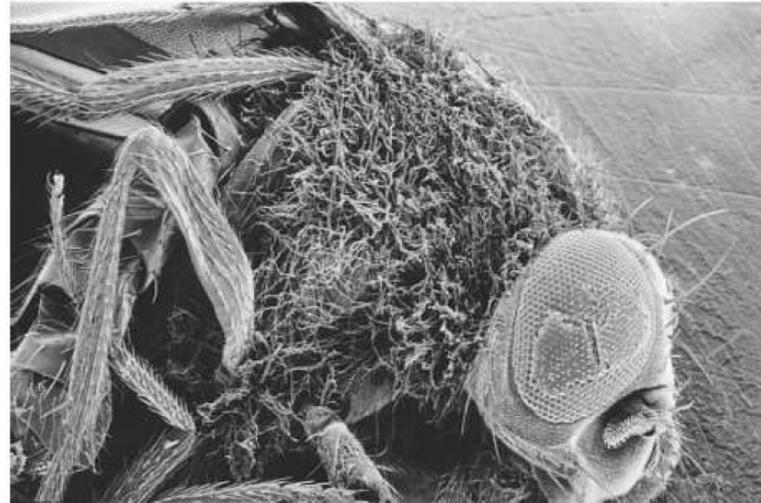
- Sont produits uniquement par les micro-organismes
- Sont invariants entre les microorganismes d'une même classe
- Sont essentiels pour la survie des micro-organismes



**SIGNAL DANGER**

# Découverte des TLR chez les insectes

## Récepteur Toll de la drosophile

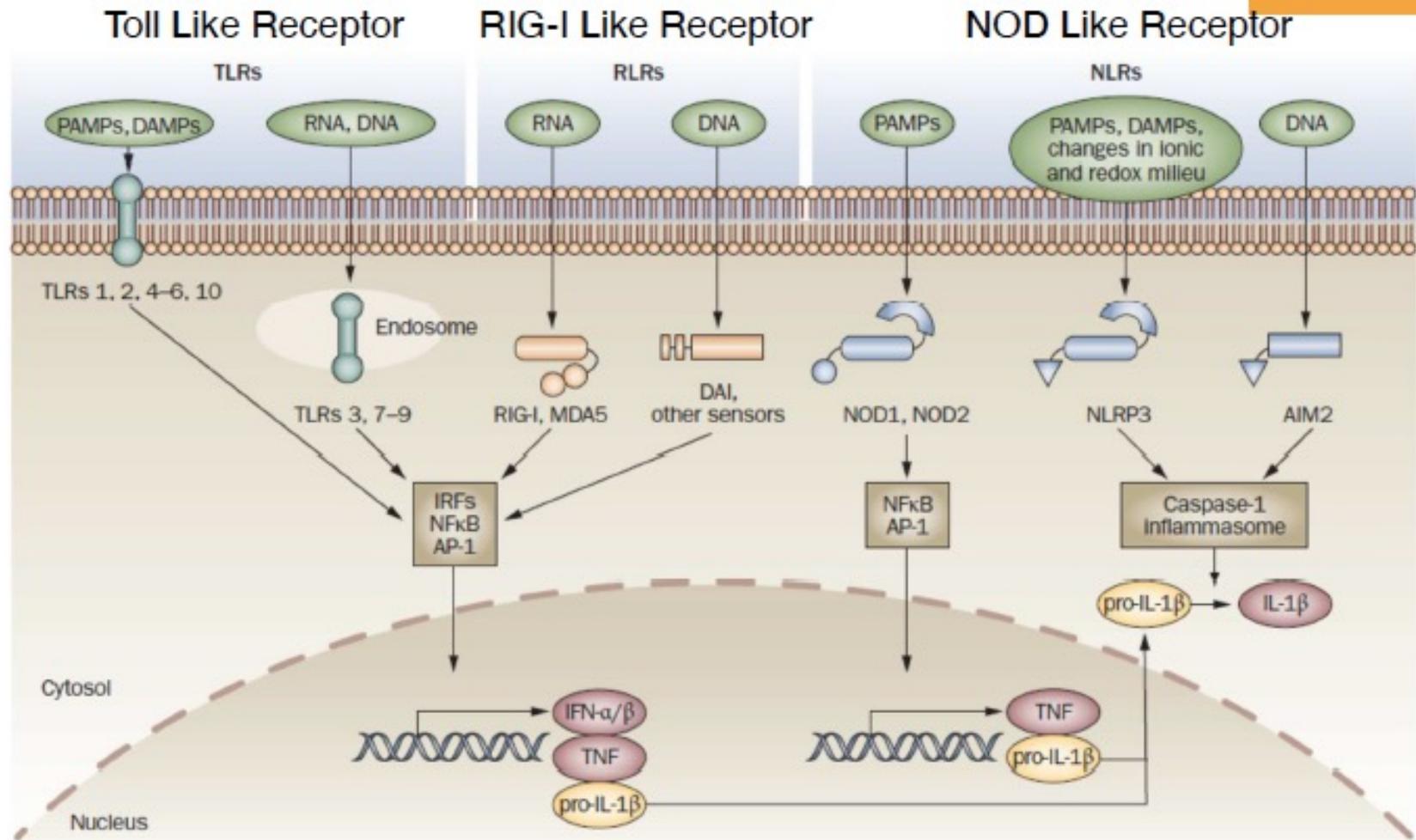


Nobel Prize in Physiology or Medicine 2011

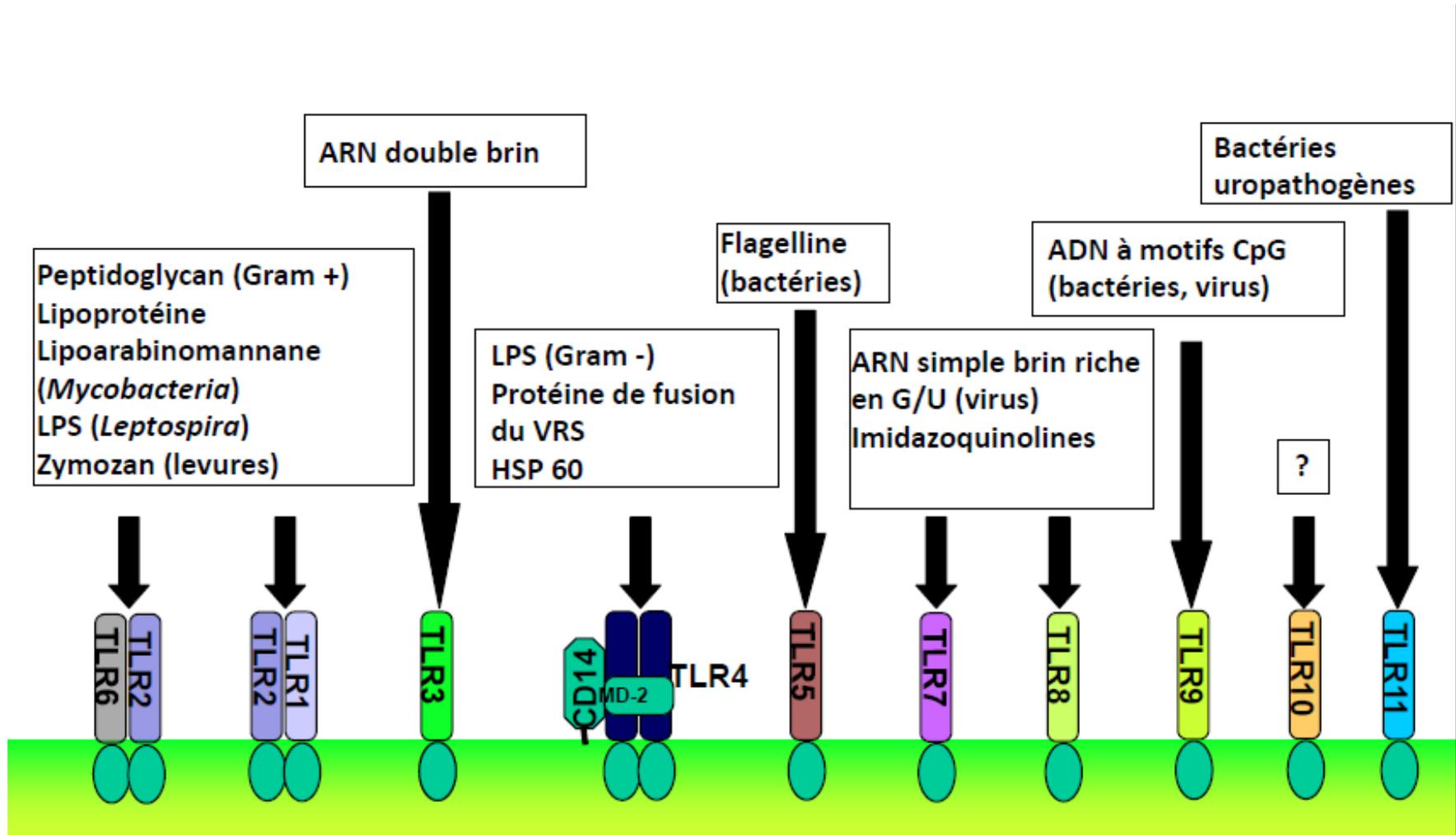


Jules Hoffman

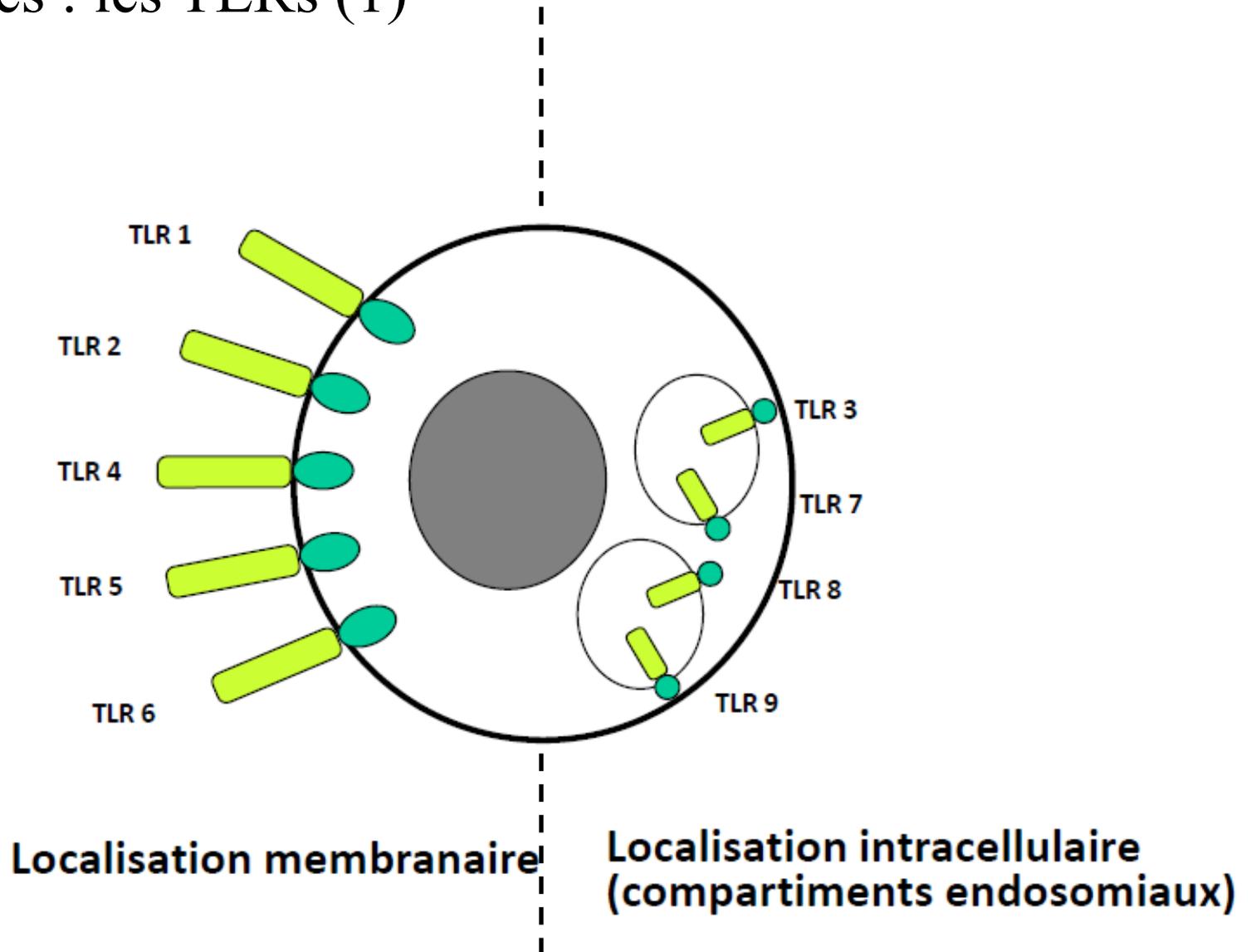
# Récepteurs de l'immunité innée (PRR) et cellules dendritiques



# Exemples : les TLRs (1)



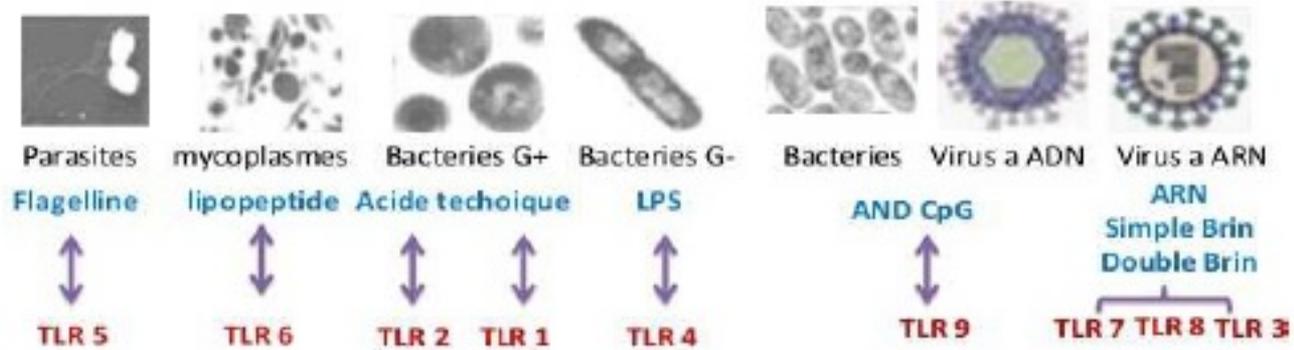
# Exemples : les TLRs (1)



Localisation membranaire

Localisation intracellulaire

# Récepteurs de l'immunité innée (PRR) et cellules dendritiques



## conventionnel DC

## Plasmacytoid DC



**cDC1**

TLR3  
TLR8



**cDC2**

TLR4  
TLR5  
TLR1/2  
TLR8



**DC  
inflammatoire**

TLR4  
TLR1/2/6  
TLR5  
TLR8



**Cellule de  
Langerhans**

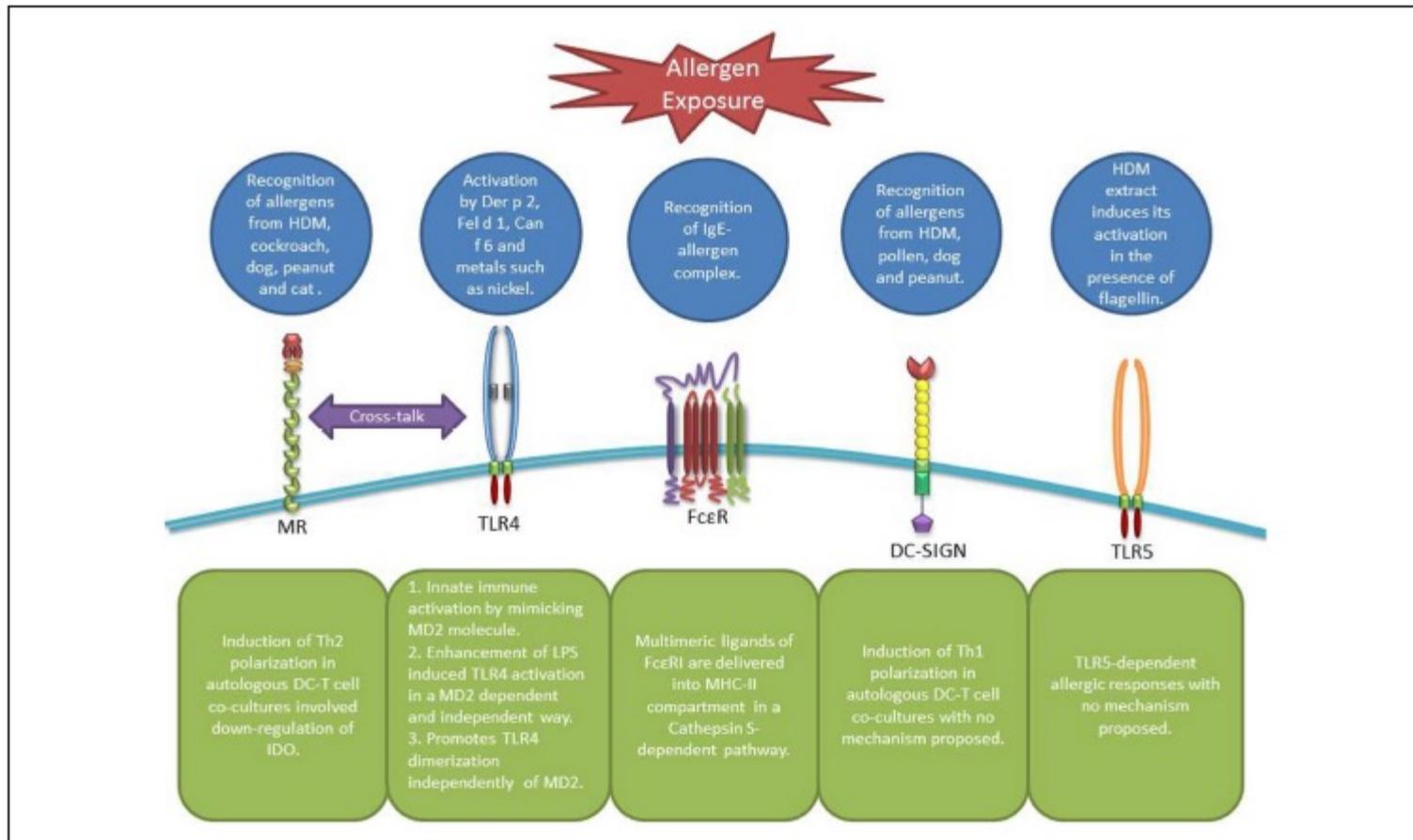
TLR1/2/6  
TLR3  
TLR5



TLR7  
TLR9

# Cellules présentatrices d'antigènes et allergie : phénotype, propriétés, fonctions

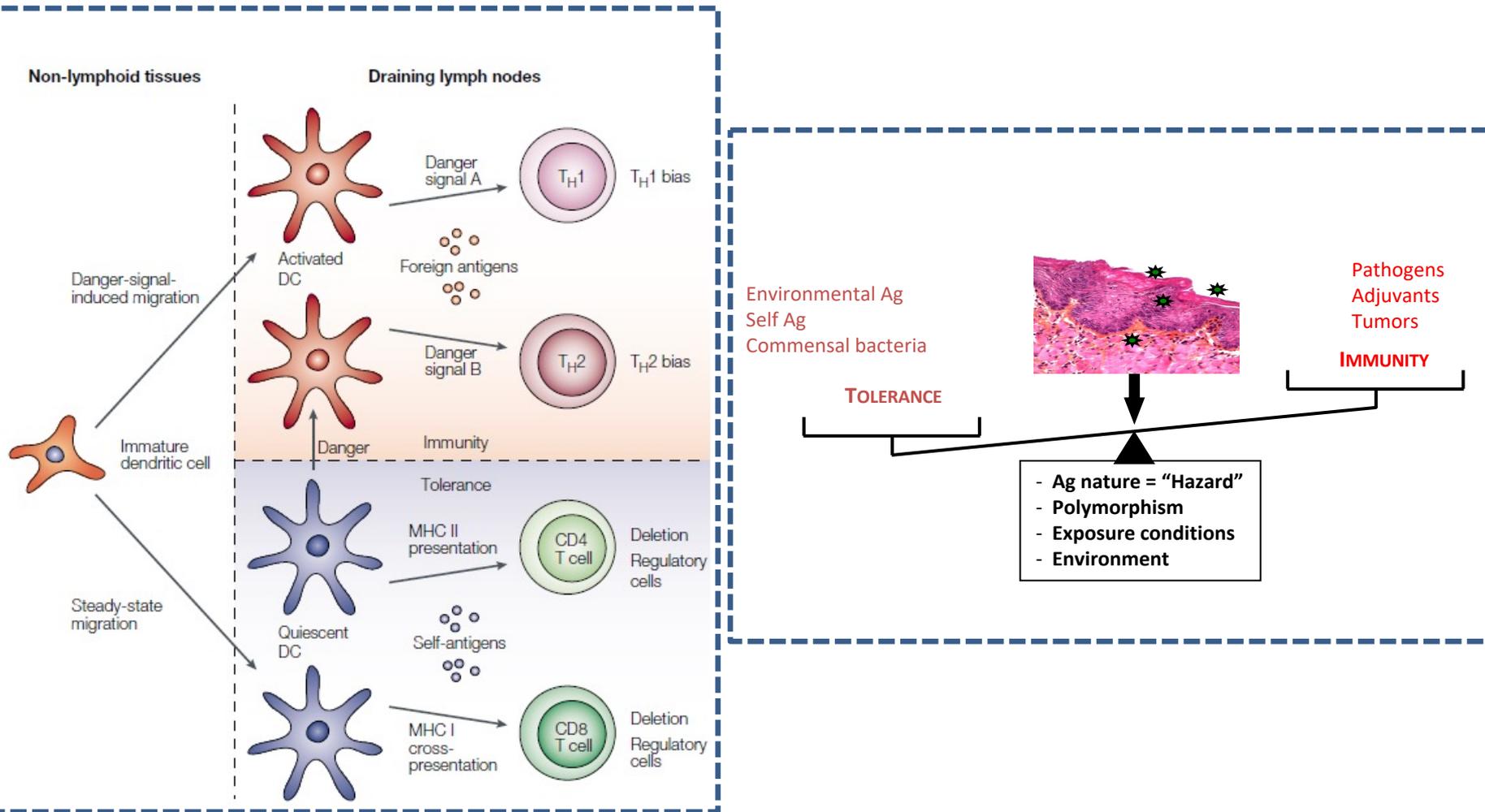
PRR= Pathogen Recognition Recepteur



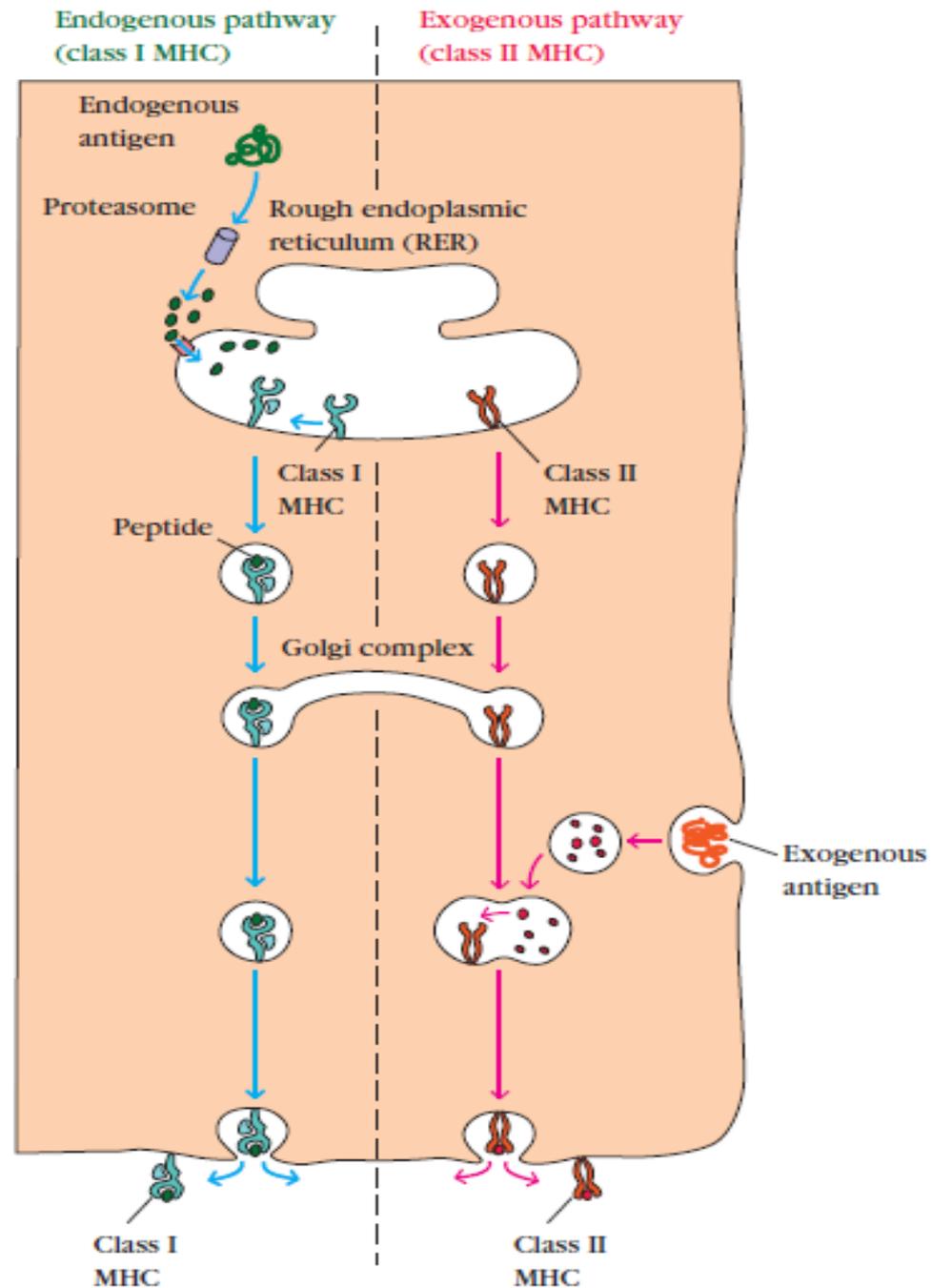
**FIGURE 1 | Receptors involved in allergen recognition and uptake by DCs.** MR can recognize allergens from diverse sources leading to Th2 polarization and IDO down-regulation in DCs involving a possible cross-talk with TLR4 (19). TLR4 itself can be activated by airborne allergens and diverse metals in an

MD2 dependent or independent way (33, 35–37). FcεR facilitate allergen uptake through the recognition of the IgE-allergen complex (41, 46). DC-SIGN can recognize diverse allergens as well, however, leading to a Th1 polarization. Finally, TLR5 can be activated by HDM extracts containing flagellin (34).

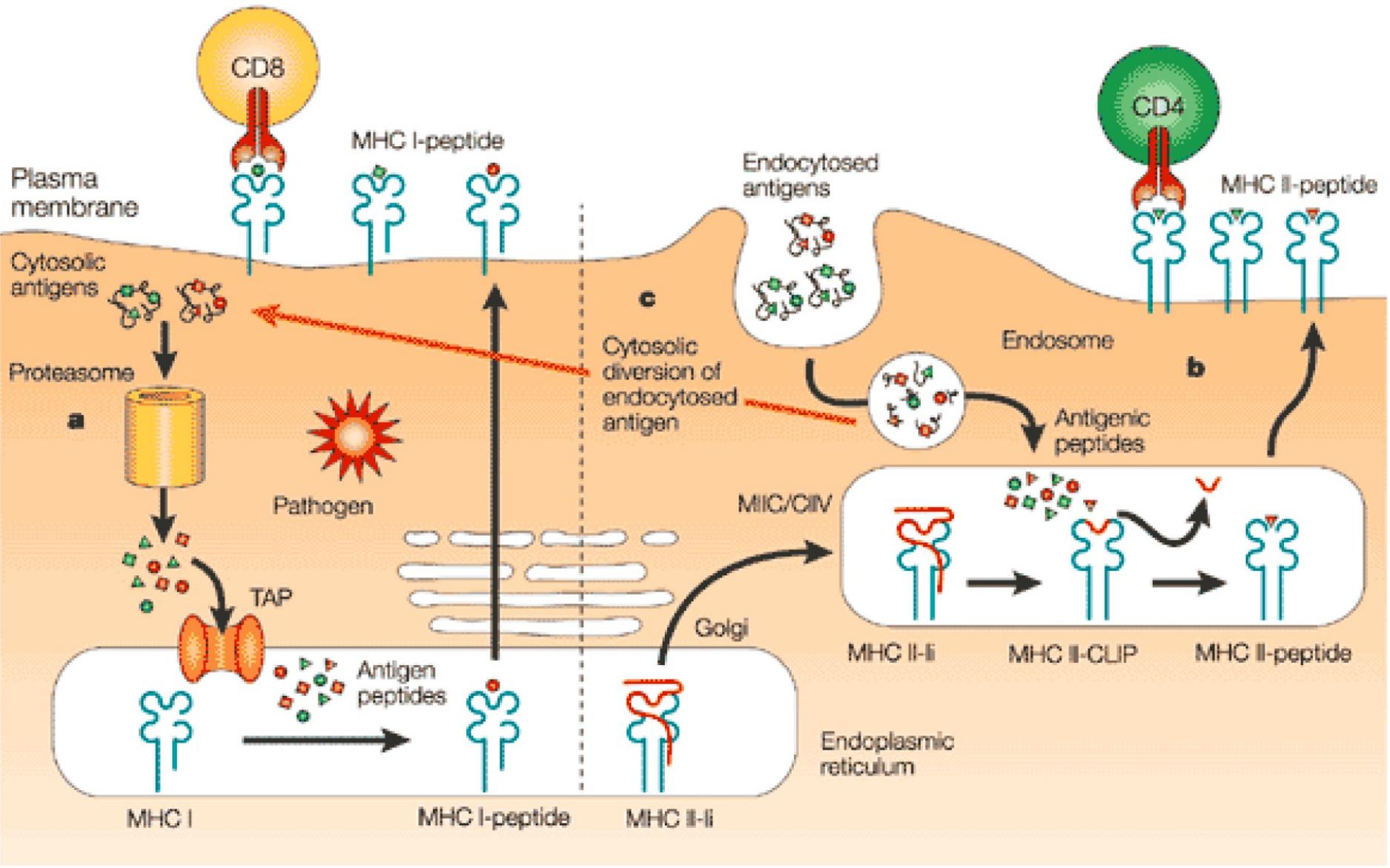
# Cellules présentatrices d'antigènes et allergie : phénotype, propriétés, fonctions



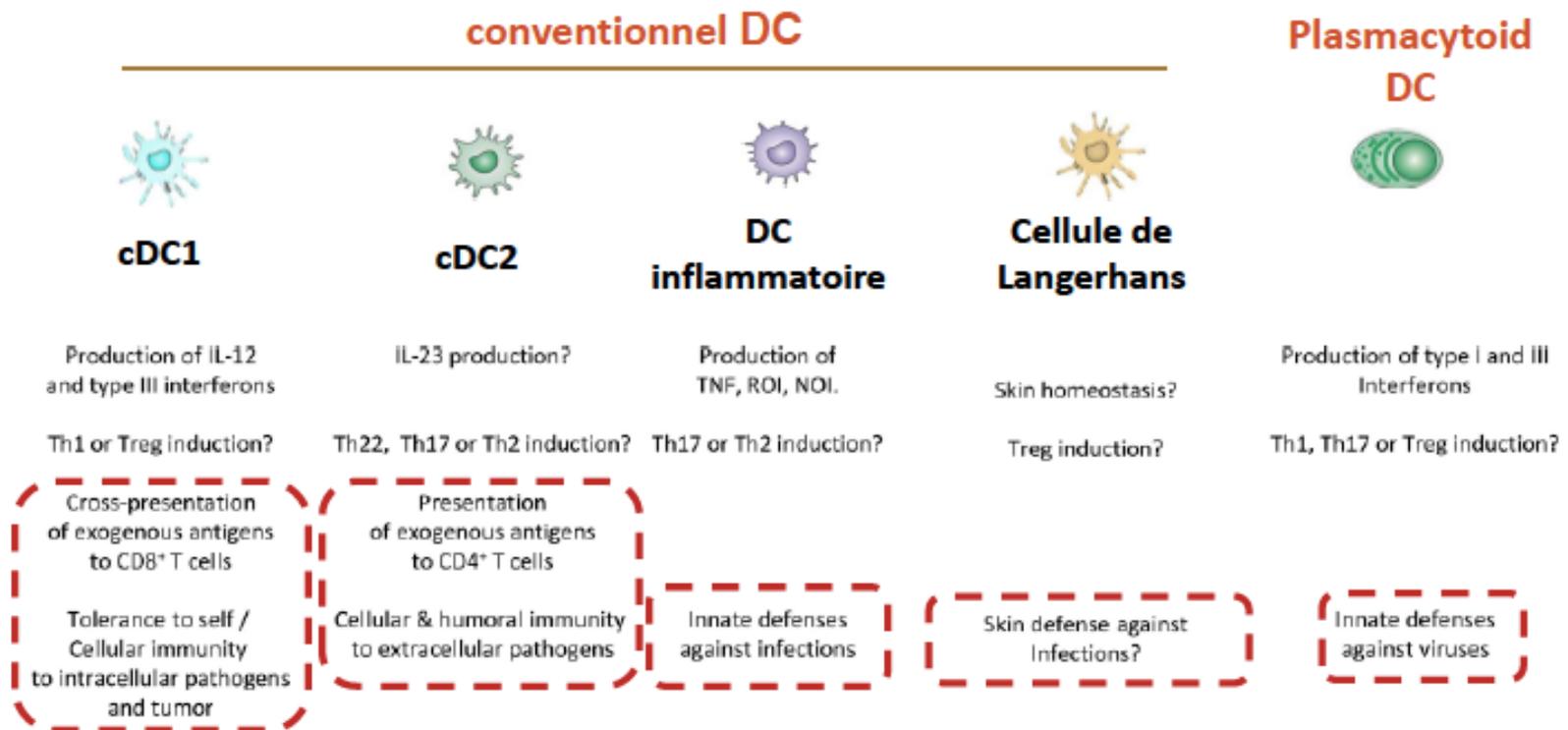
# Présentation antigénique et cellules dendritiques

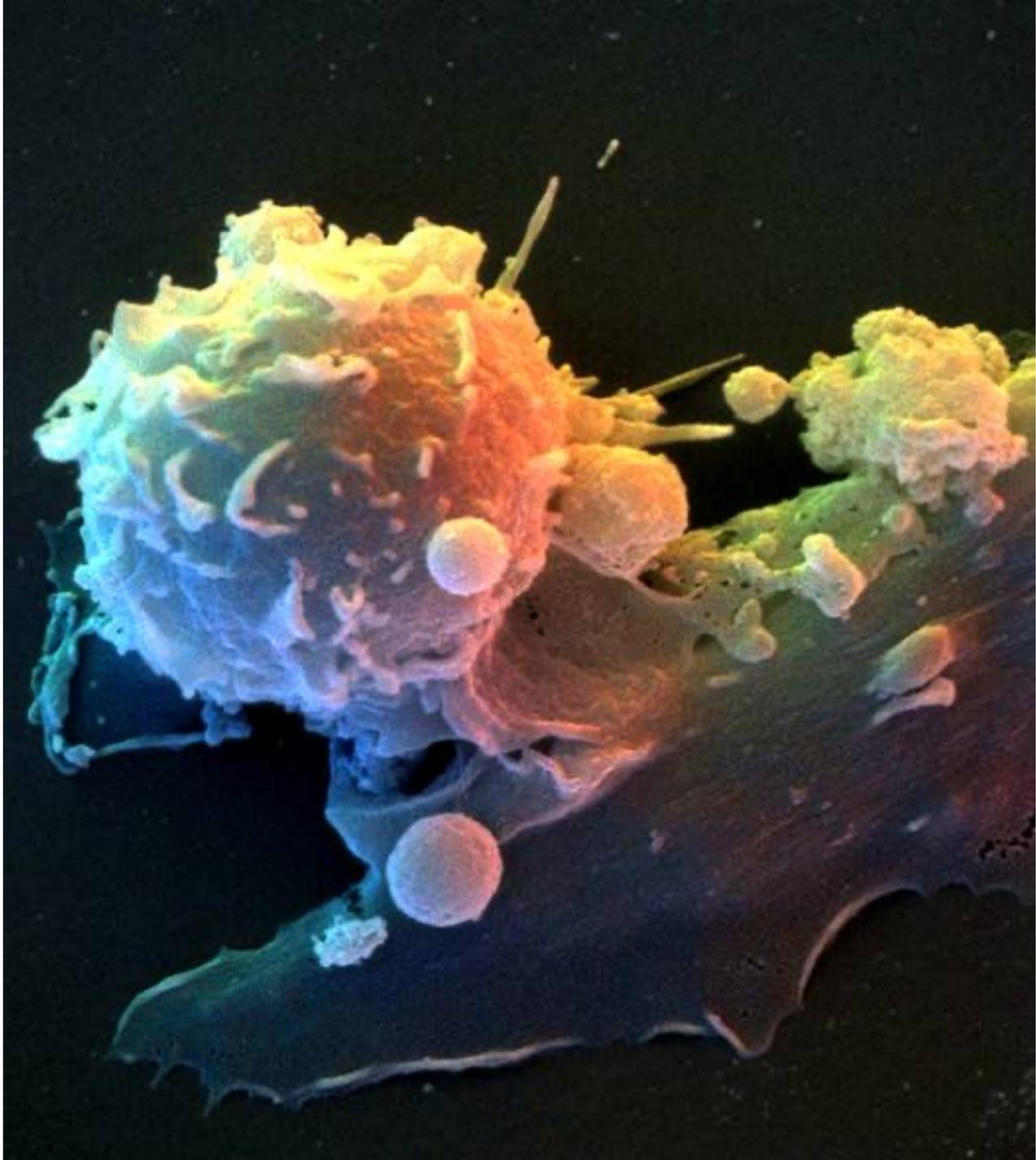


# Présentation croisée ou « cross-priming »



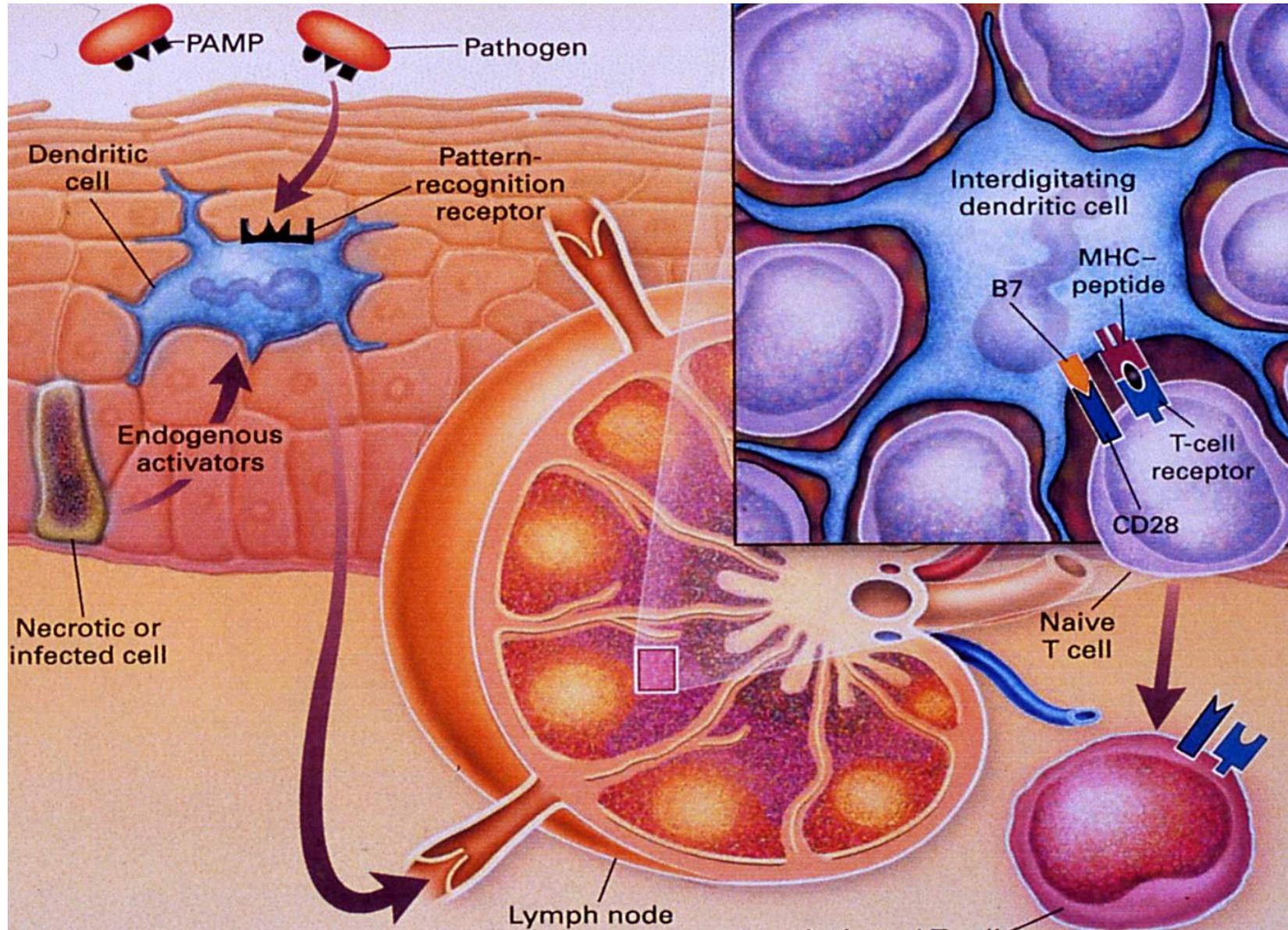
# Récepteurs de l'immunité innée (PRR) et cellules dendritiques





# Cellules présentatrices d'antigènes et allergie

## Présentation de l'antigène



# La Cellule Dendritique est un lien essentiel entre Immunité Innée et Immunité Adaptative

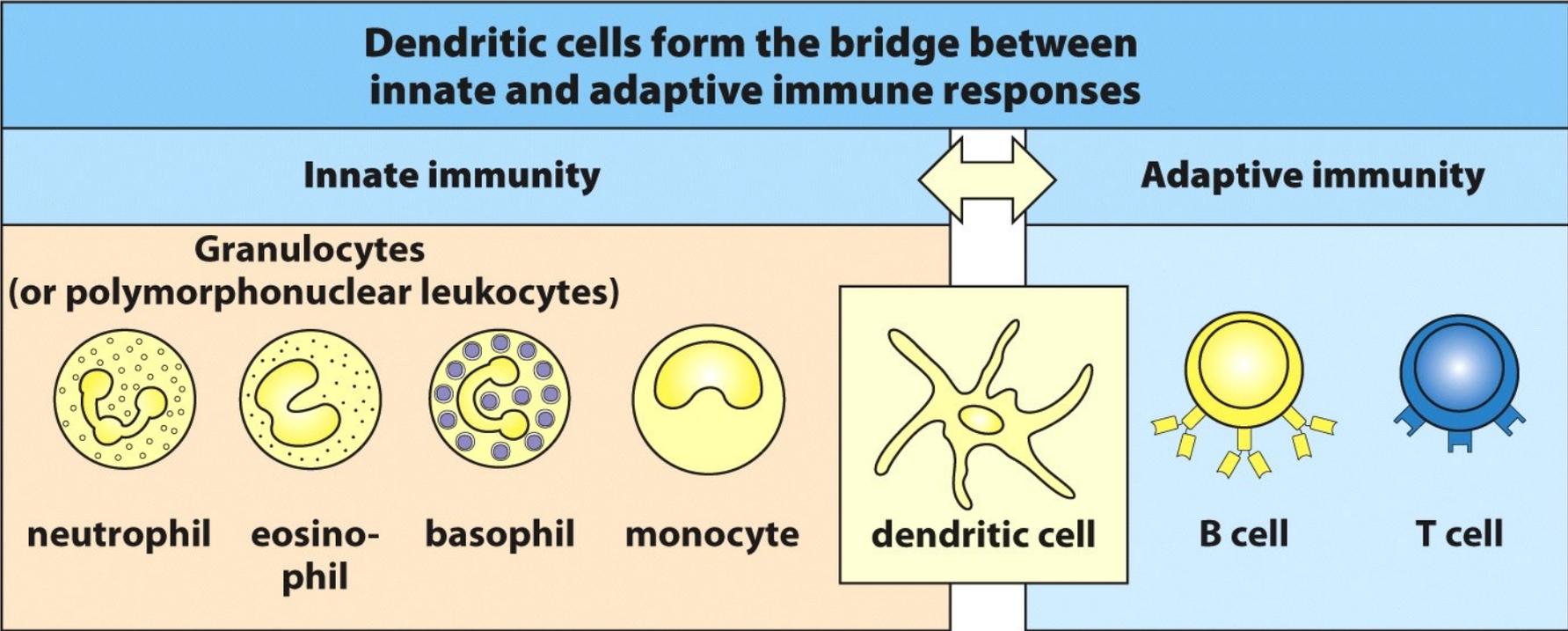
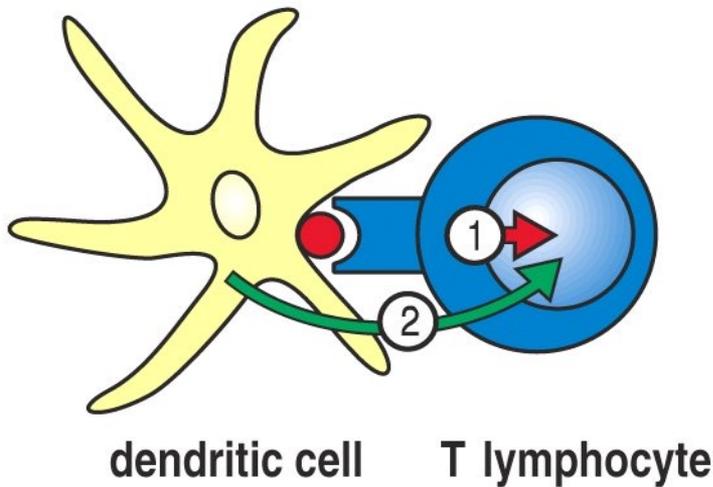


Figure 1.5 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

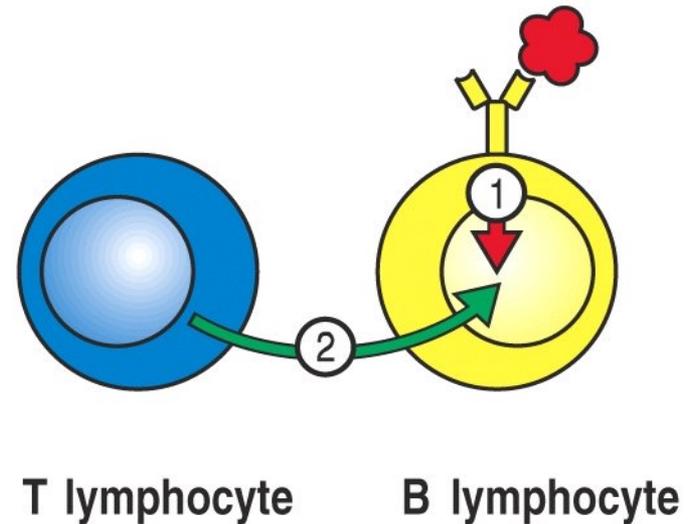
# PRESENTATION ANTIGENIQUE

Antigen:receptor binding and co-stimulation of T cell by dendritic cell



Proliferation and differentiation to effector function

Antigen:receptor binding and activation of B cell by T cell



Proliferation and differentiation to effector function

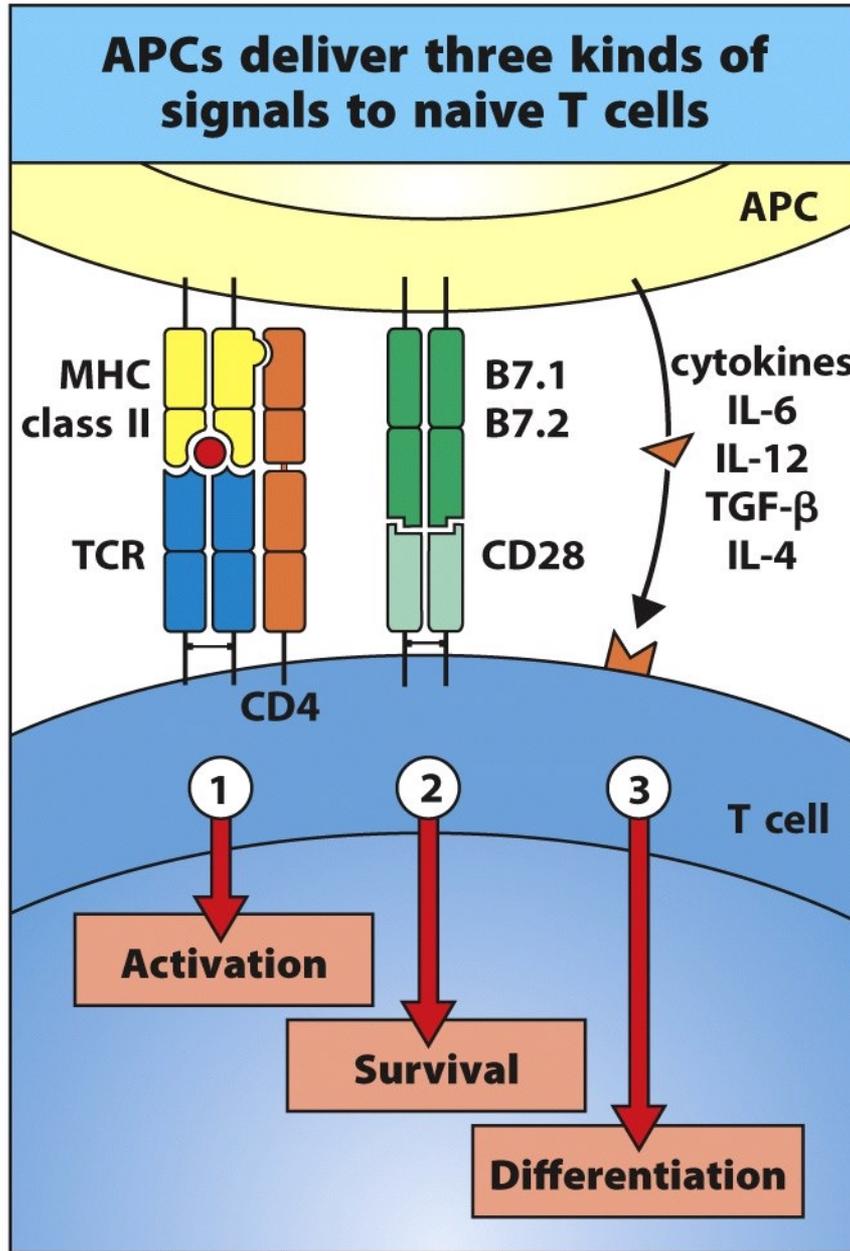
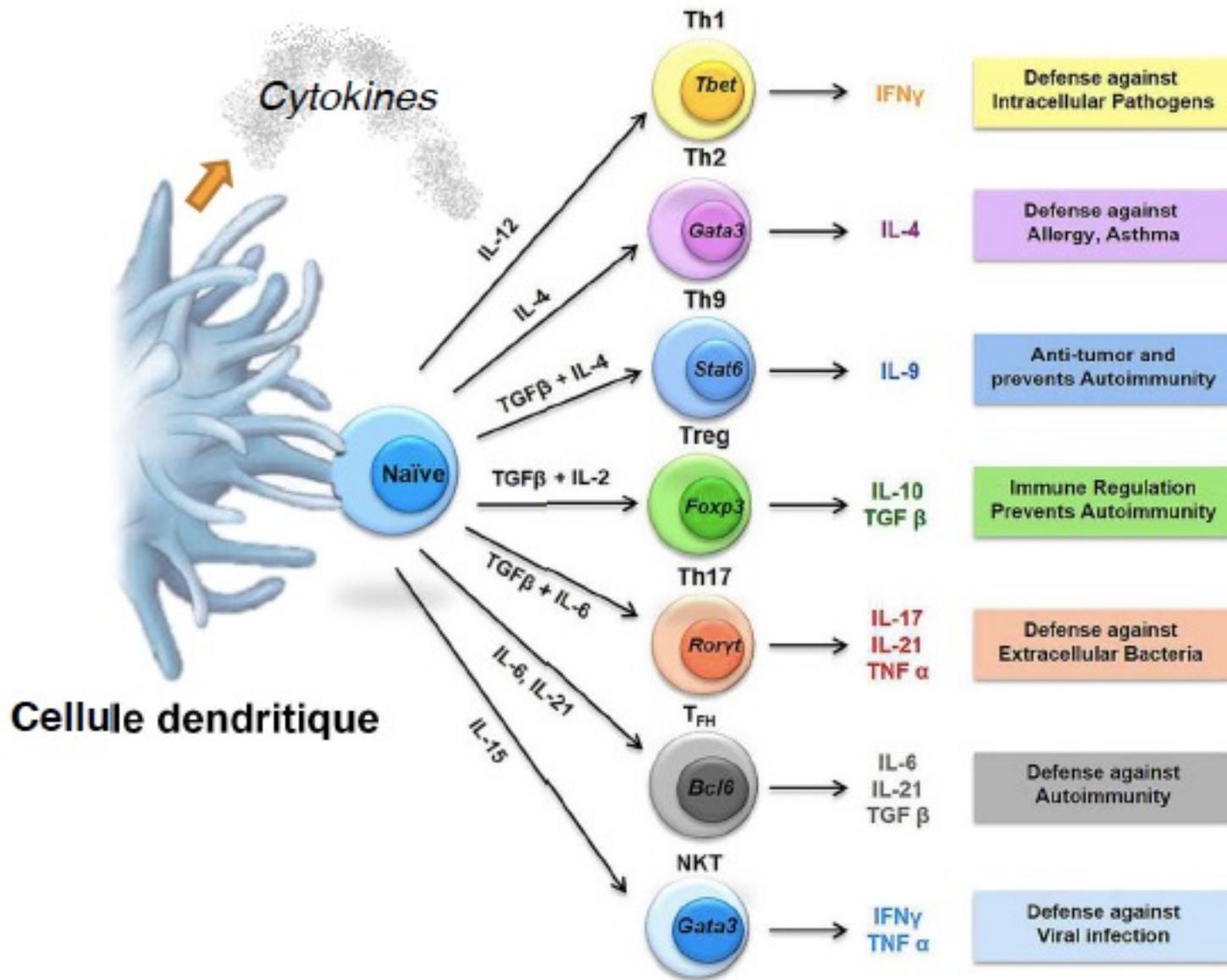


Figure 9.19 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

# Diversité des cellules dendritiques



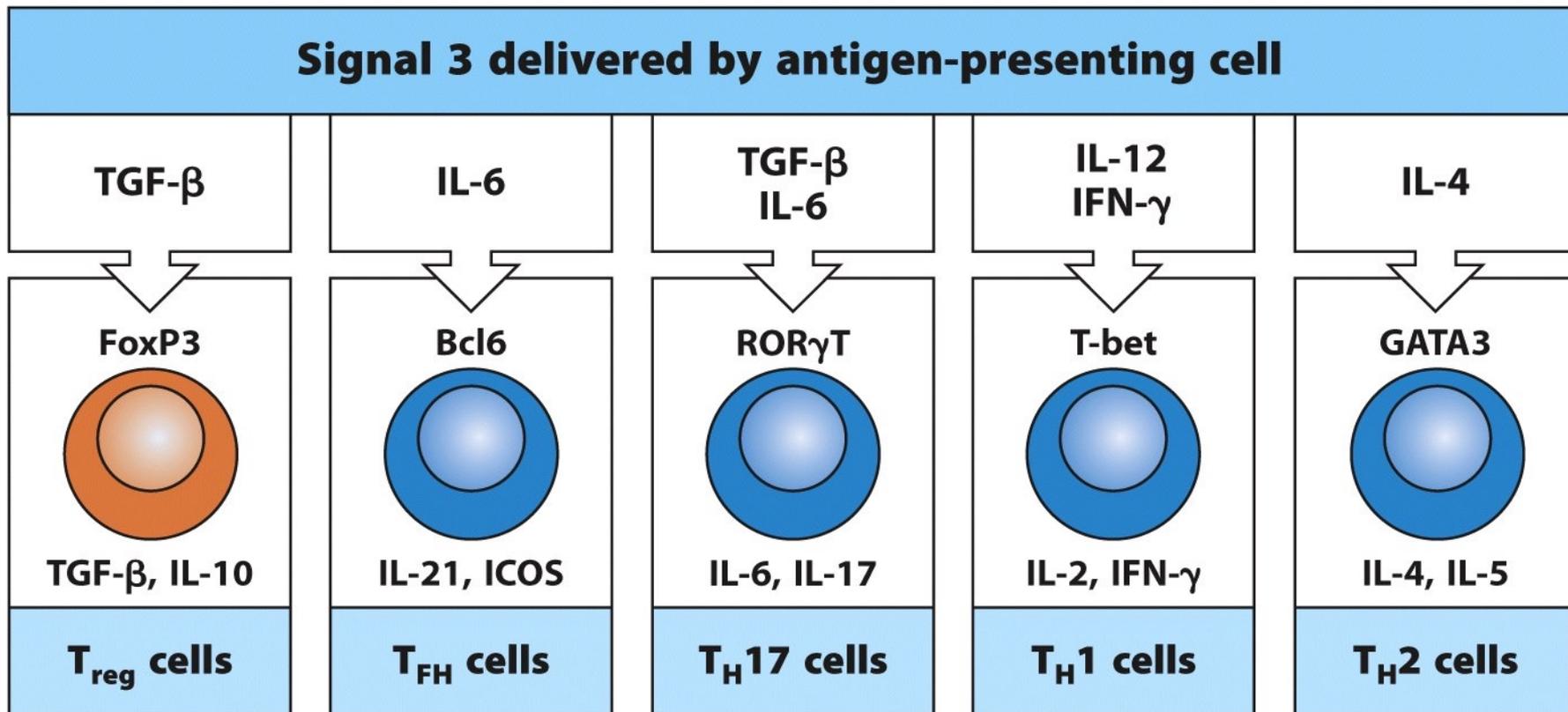


Figure 9.29 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

**CD4 T cells: peptide + MHC class II**

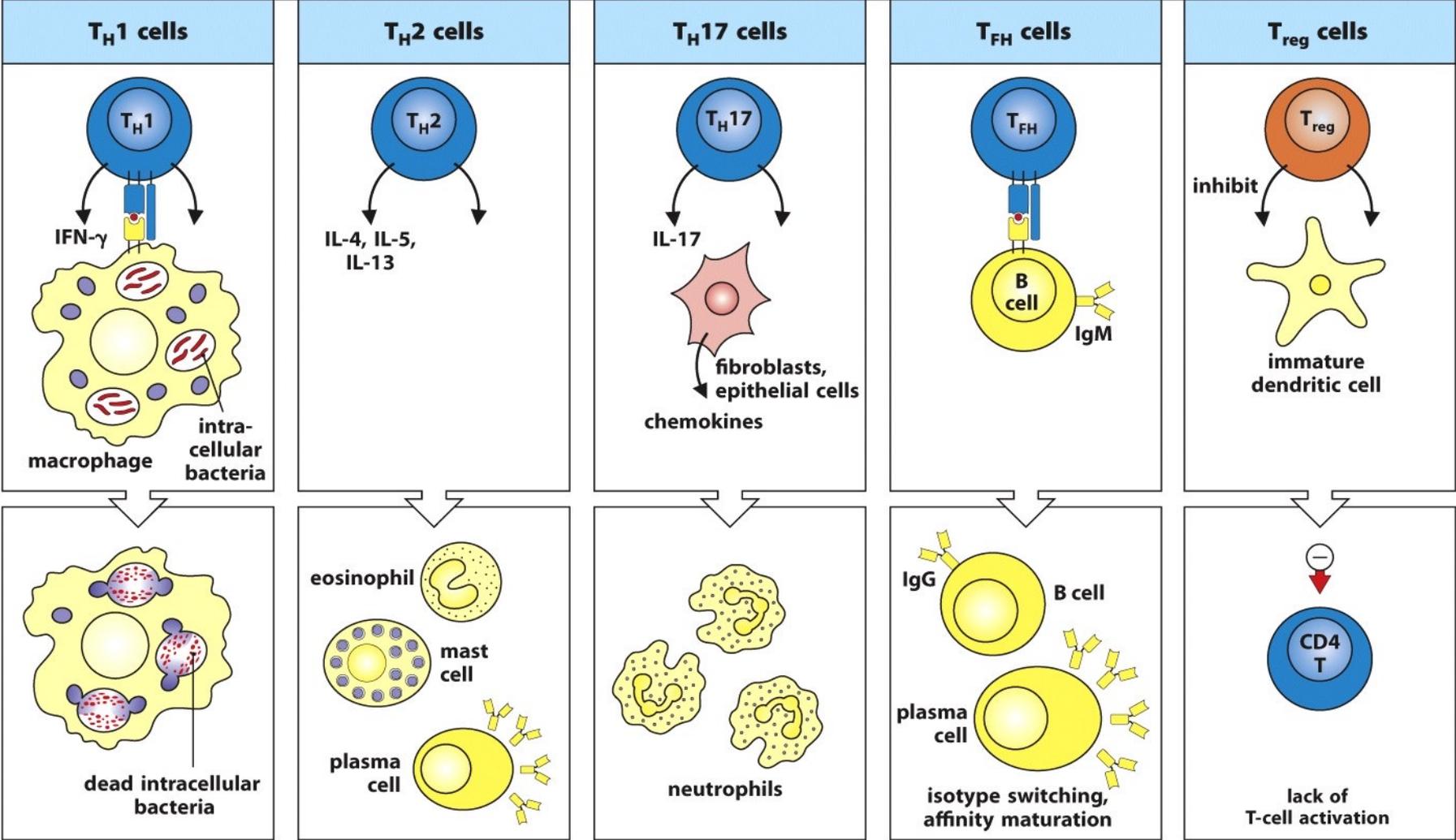


Figure 9.28 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

