Antigen-Presenting Cell, APC

NATURE REVIEWS IMMUNOLOGY
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In the late 1960s and early 1970s, a shift occurred in the focus of immunological research from Ab-dominated studies to ones involving cellular components of immunity such as T cells, B cells, and APCs.

Comment in
J Immunol. 2007 Jul 1;179(1):3-4
Paul M. Allen

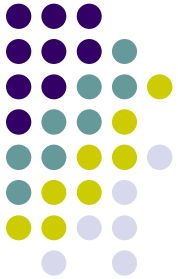
抗原被什么细胞捕获?

抗原被什么分子识别?

抗原经什么途径加工?

抗原被什么分子递呈?

Antigen-Presenting Cell, APC



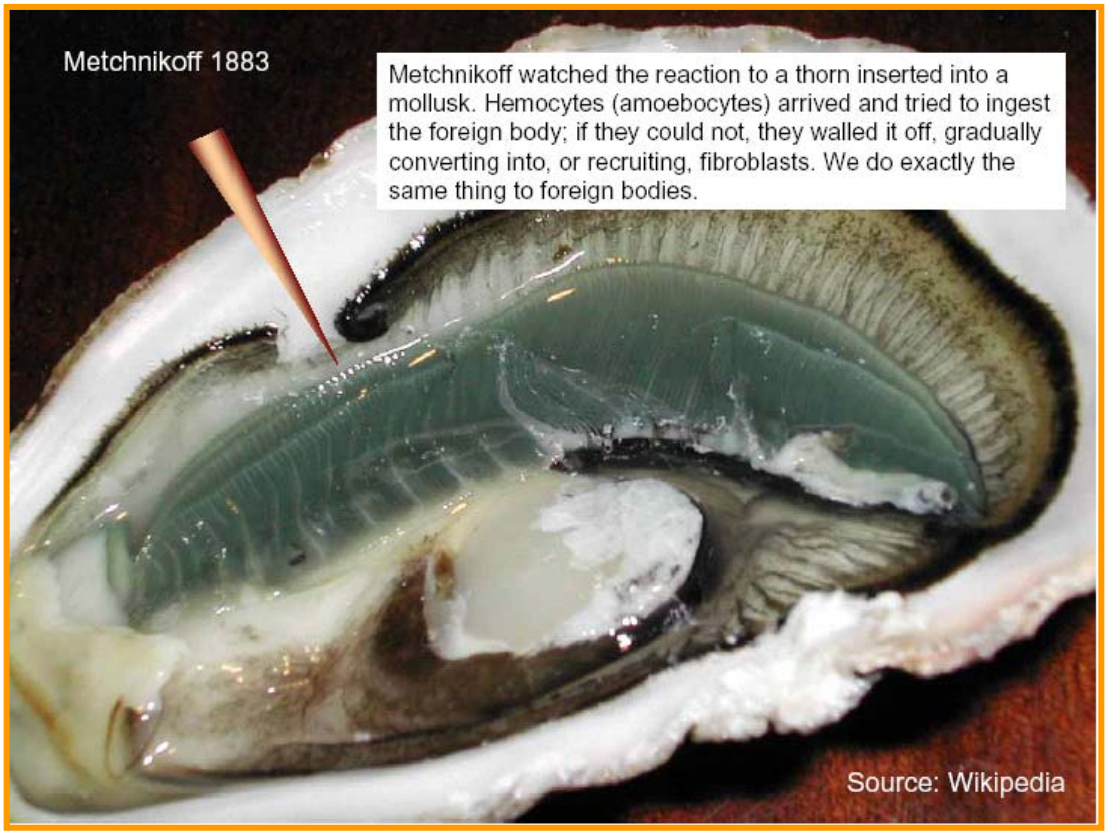
Professional APC

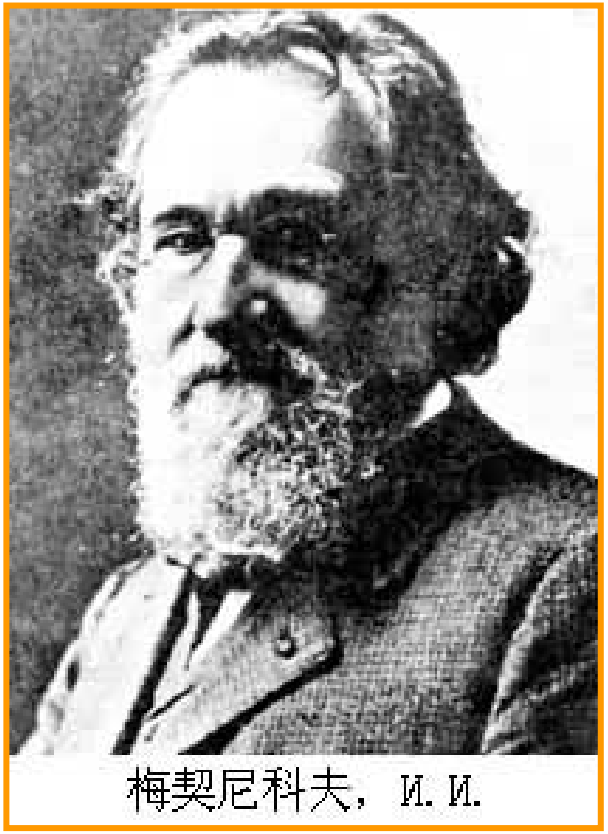
- Dendritic Cell, DC
- Mononuclear Phagocyte System, MPS
- B cell

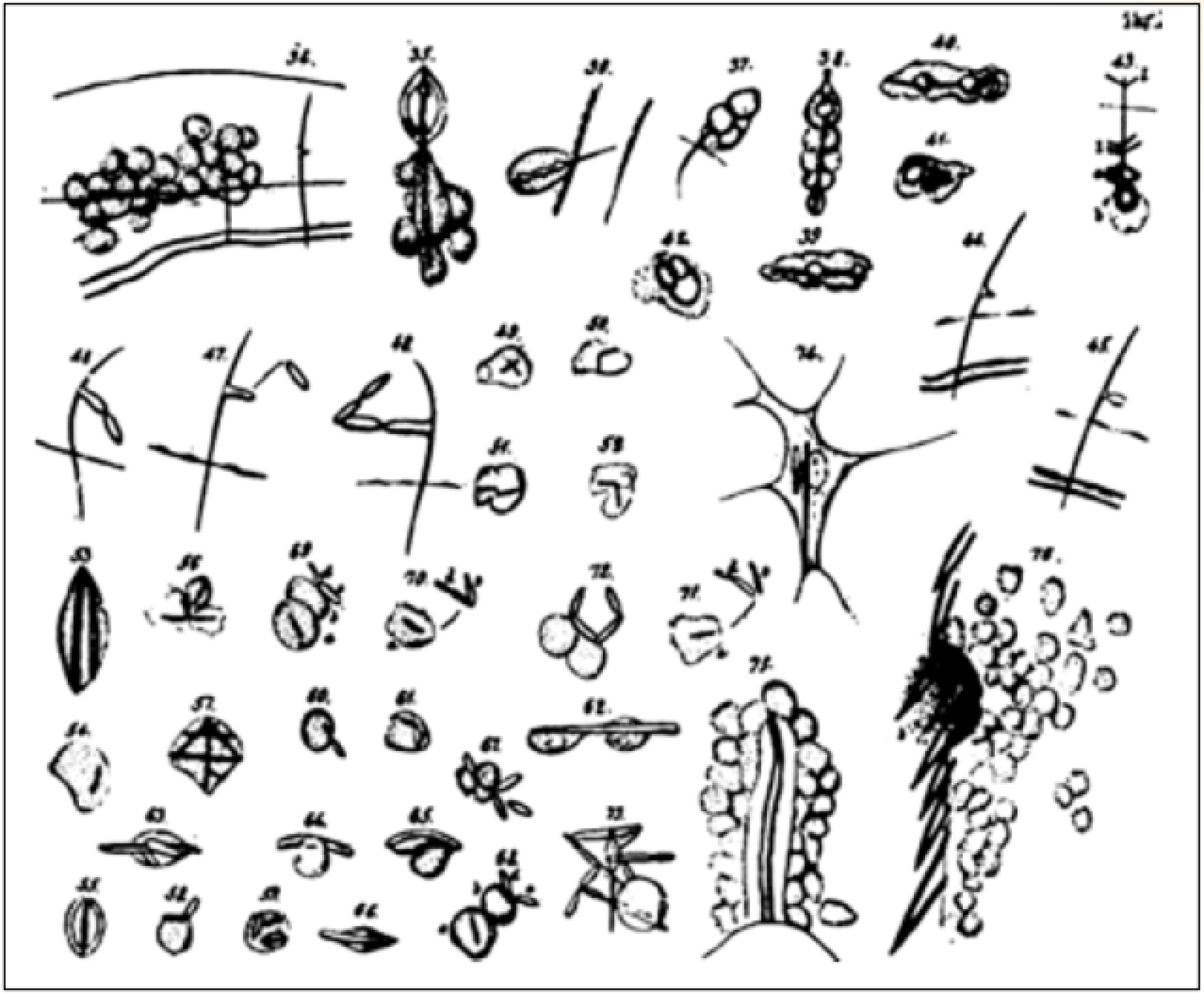
Non-professional APC

- Endothelial cell, EC
- Activated T cell
- Tumor cell
- Virus-infected cell

1. Mononuclear Phagocyte System, MPS



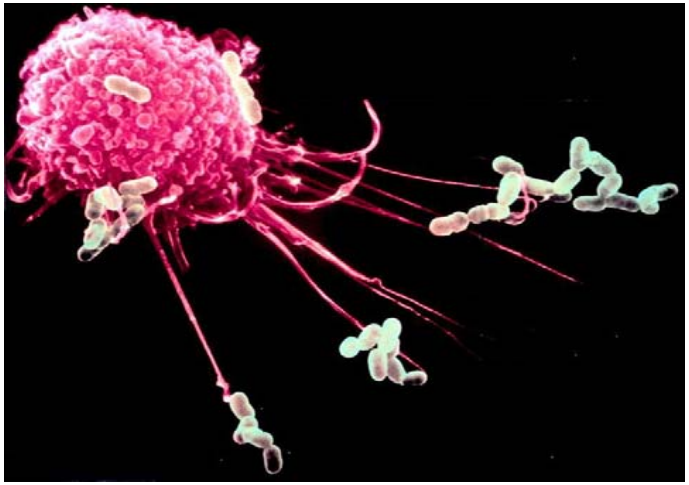

梅契尼科夫，И. И.

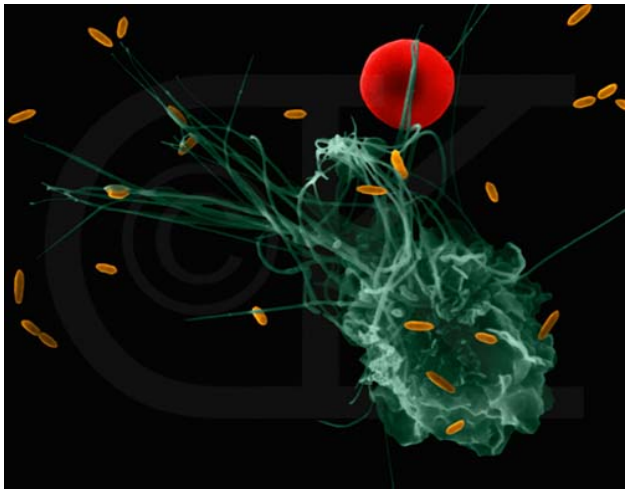


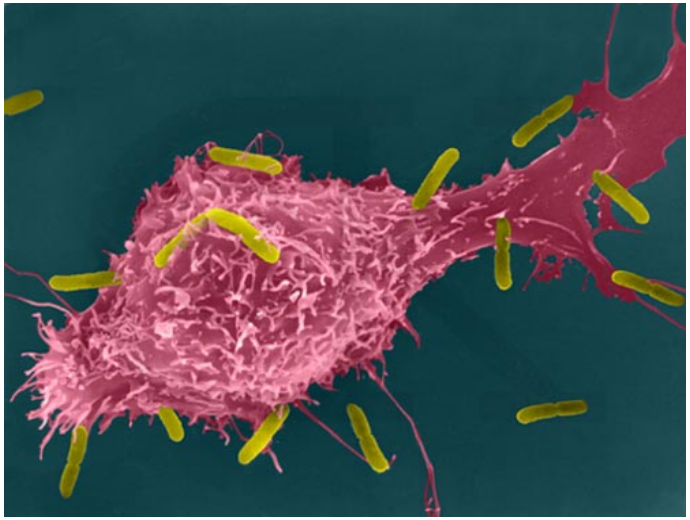
http://202.114.65.51/fzjx/wsw/newindex/wswfzjs/pdf/1884p132.pdf

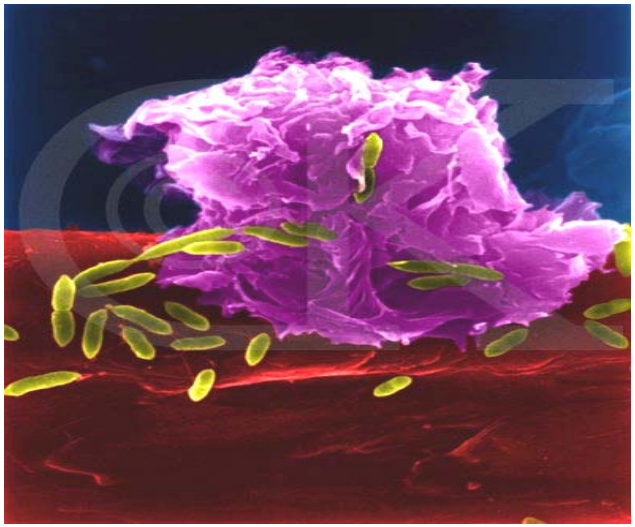
梅契尼科夫手繪的「水蚤吞噬細胞吞食酵母菌圖」。

抗原是简单结合在ＡＰＣ表面还是在代谢过程中被加工?









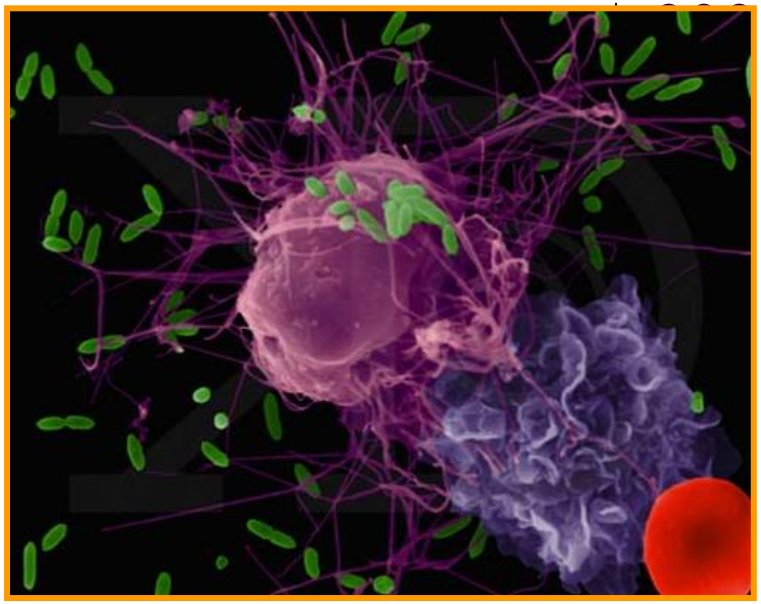
早期实验:

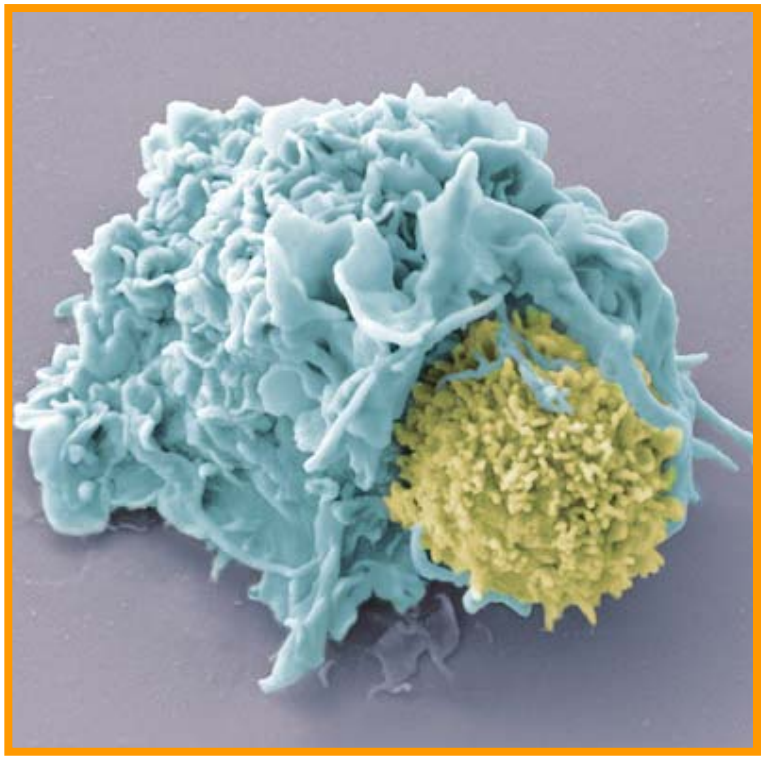
1.方法：巨噬细胞(APC)同抗原一起在4℃或37℃的条件下培养1小时后，分别检测它们激活T细胞（来源于淋巴结）的能力。

2.结果：在较低的抗原浓度条件下，巨噬细胞在37℃时对T细胞激活的效率是在4℃时的10倍。

在细胞中加入叠氮钠(细胞色素氧化酶抑制剂)，同样抑制抗原激活T细胞。

说明APC内化抗原是一个代谢事件，且需要代谢能量。





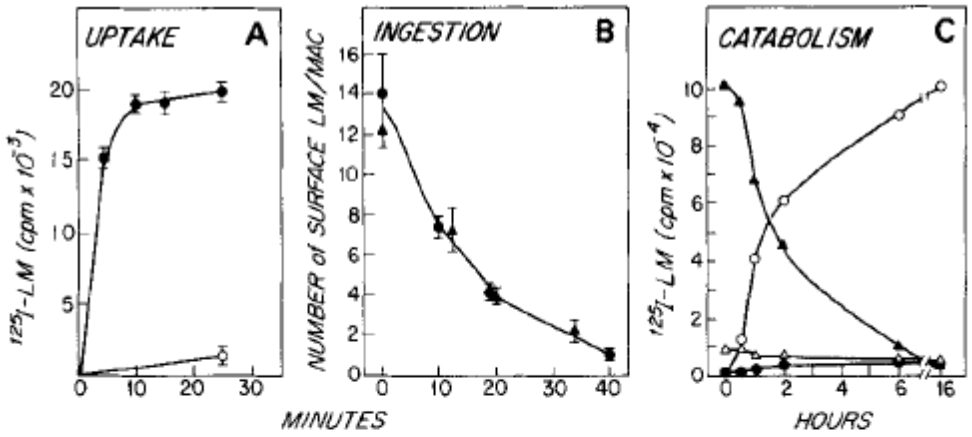


Figure 1. a. The uptake of ^{125}I-labeled *Listeria monocytogenes* by macrophages is shown as a function of time. ^{125}I-*Listeria* (0.5 ml per well, 10^5 cpm per well) was added to tissue culture wells containing macrophage monolayers formed with 10^6 PEC. The plates were centrifuged (800 × G, 5 min), incubated for the indicated periods of time at 37°C, and then washed to remove unbound bacteria. The macrophage-associated radioactivity recovered after treatment with 1% Triton X-100 is shown (*closed symbols*). Open symbol represents ^{125}I-*Listeria* associated with culture well in the absence of macrophages. *b.* The ingestion of *Listeria monocytogenes* by macrophages was monitored visually by indirect immunofluorescence with an anti-*Listeria* antibody. Bacteria on the macrophage cell surface but not those that are ingested are reactive with the antibody. Each point represents the number of surface bacteria per macrophage (mean ± SEM). Two different experiments are indicated by the different symbols. Time zero represents macrophages exposed to *Listeria* for a 5-min centrifugation period (as in Fig. 1*a*), washed, and fixed immediately. *c.* The catabolism of ^{125}I-*Listeria* macrophages was followed with time. Macrophage monolayers (10^6 PEC per well) were exposed (30 min) to ^{125}I-*Listeria* to allow uptake and ingestion as in Figures 1*a* and 1*b* and then incubated for various periods of time at 37°C. Trichloroacetic acid- (10%) soluble (*open symbols*) and -precipitable (*closed symbols*) radioactivity was followed in the macrophage (*triangles*) and in the supernatant (*circles*).

Emil Unanue, MD

Pillars of Immunology article

Ziegler K, Unanue ER.
Identification of a macrophage antigen-processing event required for I-region-restricted antigen presentation to T lymphocytes.
J. Immunol. 1981. 127: 1869-1875.
J Immunol. 2007 Jul 1;179(1):5-11

Comment in:
J Immunol. 2007 Jul 1;179(1):3-4.
Paul M. Allen

随后由Kirk Ziegler 和 Emil Unanue 做的实验证明了当细胞外抗原通过胞吞作用进入到巨噬细胞中并传递到细胞溶酶体腔内时，加工作用发生。

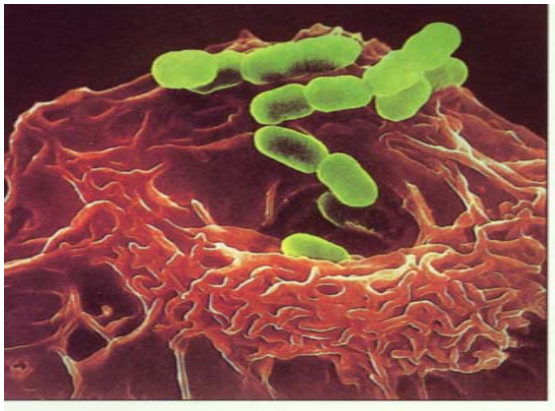
溶酶体：含有蛋白水解酶，可加工抗原。

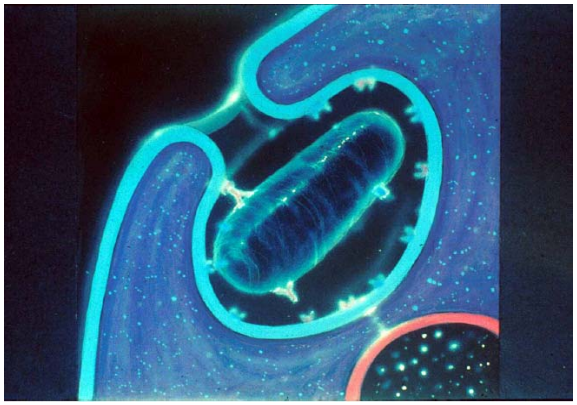
证据？在细胞里注入能使溶酶体酶类失活的物质，如氯化铵、氯喹，这两种物质能提高溶酶体腔的PH值，这种环境使酸性的水解酶失活。

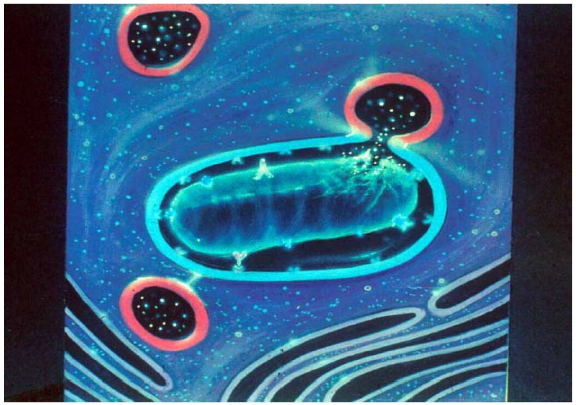
结果？这两种物质并不影响提取抗原 ，但是它们都能有效的阻止抗原加工以及限制抗原刺激T细胞结合到巨噬细胞的能力

结论：

这些证实了细胞外抗原通过溶酶体蛋白水解酶裂解可能是在抗原呈递前非常重要的一步。







1.1 Classification

Pre-monocyte

Monocyte, mon

Macrophage, Mϕ

1.2 Marker

OKM-1, Mac-120, Mol-4,CD14

1.3 Activation

Silent Mϕ,

Responsive Mϕ,

Stimulated or Primed Mϕ,

Activated Mϕ

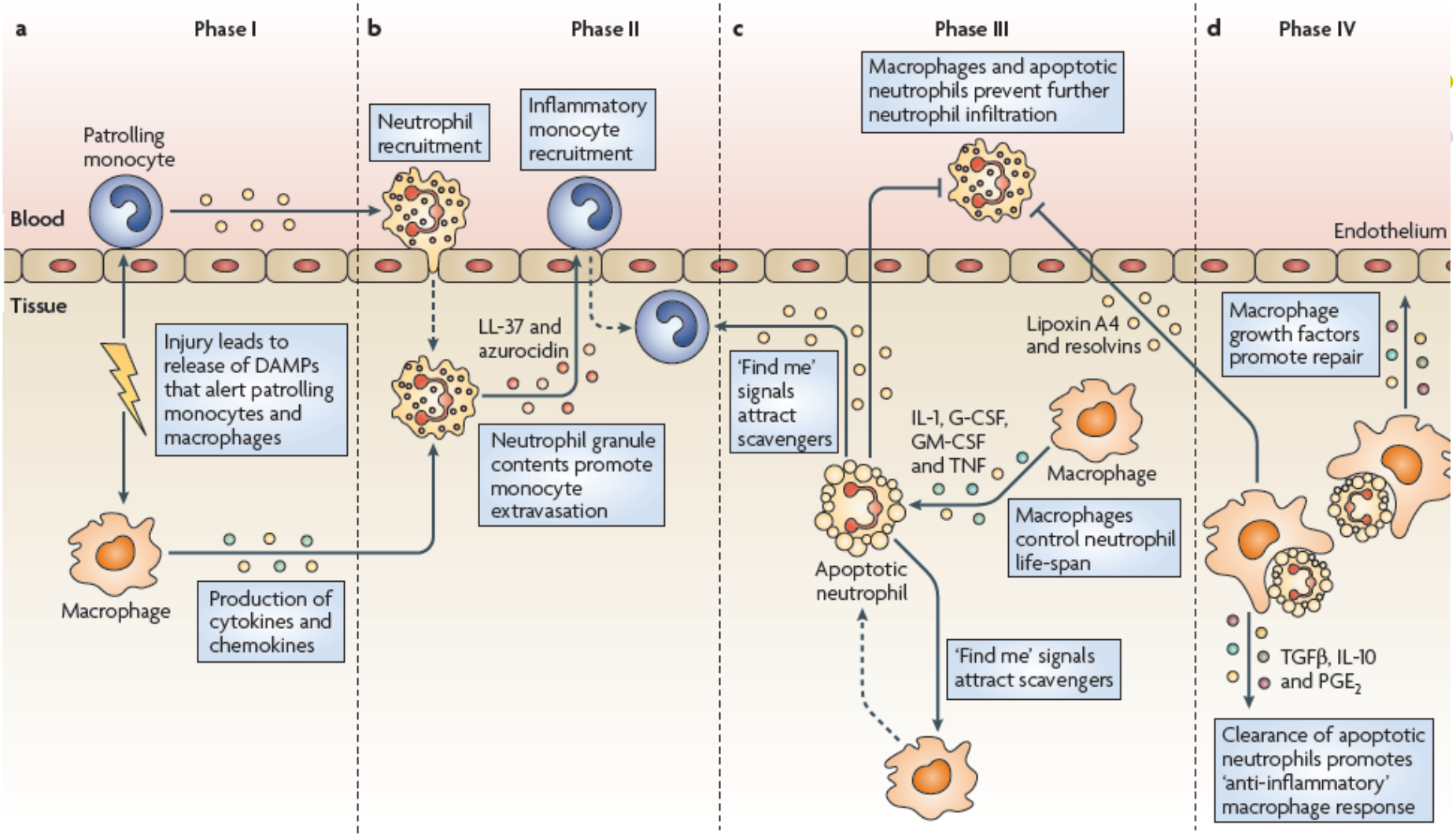
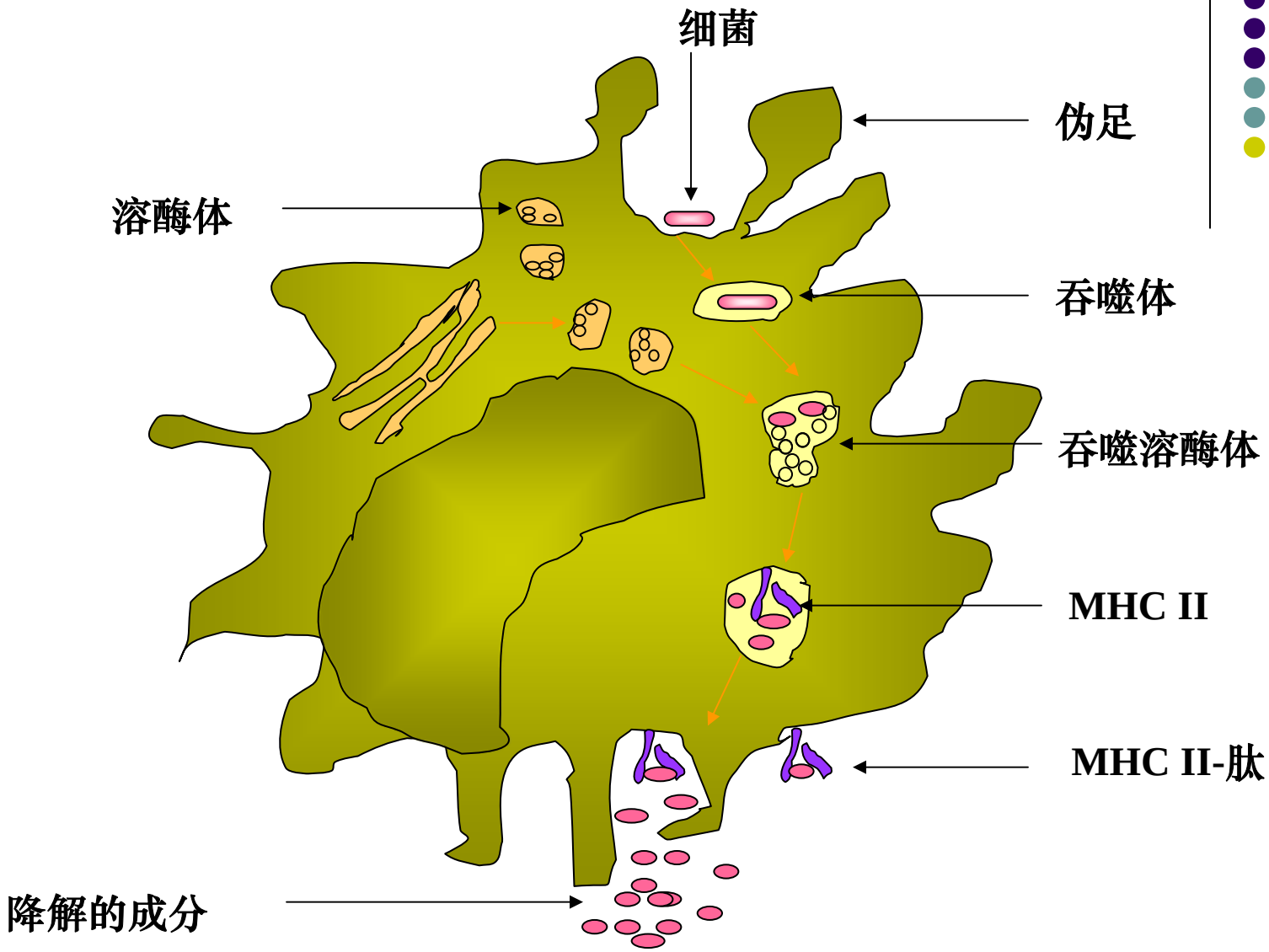


Figure 1 | **Phagocyte interactions in inflammation. a** | Phase I: patrolling non-classical monocytes and resident macrophages are among the first cells to sense a disturbance in tissue homeostasis. They rapidly produce cytokines and chemokines to alert the immune system and to recruit neutrophils. **b** | Phase II: shortly after the alarm has gone off, neutrophils invade the site of injury and release granule contents that promote the extravasation of inflammatory monocytes. **c** | Phase III the life-span of emigrated neutrophils is rather short and is subject to modification by pro- or anti-apoptotic signals, some of which are produced by macrophages. Macrophages and apoptotic neutrophils prevent further infiltration of neutrophils, but signals from apoptotic neutrophils promote continued monocyte influx. **d** | Phase IV: the clearance of apoptotic neutrophils promotes an anti-inflammatory programme in macrophages, which leads, ultimately, to the reconstitution of tissue homeostasis. G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–monocyte colony-stimulating factor; IL, interleukin; PGE_2, prostaglandin E_2; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor.

Phagocyte partnership during the onset and resolution of inflammation
Oliver Soehnlein and Lennart Lindbom
Nat Rev Immunol,
2010 Vol 10 No 6 p427



单核巨噬细胞吞噬杀伤过程示意图

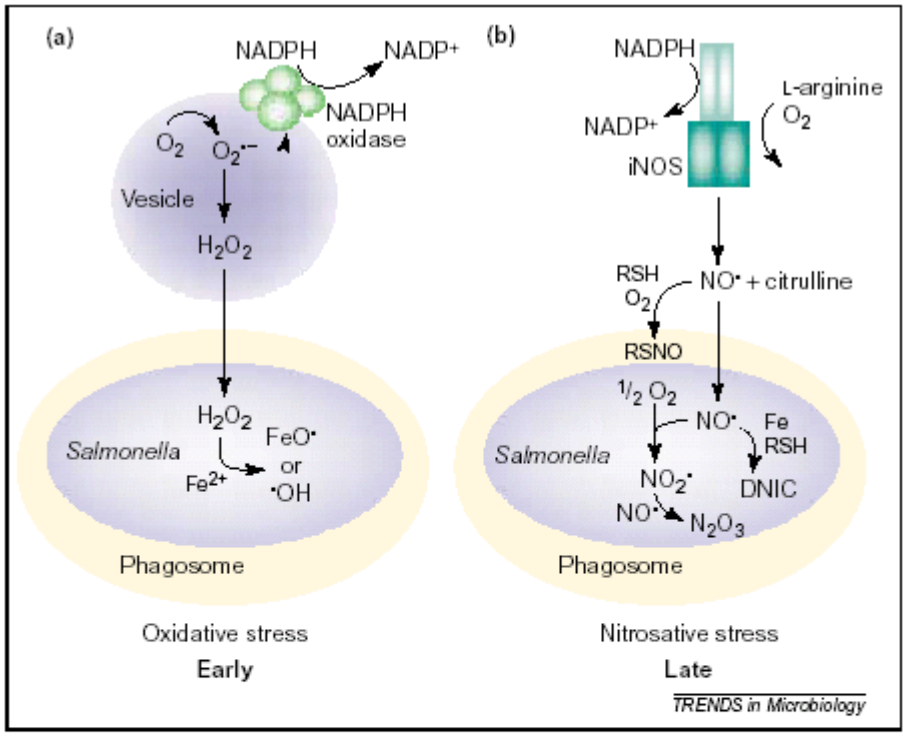


Fig. 3. Model for sequential oxygen-dependent anti-*Salmonella* actions of macrophages. (a) Assembly of gp91 and p22 vesicle-bound subunits with the p47, p67 and Rac1 cytosolic proteins activates the respiratory burst oxidase for the production of superoxide. In the process, molecular oxygen is reduced in the luminal side of the vesicle at the expense of NADPH. The majority of superoxide reaching *Salmonella* is likely to be detoxified by periplasmic copper–zinc superoxide dismutase[26]. Within the vesicle, superoxide is rapidly dismutated to hydrogen peroxide. Hydrogen peroxide-mediated cytotoxicity is largely dependent on the production of ferryl and hydroxyl radicals from the iron-catalyzed Fenton reaction. (b) The short-lived respiratory burst is followed by sustained production of NO by inducible nitric oxide synthase (iNOS), a dimeric hemoprotein that catalyzes the production of NO from L-arginine, oxygen and NADPH. Autooxidation of NO can give rise to the production of the strong oxidant nitrogen dioxide (NO_2) or the potent nitrosating species dinitrogen trioxide (N_2O_3). In the presence of iron and reduced thiols, *S*-nitrosothiols and dinitrosyl-iron complexes can also be formed from NO. NO, dinitrogen trioxide, *S*-nitrosothiols or dinitrosyl-iron complexes might contribute to reversible inhibition of bacterial replication. Abbreviation: DNIC, dinitrosyl iron complexes.

2.Dendritic Cell, DC

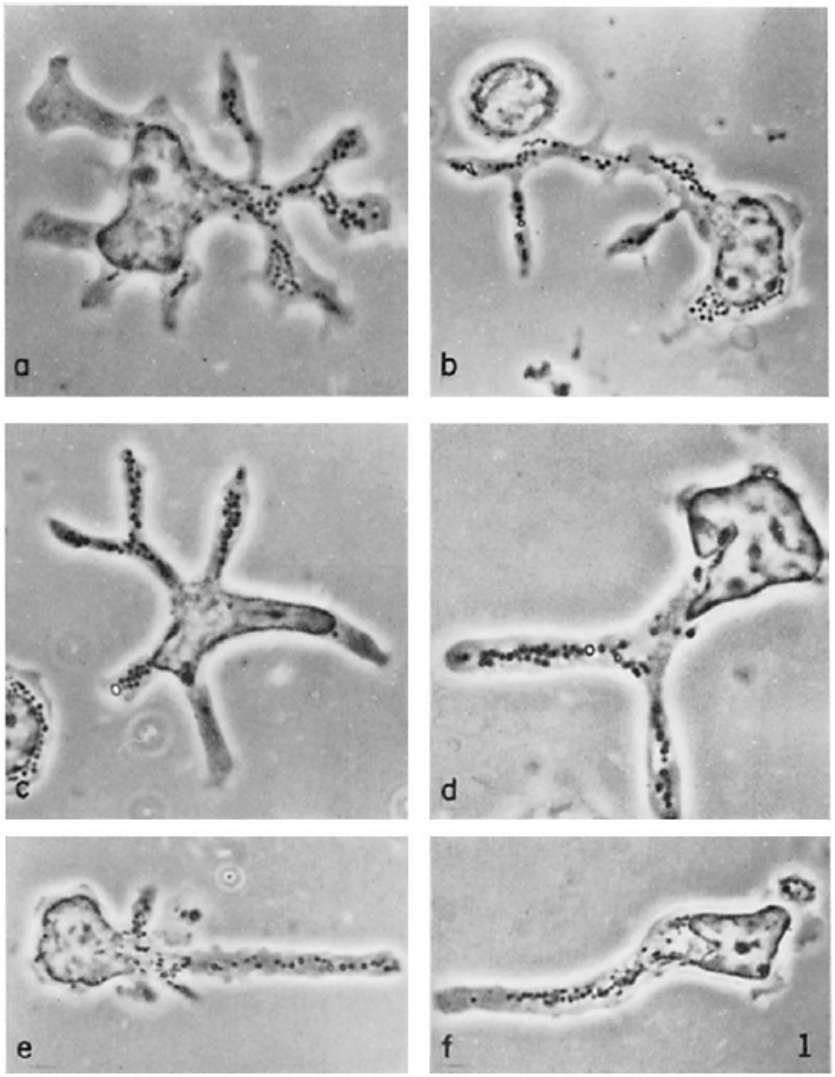
Katsnelson A.
Kicking off adaptive immunity: the discovery of dendritic cells.
JEM,Vol. 203, No. 7, July 10, 2006 1622

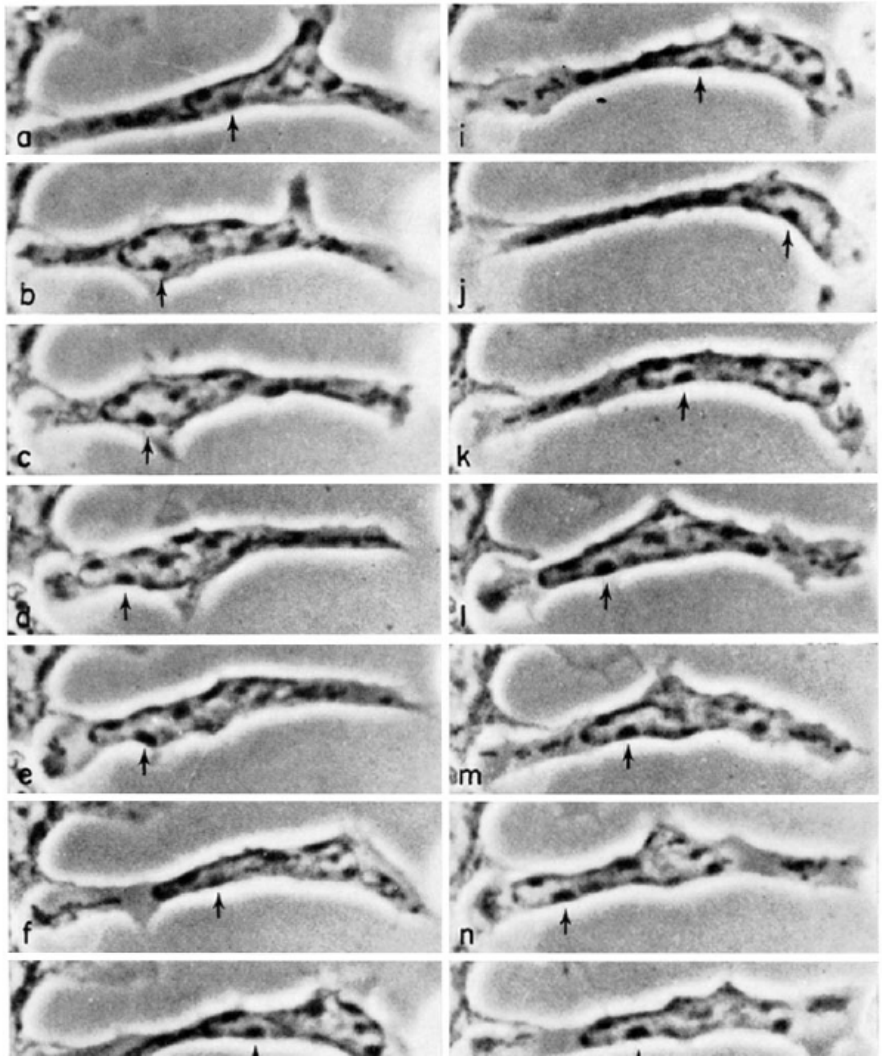
In 1973, Ralph Steinman and Zanvil Cohn discovered an unusual looking population of cells with an unprecedented ability to activate naive T cells. Dubbed “dendritic cells,” these cells are now known as the primary instigators of adaptive immunity.

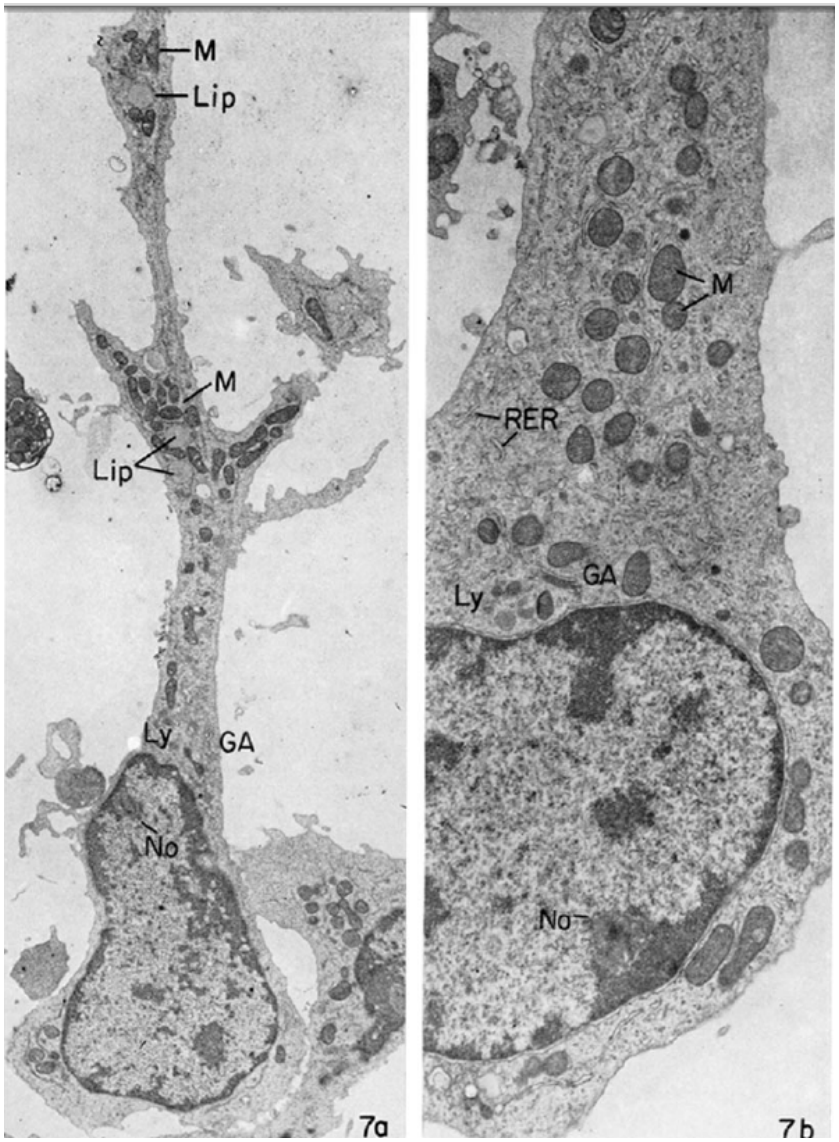
Steinman RM, Cohn ZA.

Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution.

***J Exp Med. 1973 May 1;137(5):1142-62*.**



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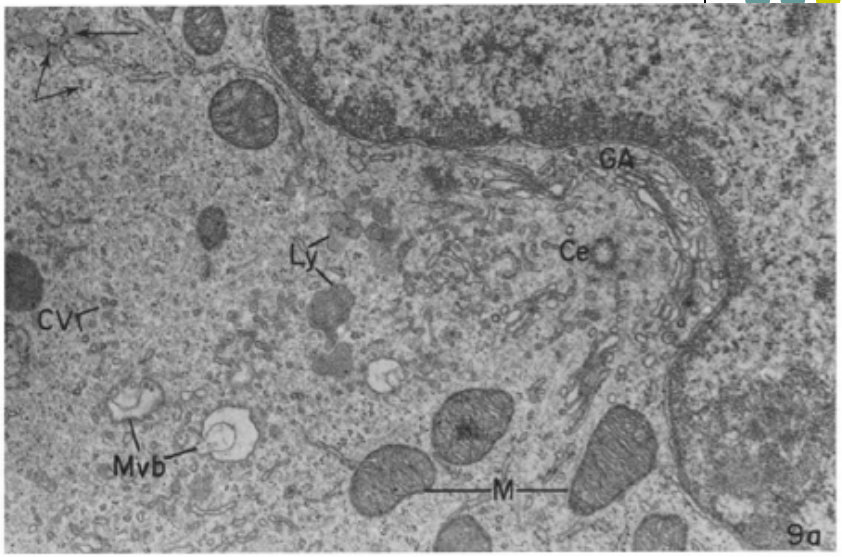
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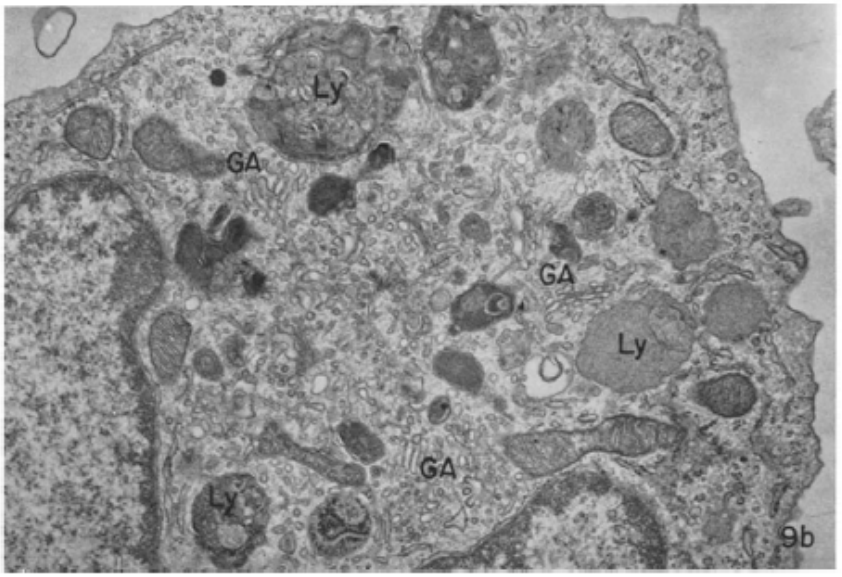
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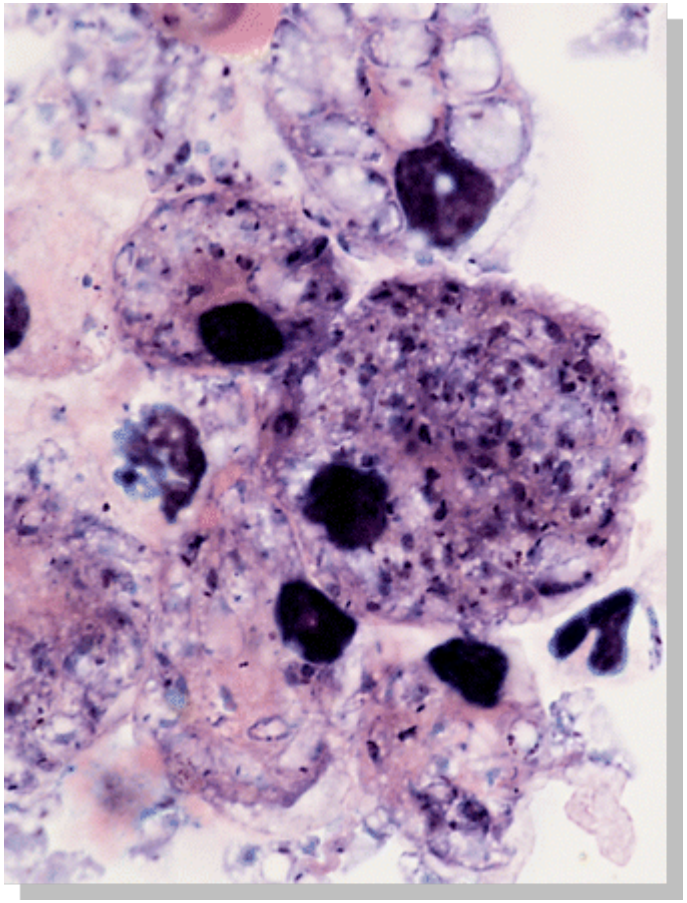
Cover Caption

The Journal of Immunology



Dendritic cells (DC) infected with *Leishmania major* are stained with Giemsa. The dark purple large mass in each DC is the host cell nucleus and smaller dots are the nuclei of intracellular L. major. DM-deficient BALB/c mice are resistant to L. major infections whereas the wild-type mice are susceptible even though the parasite can infect the wild-type and DM−/− DC in a comparable manner.

DM, a nonclassical MHC class II molecule

Kamala, T., and N. Nanda. 2009. Protective response to *Leishmania major* in BALB/c mice requires antigen processing in the absence of DM. *J. Immunol.* 182: 4882–4890.

The glittering prizes

The Nobel Prizes will be announced at the beginning of October. Is there a possibility that **immunology might make the list?**

A prize that assigns credit for recent advances in **innate immunity would be particularly intriguing.**

The two names that now appear on both the Gairdner and Lasker lists are **Ralph Steinman** for the dendritic cell and **Emil Unanue** for antigen processing.

Peter C Doherty. Nature Immunology, 2010;10:875-878

2.Dendritic Cell, DC

2.1 Classification

Follicular Dendritic Cell, FDC

Interdigitating Cell, IDC

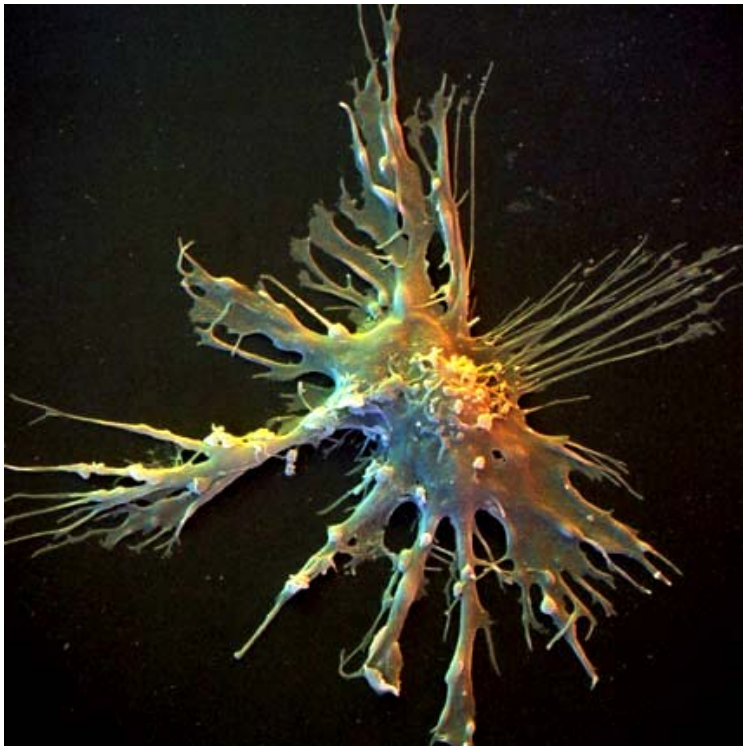
Thymic Dendritic Cell

Langerhans' Cell, LC

Interstitial DC

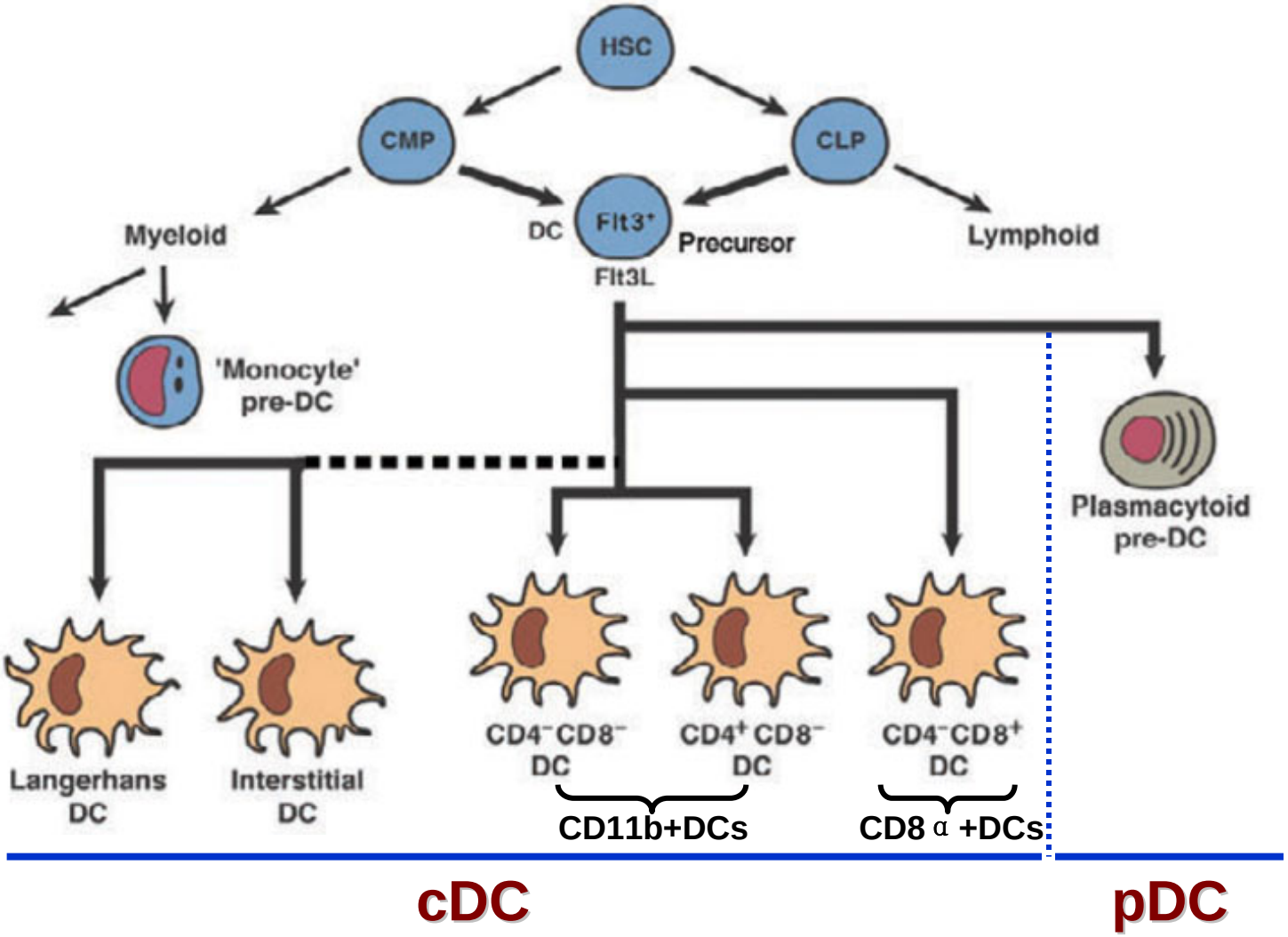
Sentinel Cell

Circulating Dendritic Cell



Nature Immunology **7**, 117 - 120 (2006)
Colonna M, Pulendran B & Iwasaki A. **Dendritic cells at the host-pathogen interface**

Dendritic cells



DC differentiation in the steady state.
The common myeloid precursors (CMP) and common lymphoid precursors (CLP) give rise to all blood and tissue DCs through a Fms-like tyrosine kinase 3–positive (Flt3+) precursor.

Table 1. DC subsets, surface phenotype, and some important properties

DC type	Surface phenotype						Derivation	Distinguishing properties
	CD11c	CD8	CD4	CD205	CD11b	CD45RA		
CD8 DC	+	+	–	+	–	–	Blood	High IL-12 Cross-presentation of cellular antigen Cross-priming Cross-tolerance
CD4 DC	+	–	+	–	+	–	Blood	Most numerous DCs in spleen
$CD4^-CD8^-$ DC	+	–	–	–	+	–	Blood	High IFN-γ
Langerhans' cell	+	–/low	–	Very high	+	–	Skin epithelia	Traffic to lymph node from skin Present contact sensitizing antigens
Dermal/interstitial DC	+	–	–	+	±	–	Tissue	In all tissues Traffic to draining lymph nodes Prime CD4 T-cell immunity to tissue infections
Plasmacytoid DC	Low	±	±	–	–	+	Blood/tissues	High IFN-α, do not look like DCs until stimulated

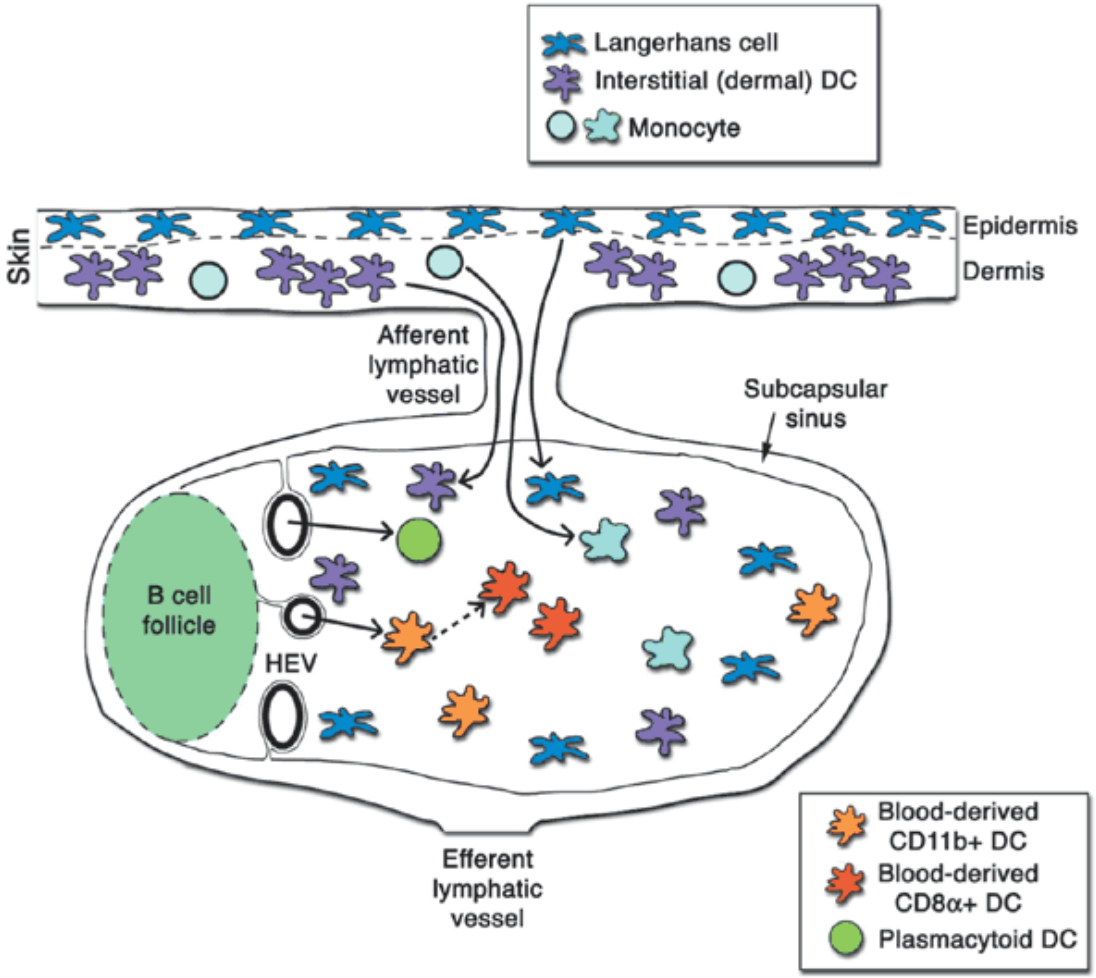
DC, dendritic cell; IFN, interferon; IL-12, interleukin-12.

Nature Reviews Immunology 7, 543-555 (2007);

Table 1 | **Mouse dendritic-cell subsets**

Features	Lymphoid-organ-resident DC subsets			Migratory DC subsets		Monocyte derived
	$CD4^+$ DCs	$CD8^+$ DCs	DN DCs	Interstitial DCs	Langerhans cells	
Location						
Spleen	Yes	Yes	Yes	No	No	Sites of inflammation
Subcutaneous lymph nodes	Yes	Yes	Yes	Yes	Yes	
Visceral lymph nodes	Yes	Yes	Yes	Yes	No	
Thymus	Yes	Yes	Yes	No*	No	
Surface markers						
CD11c	+++	+++	+++	+++	+++	+++
CD4	+	–	–	–	–	–
CD8	–	++	–	–	–/+	–
CD205	–	++	–/+	+	+++	–/+
CD11b	++	–	++	++‡	++	++
Langerin	–	+	–	–	+++	–
CD24	+	++	+	ND	ND	ND
SIRPα	+	–	+	+	+	ND
Functional features in the steady state						
Maturity	Immature	Immature	Immature	Mature	Mature	N/A
Co-stimulatory§	+	+	+	++	++	N/A
Antigen processing and presentation‖	+++	+++	+++	+/–	+/–	N/A
MHC class II	++	++	++	+++	+++	N/A
In vitro *equivalent*						
	Bone-marrow precursors plus FLT3L	Bone-marrow precursors plus FLT3L	Bone-marrow precursors plus FLT3L	Bone-marrow precursors plus GM-CSF, TNF and TGFβ	Bone-marrow precursors plus GM-CSF, TNF and TGFβ	Bone-marrow, spleen or blood precursors plus GM-CSF

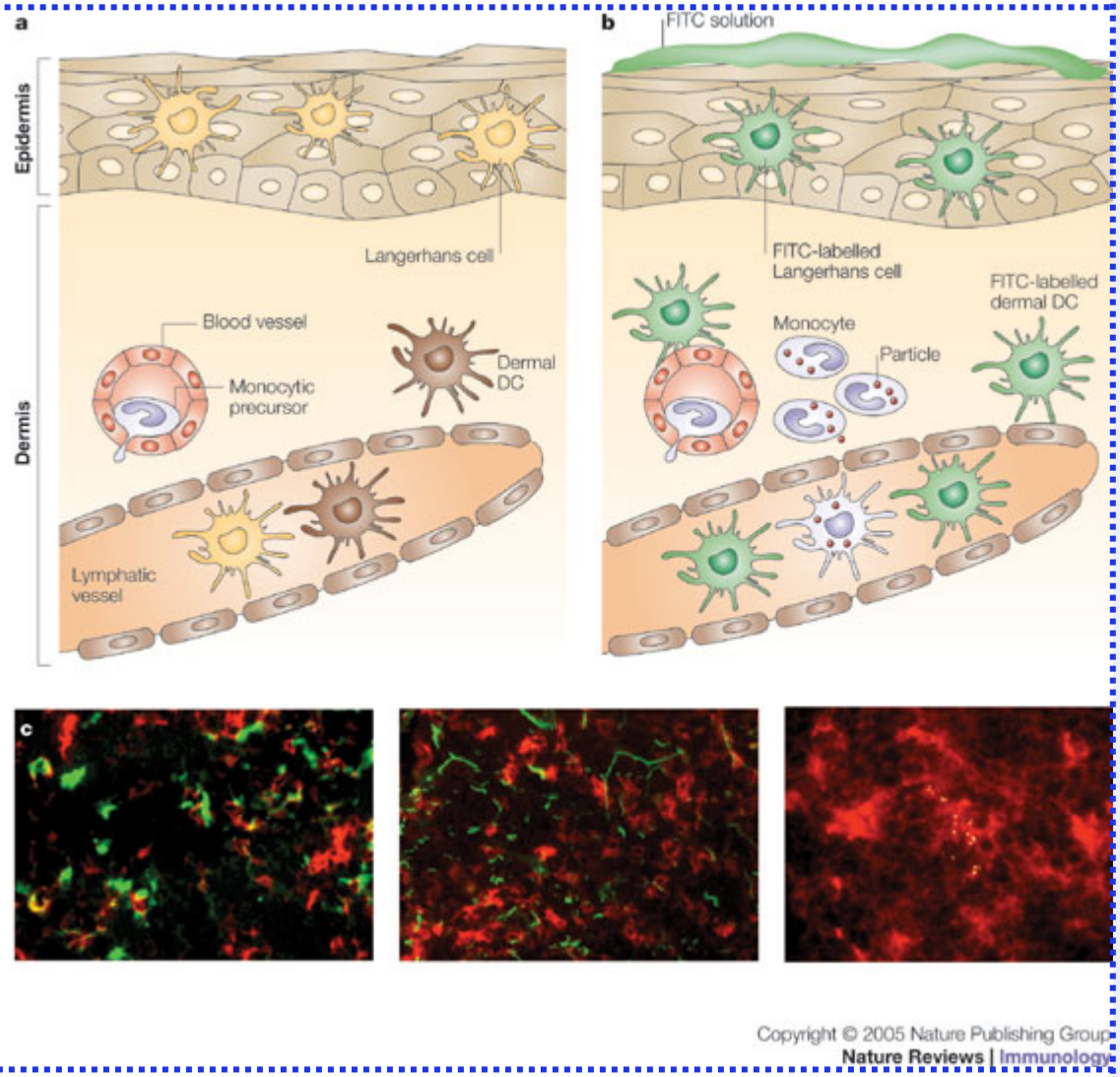
2.2 DC subset distribution and migration



皮肤及血液来源的DC进入淋巴结

Itano AA & Jenkins MK. Antigen presentation to naive CD4 T cells in the lymph node. *Nat Immunol* **4**, 733 (2003)

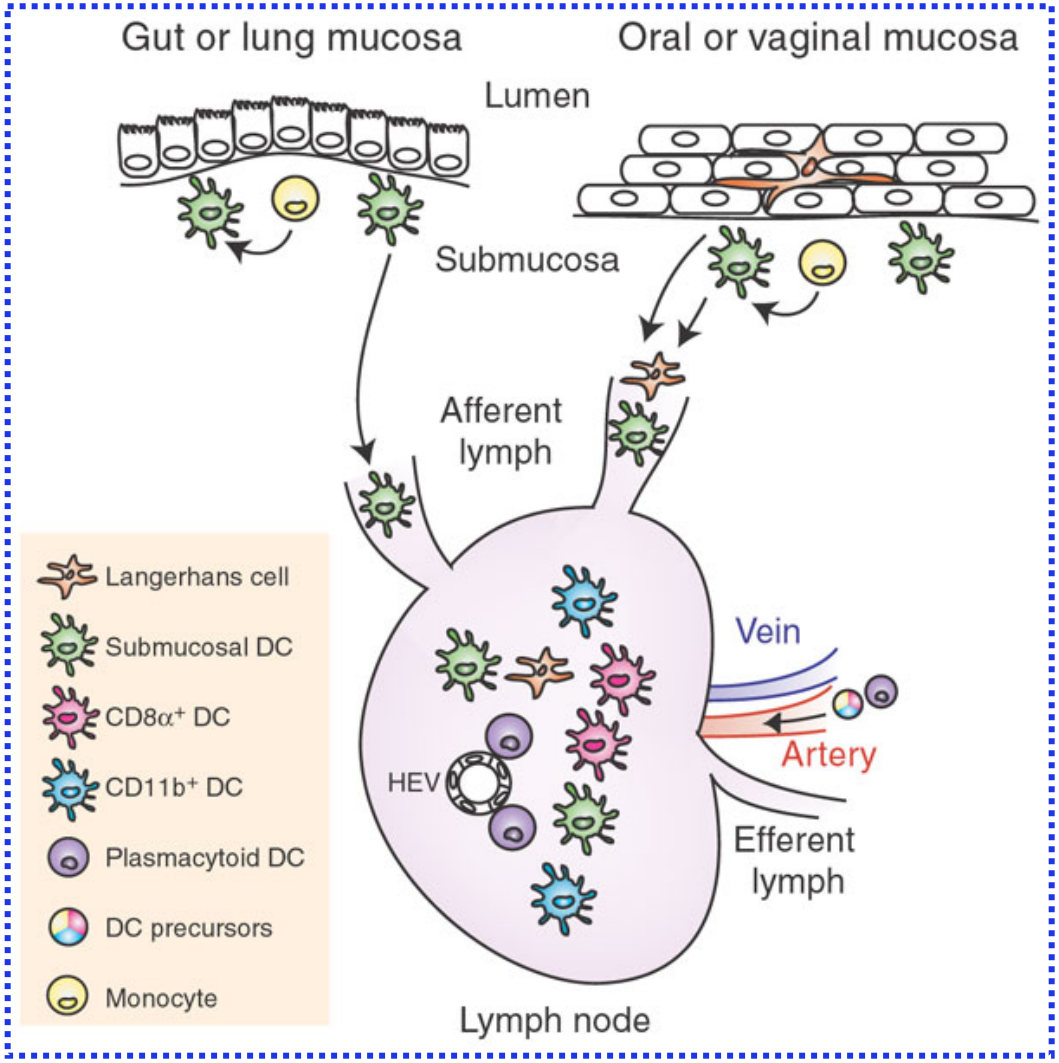
Nature Reviews Immunology **5**, 617-628 (2005);



a | The diversity of dendritic-cell (DC) populations in the skin under homeostatic conditions is shown. Langerhans cells reside in the epidermis, and there is a distinct population of resident dermal DCs. In addition, precursors from the blood, including monocytes, constitutively traffic from the blood to the skin, where some become DCs. Under homeostatic conditions, the origins of the DCs present in lymphatic vessels are not fully defined, but these DCs include a small number of Langerhans cells. **b** | When fluorescein isothiocyanate (FITC) dissolved in a contact-sensitization solution is applied to the skin (known as FITC painting), labelling of Langerhans cells and resident dermal DCs occurs. By contrast, 1 m particles (red) that are injected into the skin are engulfed by newly recruited monocytes. **c** | The left panel shows that, after FITC (green) painting, CD11c+ DCs (red) can be identified in the lymph node within 18 hours. The centre panel shows that, in mice with an impaired capacity for DC migration (a deficiency in multiple-drug-resistance-associated protein 1 (also known as ABCC1)26 in this case), free FITC that drains from the skin through the lymphatic vessels accumulates in lymph-node conduits119, but CD11c+ DCs are rarely heavily labelled, which is consistent with the concept that DCs migrating from the periphery bring in most of the peripheral antigens that are presented in the lymph node120. The right panel shows the accumulation of CD205+ DCs (red) containing microspheres (green) that were engulfed in the skin before transport to the T-cell zone of the draining lymph node.

皮肤及血液来源的DC进入淋巴结

Nature Immunology **5**, 987 - 995 (2004)



粘膜来源的DC进入淋巴结

DC subset distribution and migration *in vivo*.
In the peripheral mucosal tissues, monocytes give rise to interstitial DCs or macrophages that reside within the submucosa. In the stratified squamous epithelial layer of oral and vaginal mucosa and in the skin, Langerhans cells occupy their niche. After being stimulated, tissue DCs migrate to the lymph node to initiate naive lymphocyte activation. Within the lymph nodes, blood-derived DC subsets survey for lymph borne pathogens. The pDCs enter the lymph node via the high endothelial venules (HEVs) and 'survey' for viral pathogens. Although TLR expression of the blood-derived DCs is well characterized (Tables 1 and 2), TLR expression by tissue DCs is unknown. Figure 1 shows TLR expression by the corresponding color-coordinated DC subsets.

Nature Reviews Immunology 7, 543-555 (2007);

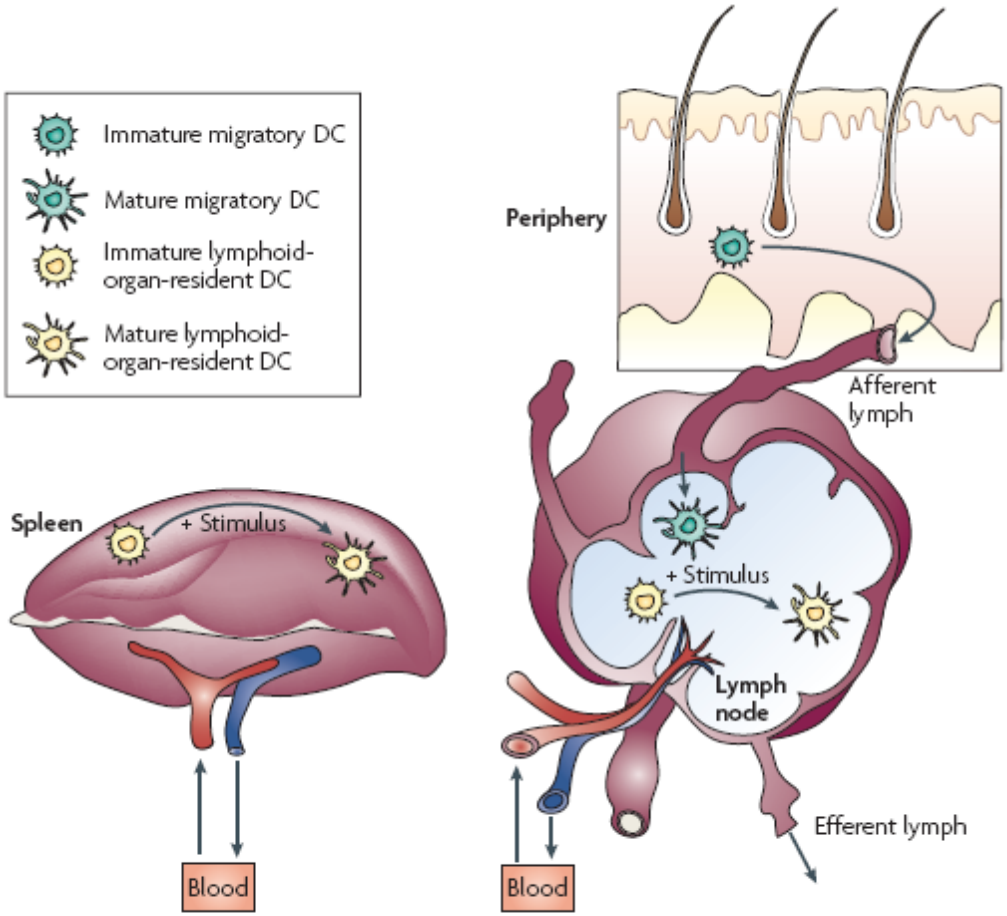
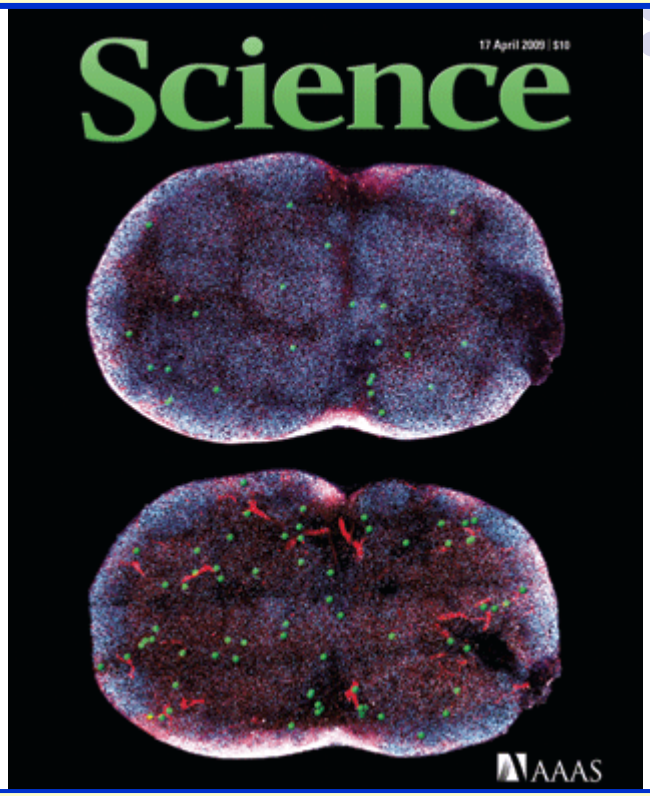


Figure 1 | **The developmental pathway of migratory and lymphoid-organ-resident DCs.** Migratory dendritic cells (DCs) have an immature phenotype in peripheral tissues,

Liu K,…, and Nussenzweig M.
In Vivo Analysis of Dendritic Cell Development and Homeostasis.
Science 17 April 2009: 392-397



COVER Multiphoton laser scanning images showing cortical (top) and medullary (bottom) portions of a mouse inguinal lymph node. Green spheres represent dendritic cell precursors 5 hours after transfer from bone marrow; B cell follicles are shown in blue; blood vessels and T cells are in red. During development, these precursors migrate through the blood to lymphoid tissues where they divide and disperse into the dendritic cell network.

Nature Immunology **5**, 1219 - 1226 (2004)

Plasmacytoid dendritic cells in immunity

Marco Colonna, Giorgio Trinchieri & Yong-Jun Liu

Plasmacytoid dendritic cells

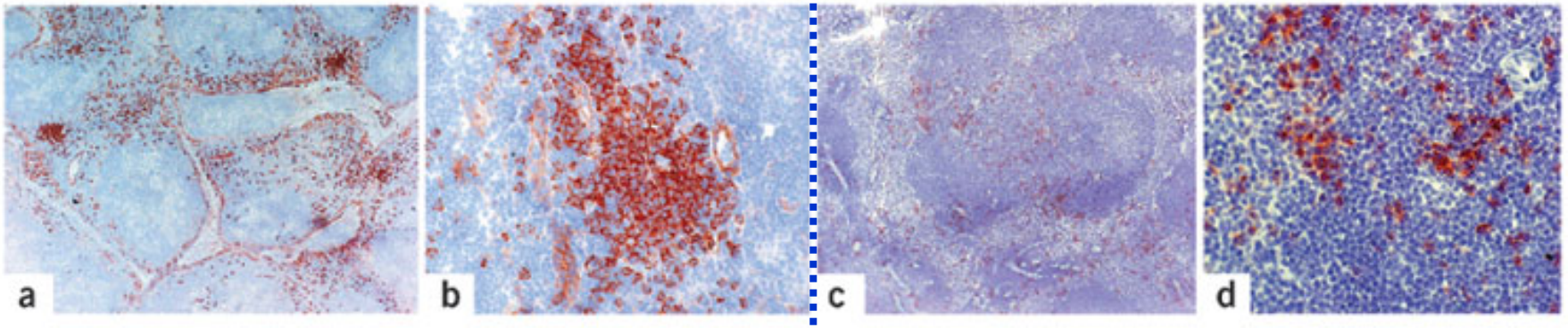


Figure 1. Localization of pDCs.

The pDCs are present mostly in clusters in the T cell–rich area of secondary lymphoid organs. (**a**,**b**) In human lymph nodes, they are closely associated with high endothelial venules. (**c**,**d**) In mouse spleens, pDCs are found mostly in the periarteriolar lymphoid sheaths, but scattered pDC are present in the marginal zone and red pulp, with a distribution distinct from that of DCs. Inflammatory conditions induce the clustering of pDCs either in the marginal zone or in the T cell area of the spleen (C. Asselin-Paturel, unpublished data) and their recruitment to the sentinel lymph nodes. Images show pDCs in human lymph nodes (**a**,**b**) and mouse spleens (**c**,**d**) at various magnifications after staining with antibodies CD123 (**a**,**b**) and 440c (**c**,**d**). Courtesy of F. Facchetti (Department of Pathology, University of Brescia, Brescia, Italy). Original magnifications, 50 (**a**,**c**), 400 (**b**) and 200 (**d**).

Table 4 | **Human dendritic cell (DC) precursors**

	pDC1 (monocytes)	pDC2 (plasmacytoid interferon producers)
Markers		
CD11c	+	−
CD11b	+	−
CD14	+	−
pTα	−	+
CD4	+	+++
CD45RA	−	++
CD45RO	+	−
IL-3 receptor	+	+++
GM-CSF receptor	++	+
Pattern-recognition receptors		
BDCA2	−	+
TLR1	++	+
TLR2	++	−
TLR3	−	−
TLR4	++	−
TLR5	++	−
TLR6	+	+
TLR7	−	++
TLR8	++	−
TLR9	−	++
TLR10	−	+/−
Function		
IFN-α/β production	+	+++
Phagocytosis	++	−

BDCA2, a C-type lectin; IFN, interferon; pTα, pre-T-cell receptor-α; TLR, Toll-like receptor.

2.3 Function

Immunoregulation

Antigen presentation

Immunoregulation

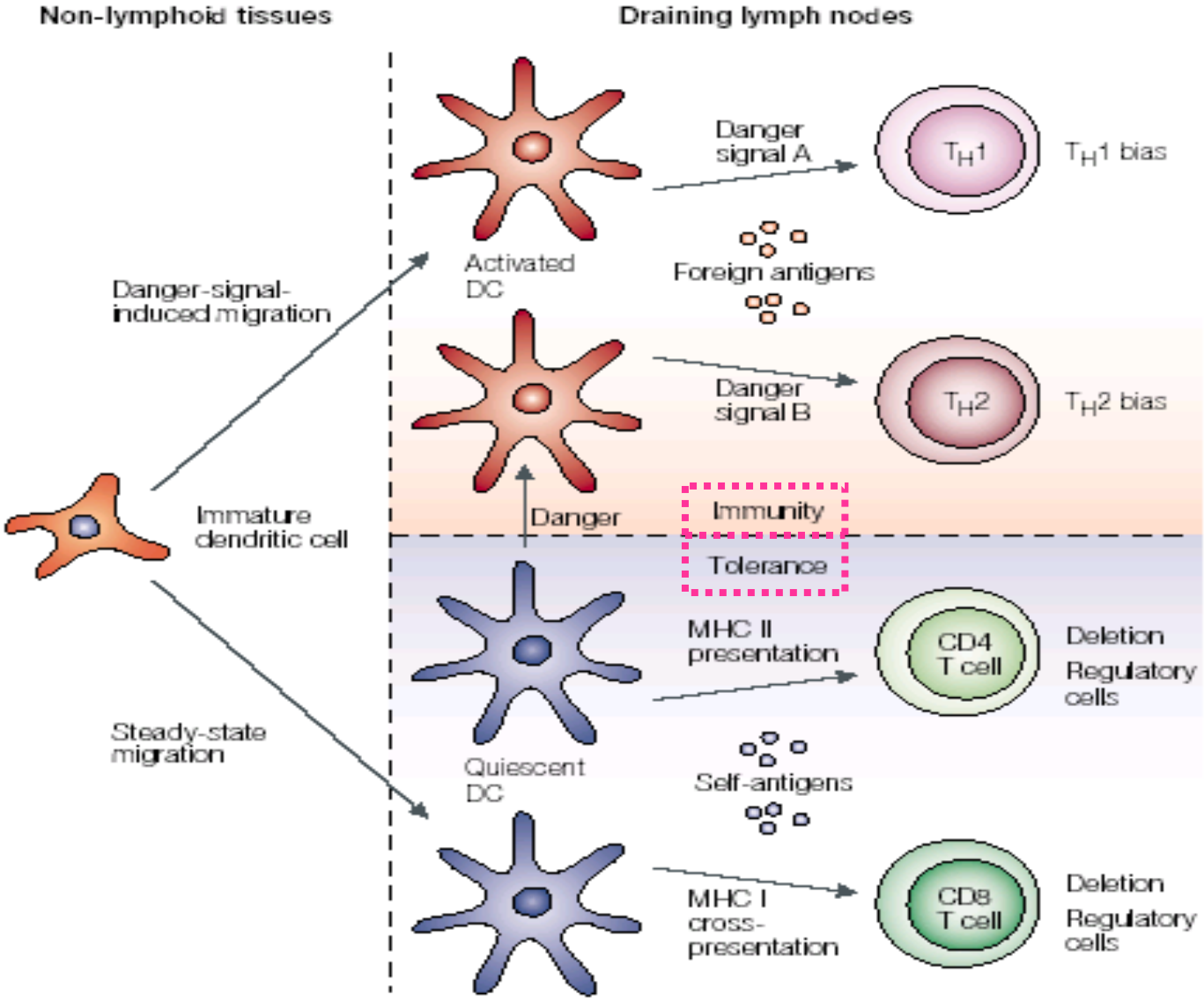
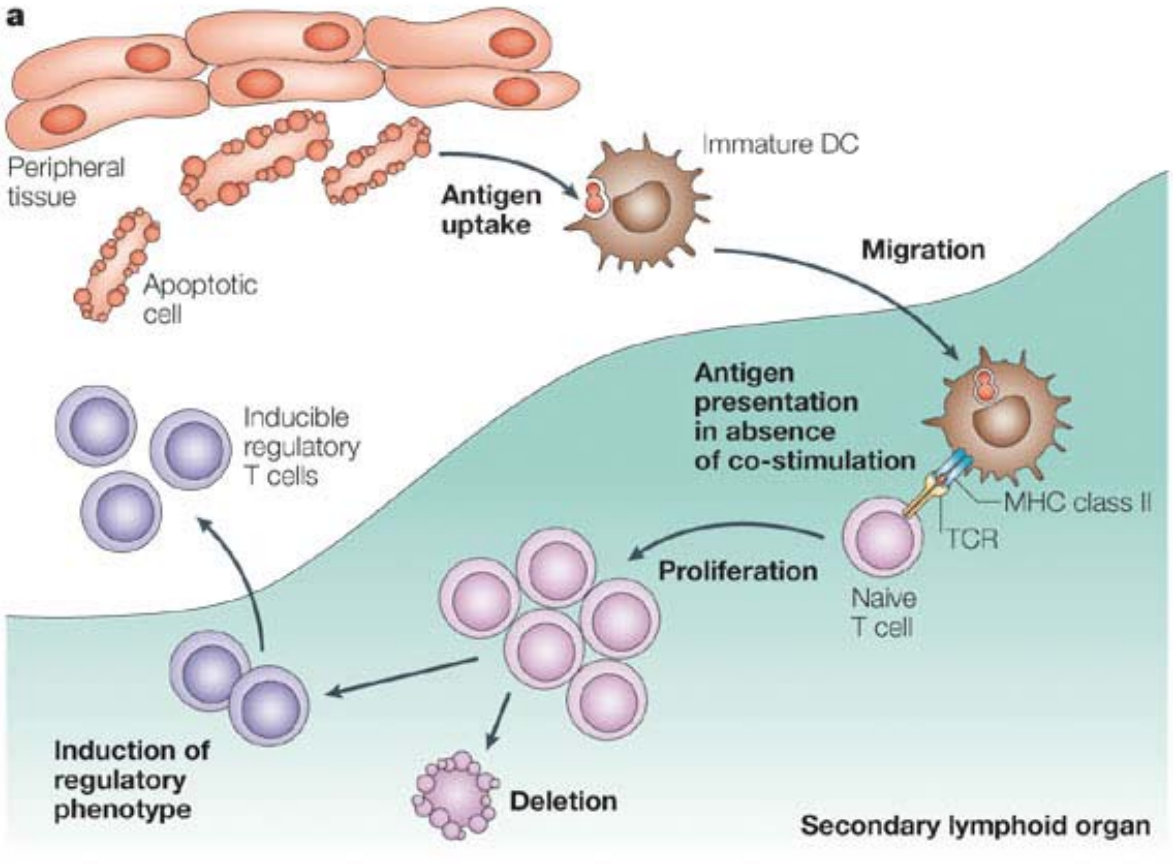


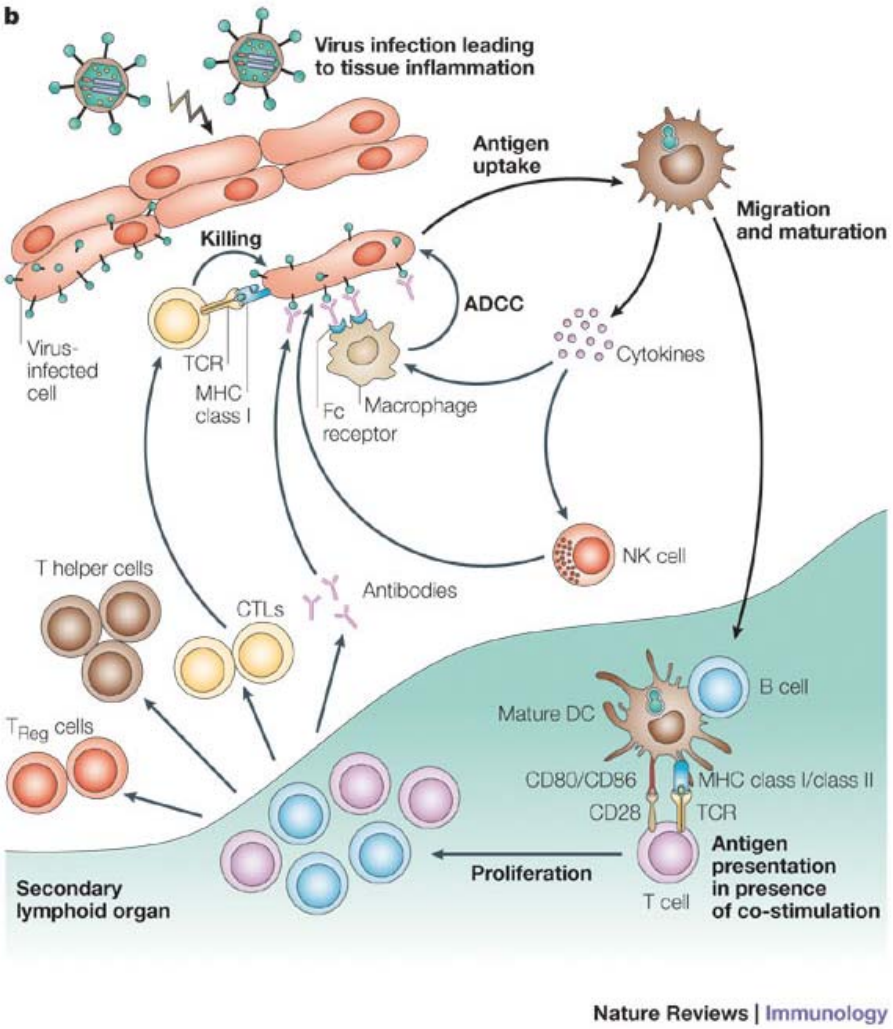
Figure 1 | **Dendritic cells and immunoregulation.** The current view of the ways in which the

Immature dendritic cells (DCs) induce tolerance



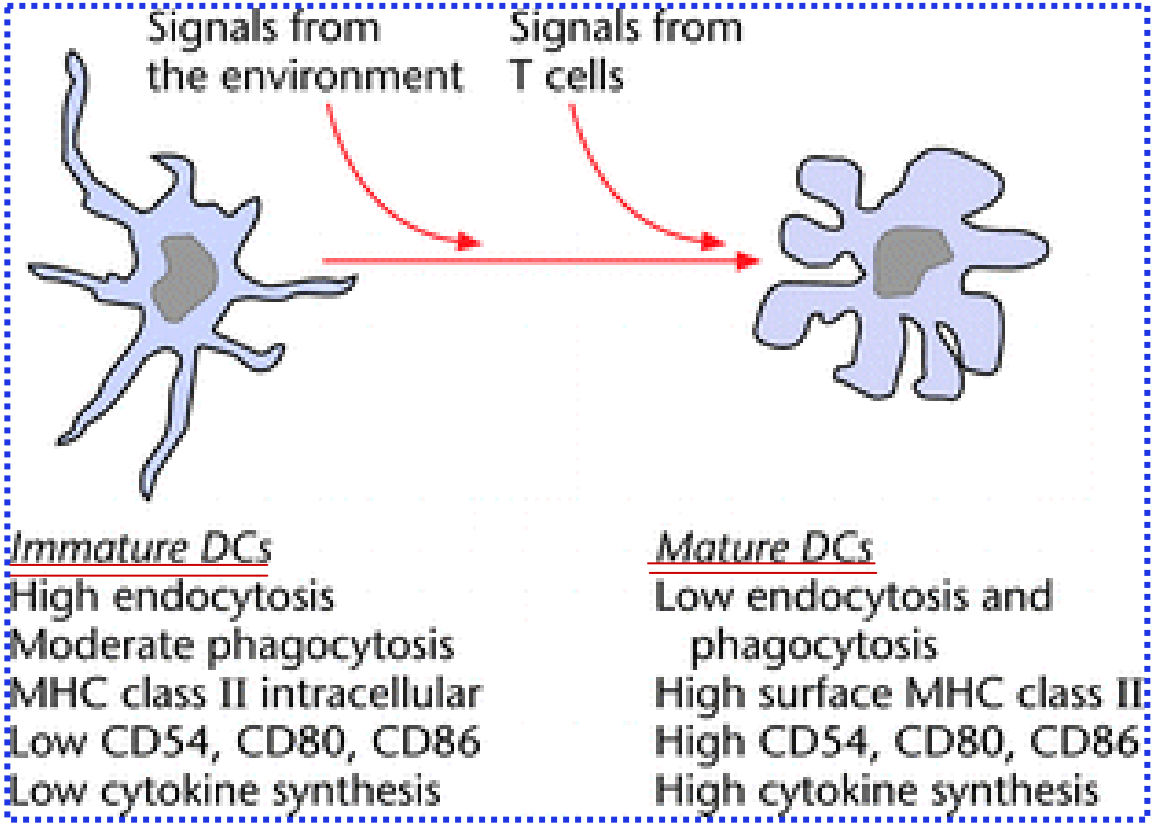
Nature Reviews Immunology **5**, 296-306 (2005); doi:10.1038/nri1592
DENDRITIC CELLS AS THERAPEUTIC VACCINES AGAINST CANCER

Mature DCs induce immunity



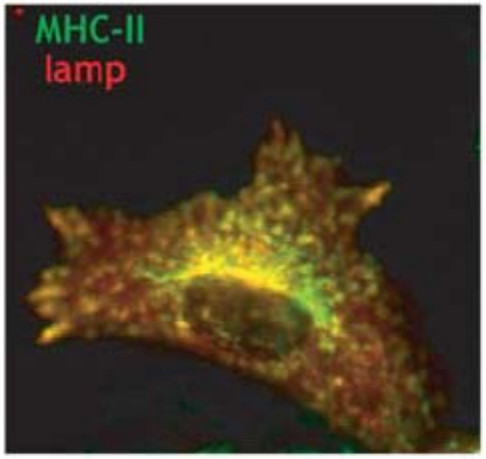
Nature Reviews Immunology **5**, 296-306 (2005); doi:10.1038/nri1592
DENDRITIC CELLS AS THERAPEUTIC VACCINES AGAINST CANCER

Antigen presentation



Antigen presentation

Immature DC



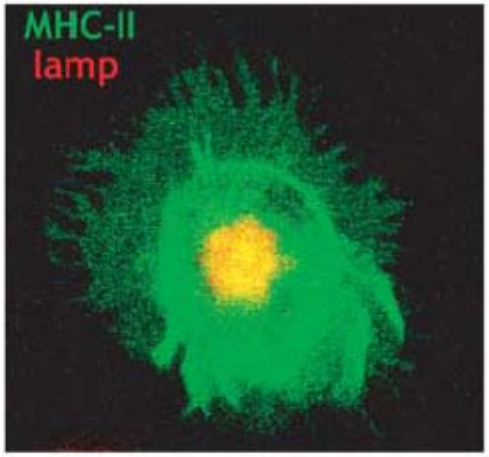
Peripheral and lymphoid tissues

Highly endocytic

Low surface MHC-II and costimulators

Antigen accumulation

Mature DC



Lymphoid tissues

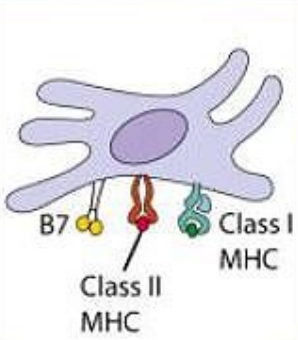
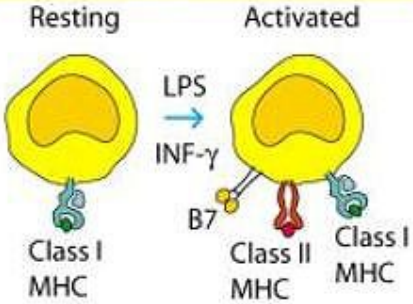
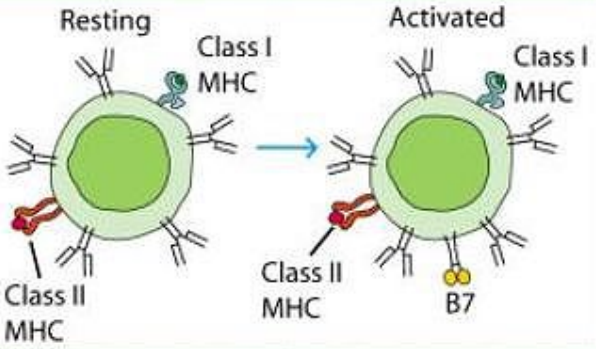
Endocytosis reduced

High surface MHC-II and costimulators

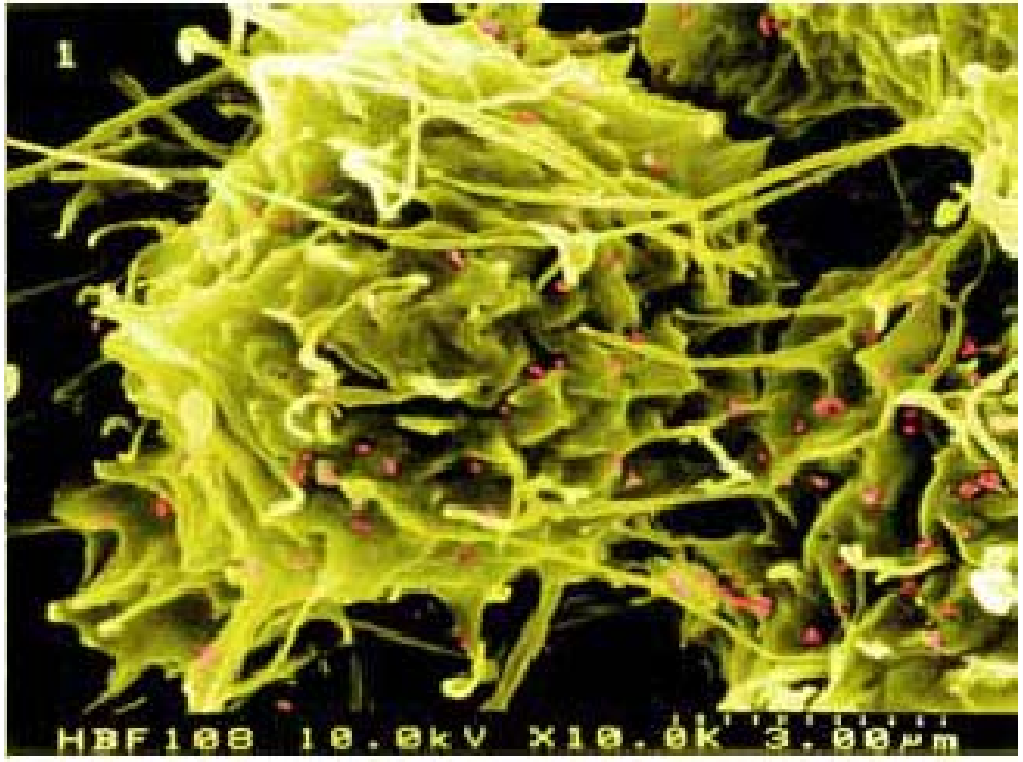
T cell stimulation

TABLE 8-1 Antigen-presenting cells

Professional antigen-presenting cells	Nonprofessional antigen-presenting cells	
Dendritic cells (several types)	Fibroblasts (skin)	Thymic epithelial cells
Macrophages	Glial cells (brain)	Thyroid epithelial cells
B cells	Pancreatic beta cells	Vascular endothelial cells

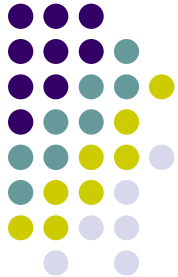
	Dendritic cell	Macrophage		B Lymphocyte	
					
Antigen uptake	Endocytosis phagocytosis (by Langerhans cells)	Phagocytosis	Phagocytosis	Receptor-mediated endocytosis	Receptor-mediated endocytosis
Class II MHC expression	Constitutive (+++)	Inducible (–)	Inducible (++)	Constitutive (++)	Constitutive (+++)
Co-stimulatory activity	Constitutive B7 (+++)	Inducible B7 (–)	Inducible B7 (++)	Inducible B7 (–)	Inducible B7 (++)
T-cell activation	Naive T cells Effector T cells Memory T cells	(–)	Effector T cells Memory T cells	Effector T cells Memory T cells	~~Naive T cells~~ Effector T cells Memory T cells

3 Recognition of APC



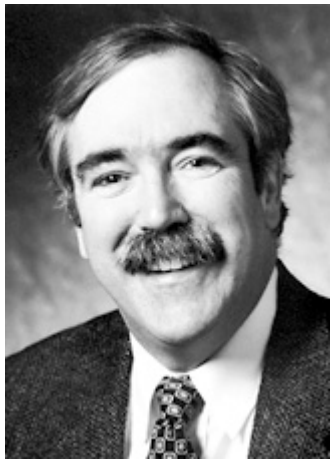
Mouse macrophage

The Nobel Prize in Physiology or Medicine 1995
"for their discoveries concerning
the genetic control of early embryonic development"



Edward B. Lewis
California Institute of Technology (Caltech)
Pasadena, CA, USA
b. 1918
d. 2004

Christiane Nüsslein-Volhard
Max-Planck-Institut für Entwicklungsbiologie
Tübingen, Federal Republic of Germany
b. 1942



Eric F. Wieschaus
Princeton University
Princeton, NJ, USA
b. 1947

Kathryn V. Anderson

Anderson, K.V., Jürgens, G. and Nüsslein-Volhard, C. (1985) Establishment of dorsal-ventral polarity in the Drosophila embryo: genetic studies on the role of the *Toll* gene product. *Cell* 42: 779-789.

Hashimoto, C., Hudson, K.L. and Anderson, K.V. (1988) The *Toll* gene of Drosophila, required for dorsalventral embryonic polarity, appears to encode a transmembrane protein. *Cell* 52: 269-279.

Chromosomal Localization of *TIL*, a Gene Encoding a Protein Related to the *Drosophila* Transmembrane Receptor Toll, to Human Chromosome 4p14

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Received September 25, 1995; accepted December 18, 1995

The *Drosophila* transmembrane receptor Toll and the mammalian interleukin-1 (IL-1) receptor are known to share

[1] To whom correspondence should be addressed at Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111. Telephone: (215) 728-2610. Fax: (215) 728-2741.

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0888-7543/96 $18.00

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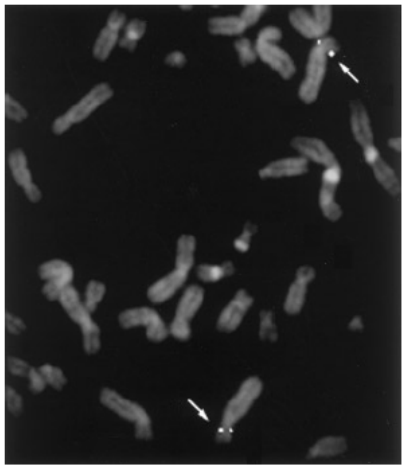

FIG. 1. Chromosomal localization of the *TIL* gene by FISH to chromosome band 4p14. Image represents computer-enhanced, merged images of fluorescein isothiocyanate signals (arrows) and diamidino-2-phenylindole-stained chromosomes.

similarities in both amino acid sequence and function (5, 13). Toll is involved in establishing the dorsal/ventral axis in the developing *Drosophila* embryo (6). In response to its ligand, spatzle, Toll causes activation of DNA binding by the dorsal gene product, a homolog of NFκB. IL-1 is a prime mediator of inflammatory responses (2). One of the consequences of IL-1 stimulation of cells is activation of DNA binding by the transcription factor NFκB. This functional similarity reflects high sequence conservation of the cy domains the 1 rec or an sequenc ation d s not th ligand-b port as t molecul The l omain Targ art serie cine h re is whereas that of the IL-1 recep shr globulin-like domains (14). Not surprisingly, the ligands for these receptors, spatzle (10) and IL-1, show no sequence similarity.

Recently, it has become apparent that there are a number of other genes that share homology with the cytoplasmic domains of the genes encoding the Toll and IL-1 receptors (3, 7, 9, 16, 17; J. L. Mitcham, S. K. Dower, and J. E. Sims, unpublished data). Among these is a human cDNA clone called rsc786 (11), which encodes a protein that we refer to as TIL (Toll/interleukin-1 receptor-like). The *TIL* gene is very similar to two *Drosophila* genes, *Toll* and *18-wheeler*, in that it encodes a protein whose predicted extracellular portion is composed primarily of leucine-rich repeats and a cytoplasmic domain homologous to that of the type I IL-1 receptor. Unlike the IL-1 receptor, whose extracellular portion is composed of immunoglobulin domains, both of these *Drosophila* genes code for proteins that play important roles in early development. It is possible that *TIL* fulfills a similar function in humans. Because of the inherent interest in this gene by virtue of its homologies, we mapped its human chromosomal location by fluorescence *in situ* hybridization (FISH).

Metaphase spreads from phytohemagglutinin-stimulated lymphocytes of a healthy donor were prepared according to the method of Fan *et al.* (4). FISH and detection of immunofluorescence were performed according to the technique of Pinkel *et al.* (12), with minor modifications (15).

Hybridization of a 2.4-kb *TIL* cDNA probe (rsc786) to metaphase chromosomes showed specific labeling on chromosome 4 (23 of 26 metaphase spreads). Altogether, 54 of 69 signals (78%) were located specifically on chromosome 4p, with most residing at band 4p14 (Fig. 1). This is in contrast to the location of the genes encoding the type I and type II IL-1 receptors, which are genetically linked and map to 2q12–q13 in humans and the centromere-proximal region of chromosome 1 in mice (1). Because of its homology to *Drosophila* genes encoding proteins important in embryonic development, *TIL* should be considered a candidate locus for any human developmental defect that may be linked to human chromosome 4p14.

ACKNOWLEDGMENTS

This study was supported in part by National Institutes of Health Grants CA-45745 and CA-06927 and by an appropriation from the Commonwealth of Pennsylvania.

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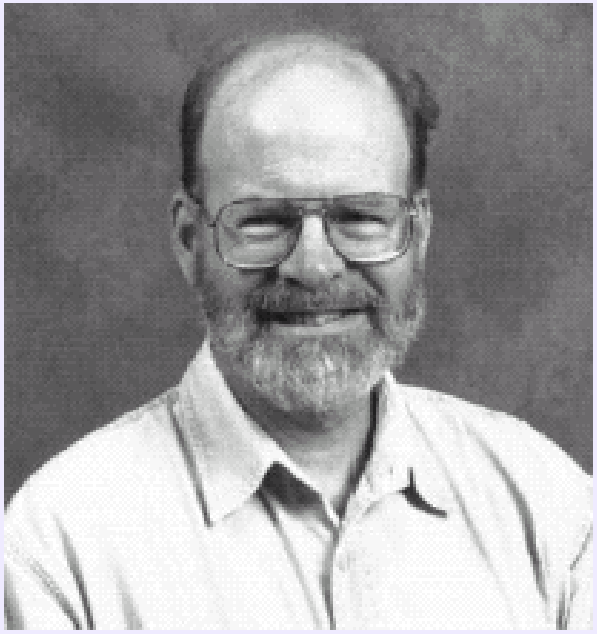
TLR1的发现

Taguchi T,et al. **Chromosomal Localization of *TIL*, a Gene Encoding a Protein Related to the *Drosophila* Transmembrane Receptor Toll, to Human Chromosome 4p14.** ***Genomics*****,** Volume 32, Issue 3, 15 March 1996, Pages 486-488



Immunologist who postulated a second law of immunology

Charles A. Janeway Jr, professor of immunobiology at Yale University School of Medicine in New Haven and one of the pre-eminent modern immunologists, died on 12 April 2003 of lymphoma.

second law of immunology
'pattern-recognition receptors'
Toll-like receptors
'pathogen-associated molecular patterns'
T inflammatory and T helper cells
— Th1 and Th2 cells
Immunobiology
president of the American Association of Immunologists

Charles A. Janeway Jr (1943–2003)

Pattern recognition receptor

CD206:Mannose receptor,MR

CD14:LPS receptor

IL-1R/TLR: TLR families, IL-1R families,

MyD88 (myeloid differentiation factor 88)

Scavenger receptor, SR

Pathogen associated molecular pattern, PAMP: LPS,LTA

Apoptotic cell associated molecular pattern, ACAMP: PS, mannose

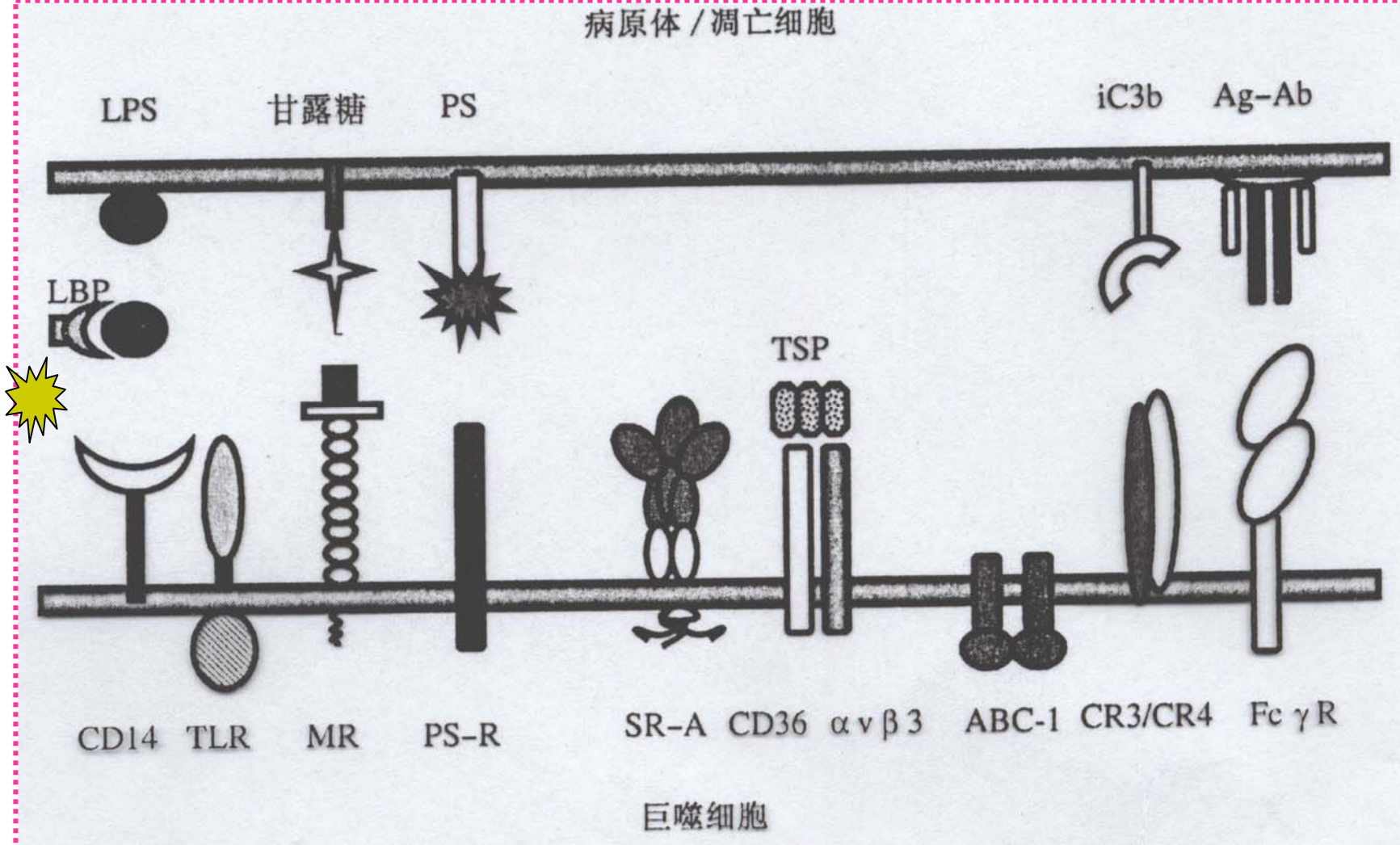
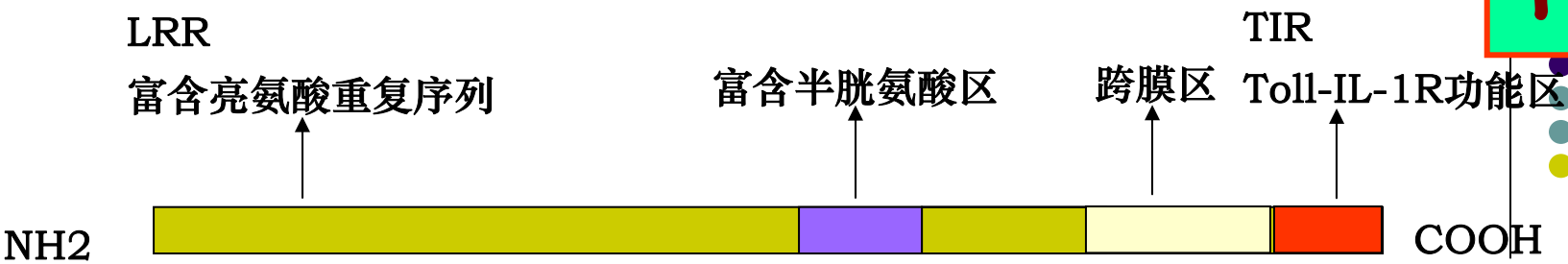


图 11-7　巨噬细胞 PRR 与 PAMP 或 ACAMP 的相互作用

TLRs



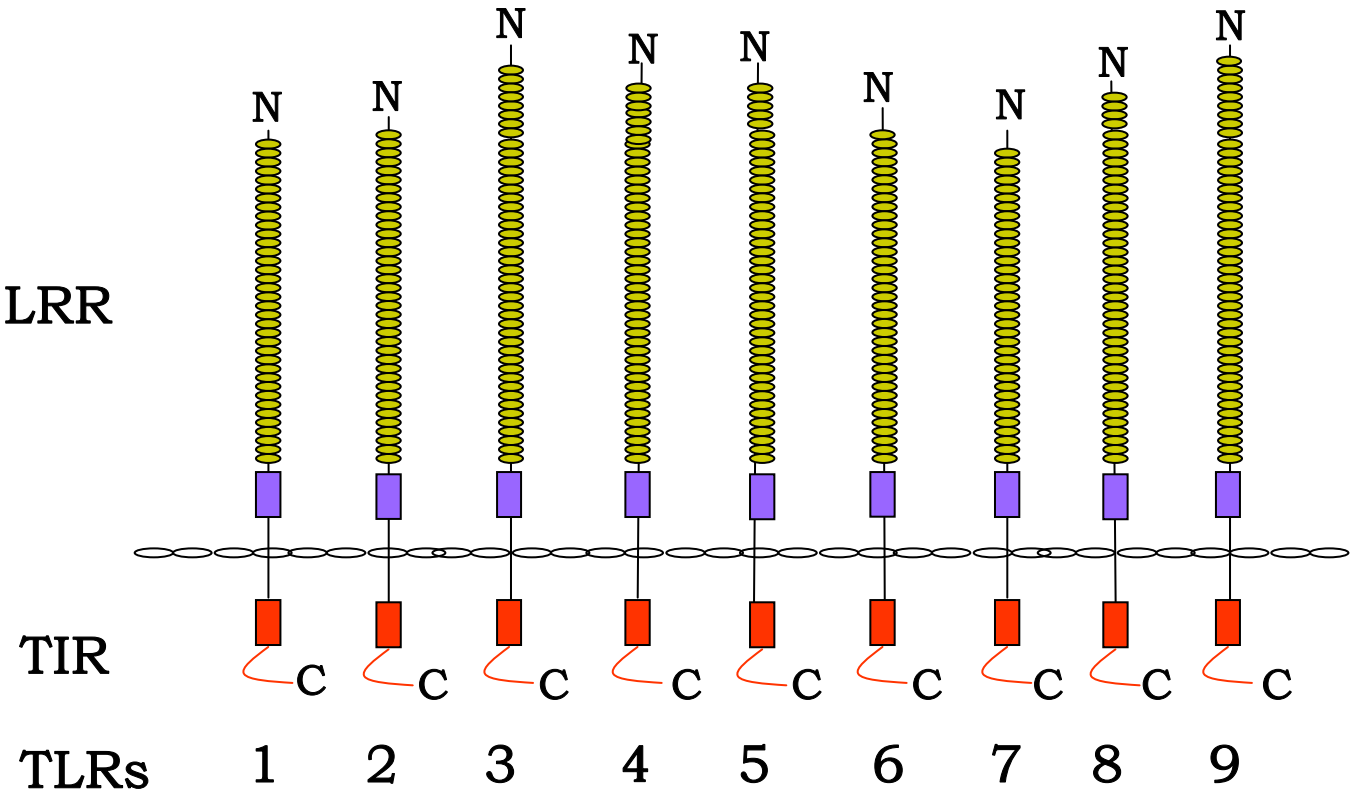


图1 人TLR家族成员的蛋白质结构示意图

TLRs

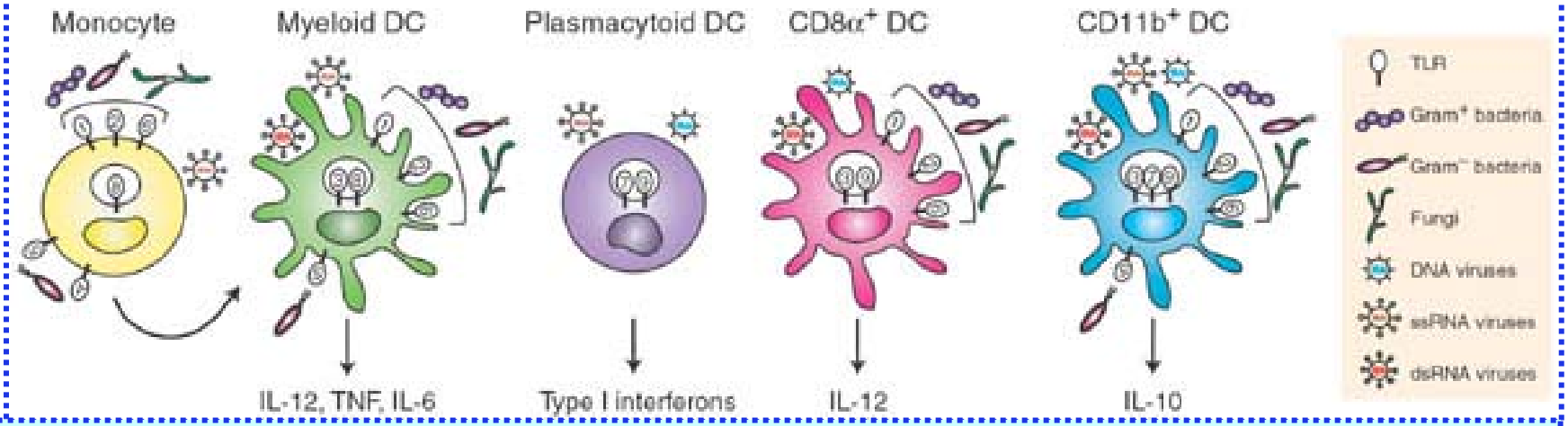
Table 1 | **Toll-like receptors and their ligands**

Receptor	Ligand	Origin of ligand	References
TLR1	Triacyl lipopeptides	Bacteria and mycobacteria	112
	Soluble factors	*Neisseria meningitidis*	113
TLR2	Lipoprotein/lipopeptides	Various pathogens	114
	Peptidoglycan	Gram-positive bacteria	115,116
	Lipoteichoic acid	Gram-positive bacteria	116
	Lipoarabinomannan	Mycobacteria	117
	Phenol-soluble modulin	*Staphylococcus epidermidis*	118
	Glycoinositolphospholipids	*Trypanosoma cruzi*	119
	Glycolipids	*Treponema maltophilum*	120
	Porins	*Neisseria*	121
	Atypical lipopolysaccharide	*Leptospira interrogans*	122
	Atypical lipopolysaccharide	*Porphyromonas gingivalis*	123
	Zymosan	Fungi	124
	Heat-shock protein 70*	Host	125
TLR3	Double-stranded RNA	Viruses	52
TLR4	Lipopolysaccharide	Gram-negative bacteria	9
	Taxol	Plants	126
	Fusion protein	Respiratory syncytial virus	127
	Envelope protein	Mouse mammary-tumour virus	128
	Heat-shock protein 60*	*Chlamydia pneumoniae*	129,130
	Heat-shock protein 70*	Host	131
	Type III repeat extra domain A of fibronectin*	Host	132
	Oligosaccharides of hyaluronic acid*	Host	133
	Polysaccharide fragments of heparan sulphate*	Host	134
	Fibrinogen*	Host	135
TLR5	Flagellin	Bacteria	136
TLR6	Diacyl lipopeptides	*Mycoplasma*	137
	Lipoteichoic acid	Gram-positive bacteria	116
	Zymosan	Fungi	138
TLR7	Imidazoquinoline	Synthetic compounds	139
	Loxoribine	Synthetic compounds	12
	Bropirimine	Synthetic compounds	12
	Single-stranded RNA	Viruses	140,141
TLR8	Imidazoquinoline	Synthetic compounds	142
	Single-stranded RNA	Viruses	140
TLR9	CpG-containing DNA	Bacteria and viruses	143
TLR10	N.D.	N.D.	–
TLR11	N.D.	Uropathogenic bacteria	144

*It is possible that these ligand preparations, particularly those of endogenous origin, were contaminated with lipopolysaccharide and/or other potent microbial components, so more-precise analysis is required to conclude that TLRs recognize these endogenous ligands. N.D., not determined; TLR, Toll-like receptor.

TLRs

Nature Immunology **5**, 987 - 995 (2004)



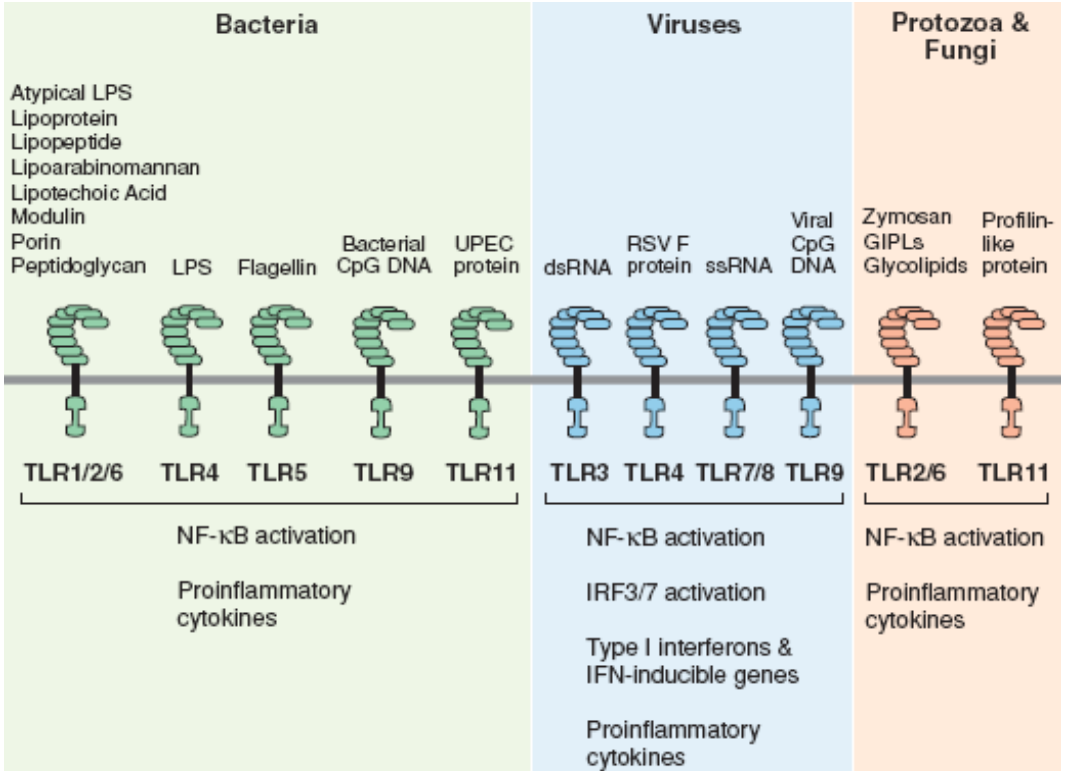
表面:TLR1,2,4,5,6	TLR1,2,5,6		TLR1,2,6	TLR1,2,5,6
胞内:TLR8	TLR3,8	TLR7,9	TLR3,9	TLR3,7,9

DC populations express nonoverlapping sets of TLRs.

Human peripheral blood **myeloid DCs and monocytes express distinct sets of TLRs** on their cell surfaces and in the lysosomal compartment. Myeloid DCs express a variety of surface TLRs and can recognize bacterial, fungal and viral pathogens and secrete the inflammatory cytokines IL-12, tumor necrosis factor (TNF) and IL-6. Although they have a similar set of TLRs, monocytes do not express TLR3 but upregulate TLR3 as they mature into DCs. Both human and mouse pDCs express TLR7 and TLR9, respond to viruses and secrete type I interferons. In the secondary lymphoid organs, blood-derived DC precursors give rise to DCs. In mice, these include CD11b+ and CD8 + DCs that express mostly overlapping, but not identical, sets of TLRs. Less is know about the lymphoid organ resident blood-derived DC subsets in humans. ss, single-stranded; ds, double-stranded. Numbers on cells indicate the TLR expressed by each DC subset.

各类细胞TLRs分子的表达和识别

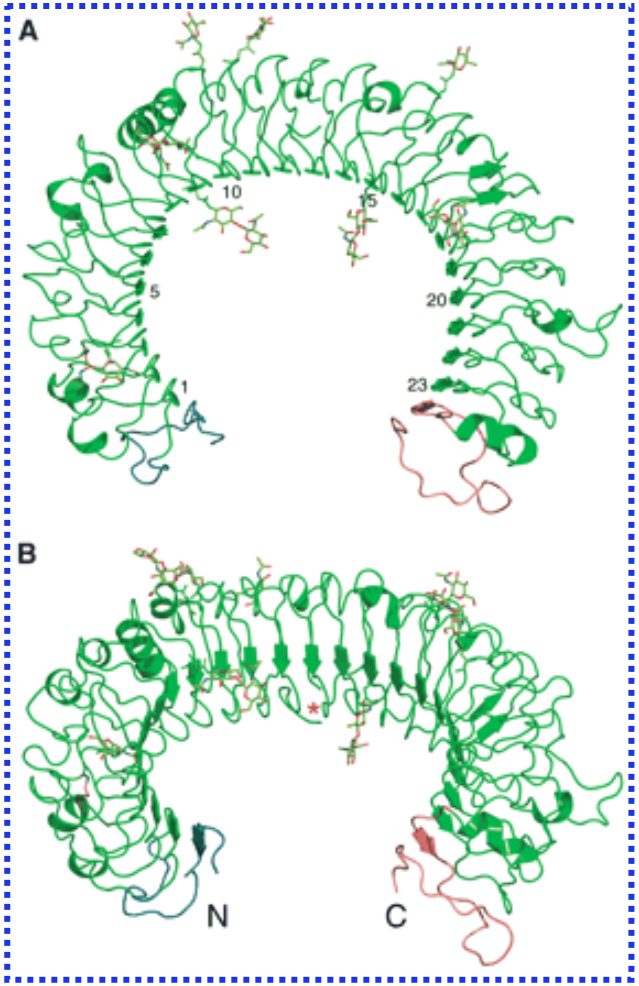
	表面表达受体	胞内表达受体	识别对象	效应分子
单核细胞	TLR1,2,4,5,6	TLR8	G+菌,G-菌,真菌, ssRNA病毒	
髓样DC	TLR1,2,5,6	TLR3,8	G+菌,G-菌,真菌,ss和dsRNA病毒	IL-12,TNF,IL-6
淋巴样DC		TLR7,9	ssRNA和DNA病毒	I型IFN
CD8α+DC	TLR1,2,6	TLR3,9	G+菌,G-菌,真菌,DNA和dsRNA病毒	IL-12
CD11b+DC	TLR1,2,5,6	TLR3,7,9	G+菌,G-菌,真菌,ss, dsRNA和DNA病毒	IL-10



West, A.P., A.A. Koblansky, and S. Ghosh, Recognition and signaling by toll-like receptors. Annu Rev Cell Dev Biol, 2006. 22: p. 409-37

Science 22 July 2005:Vol. 309. no. 5734, pp. 581 – 585

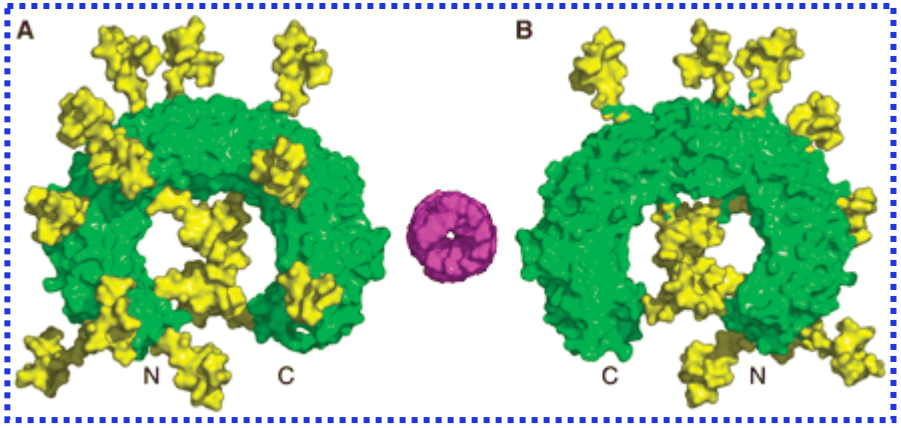
TLR-3 structure



Overall architecture of TLR3 ECD in a **ribbon representation**. The N-terminal cap region is colored blue; the 23 canonical LRRs are in green; and the C-terminal region is in pink. N-linked sugars (N-acetylglucosamines) that are observed in the electron density maps are shown in ball-and-stick representation, attached to their respective Asn residues. The disulfide bond linking LRRs 2 and 3 is drawn in orange, adjacent to the glycosylation site. (**A**) Side view of TLR3 with the convex face pointing outwards, the concave face inwards, and the heavily glycosylated side face pointing toward the viewer. (**B**) View rotated 45° from (A) that highlights the continuous ß sheet that forms the concave surface. The position of the large insertion in LRR12 that extends toward the glycosylation-free face is marked with an asterisk.

Science 22 July 2005:Vol. 309. no. 5734, pp. 581 – 585

TLR-3 structure

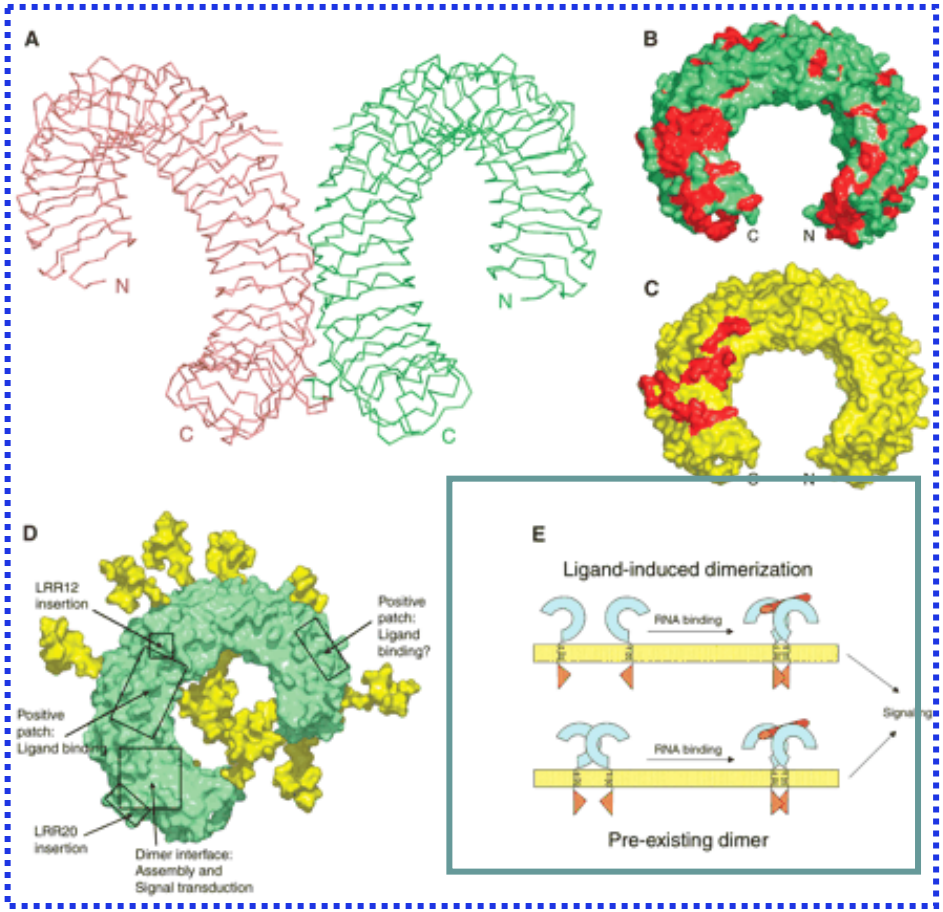


N-linked glycosylation of TLR3. (**A**) Oligomannose-type sugars, as found predominantly in insect cells (up to nine mannoses and two N-acetylglucosamines), are modeled onto the 15 predicted N-linked glycosylation sites to give a representation of the potential extent of the TLR3 surface masked by carbohydrate (same view as Fig. 1A). The TLR3 surface is represented in green and the sugars in yellow. An end view of an A-form dsRNA is also shown in pink for comparison. The exact nature of the carbohydrate, whether complex or high mannose, is not the issue here, only that glycosylation covers a large part of the TLR3 surface. (**B**) View rotated 180° from (A) showing the glycosylation-free face.

Science 22 July 2005:Vol. 309. no. 5734, pp. 581 – 585

TLR-3 structure

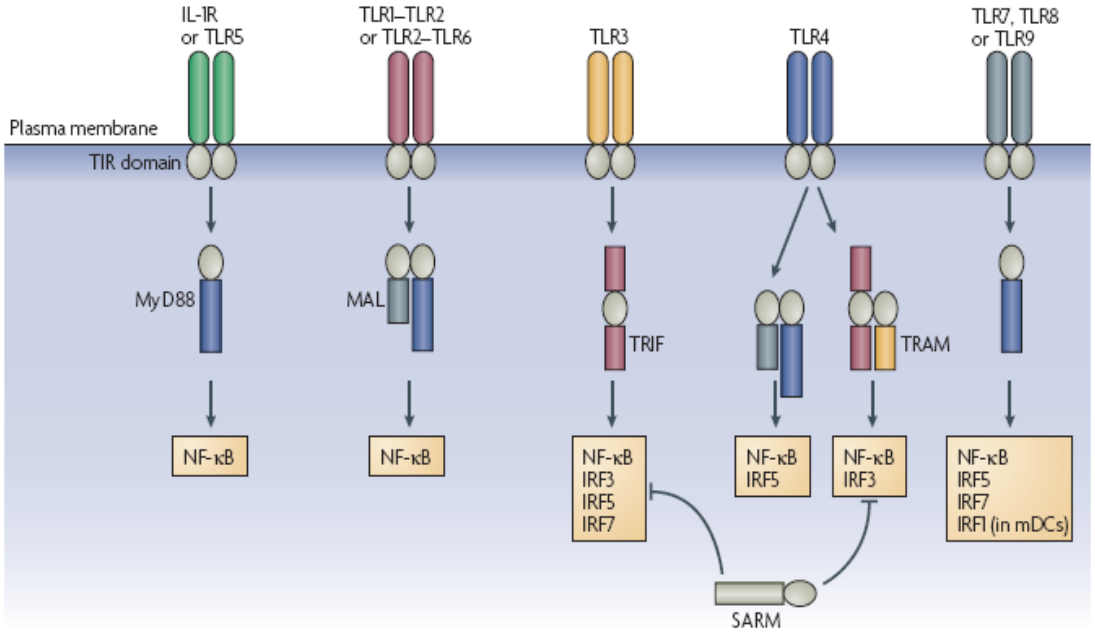
TLRs



Possible mode of TLR3 dimerization and a model for dsRNA binding and mode of signaling. (**A**) A homodimer observed in the crystal is shown with one monomer in green and the other in pink. One monomer points away from and the other toward the viewer. No other interactions between monomers in the crystal have sufficient buried surface area to warrant consideration as physiologically relevant oligomers. (**B**) Surface representation of TLR3 (green) highlights sequence conservation on the TLR3 surface (red). The largest conserved patch is on the glycosylation-free face (same view as Fig. 3B). The five TLR3 sequences used in the alignment are *Homo sapiens* (BC059372), *Pan troglodytes* (XP_526756), *Bos taurus* (NP_001008664), *Rattus norvegicus* (NM_198791), and *Takifugu rubripes* (AC156436). (**C**) The dimer interface of TLR3 also maps to the glycosylation-free face. The residues involved in the dimerization are colored in red. The large patch of conserved surface residues of TLR3 (panel B) map to this dimer interface region. (**D**) Potential functional sites on the TLR3 surface. The positions of positive patches and one of the two large insertions in the LRR motifs that are implicated for ligand binding on the glycosylation-free surface are indicated. Similarly, the conserved buried surface and the other large TLR3 LRR insertion maps to this dimerization interface region. Oligomannose-type sugars are drawn in yellow. (**E**) Binding of a dsRNA, either itself or with an accessory protein, could either induce dimerization or changes in a pre-existing dimeric assembly and trigger signal transduction in mechanism similar to those seen for other cell-surface receptors, such as cytokine receptors.

Toll信号接头分子

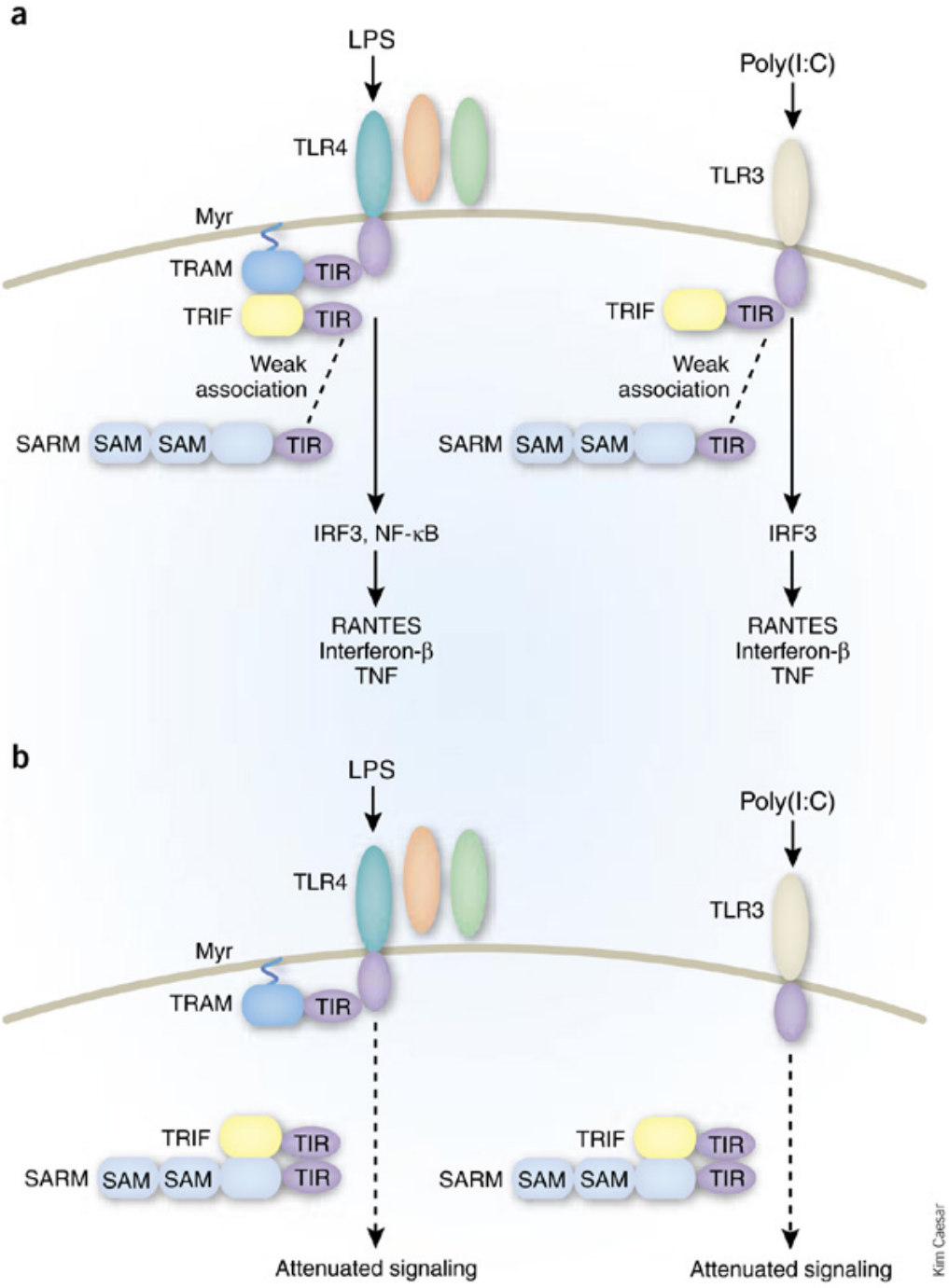
MyD88，Mal，TRIF，TRAM



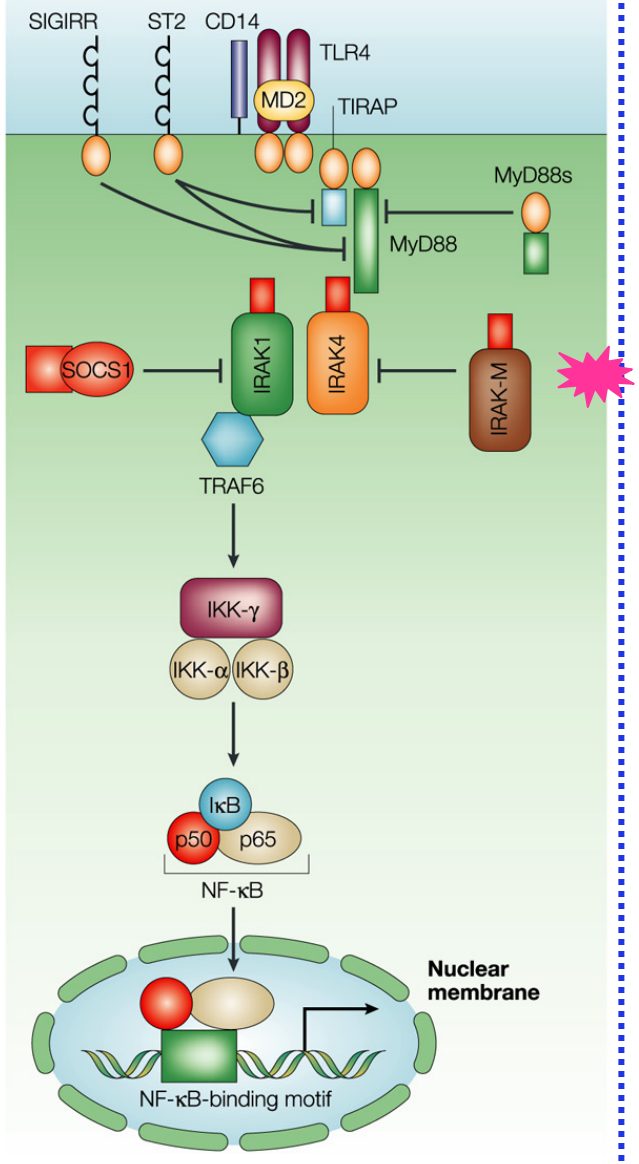
O'Neill, L.A. and A.G. Bowie, The family of five: TIR-domain-containing adaptors in Toll-like receptor signalling. Nat Rev Immunol, 2007. 7(5): p. 353-64.

The four previously characterized adaptors：MyD88, Mal,TRIF and TRAM

A fifth Toll–interleukin 1 receptor adaptor domain, SARM, has been identified as an inhibitor of TLR3 and TLR4 signaling.



Nature Immunology - **7**, 1023 - 1025 (2006)
doi:10.1038/ni1006-1023
DisSARMing Toll-like receptor signaling
Luke A J O'Neill



Negative regulation of TLR signalling. Toll-like receptor (TLR)-signalling pathways are negatively regulated by several molecules that are induced by the stimulation of TLRs. **IRAK-M** (interleukin-1-receptor (IL-1R)-associated kinase M) inhibits the dissociation of the IRAK1–IRAK4 complex from the receptor. **SOCS1** (suppressor of cytokine signalling 1) probably associates with IRAK1 and inhibits its activity. MyD88s (myeloid differentiation primary-response protein 88 short) blocks the association of IRAK4 with MyD88. The TIR (Toll/IL-1R)-domain-containing receptors SIGIRR (single immunoglobulin IL-1R-related molecule) and ST2 have also been shown to negatively modulate TLR signalling. I B, inhibitor of NF- B; IKK, I B kinase; NF- B, nuclear factor- B; TIRAP, TIR-domain-containing adaptor protein; TRAF6, tumour-necrosis-factor-receptor-associated factor 6.

Cell 140, 805–820, March 19, 2010

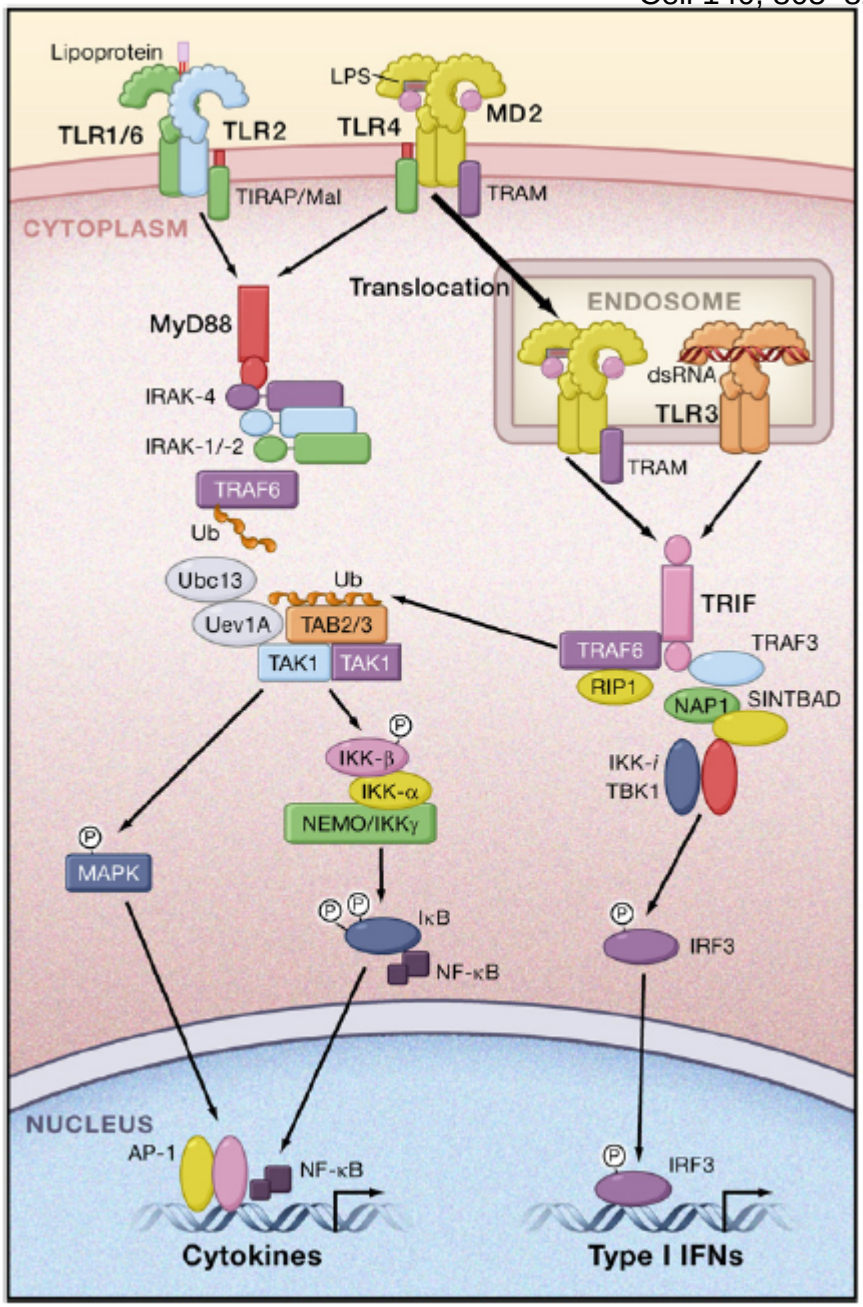


Figure 1. TLR2, TLR3, and TLR4 Signaling Pathways

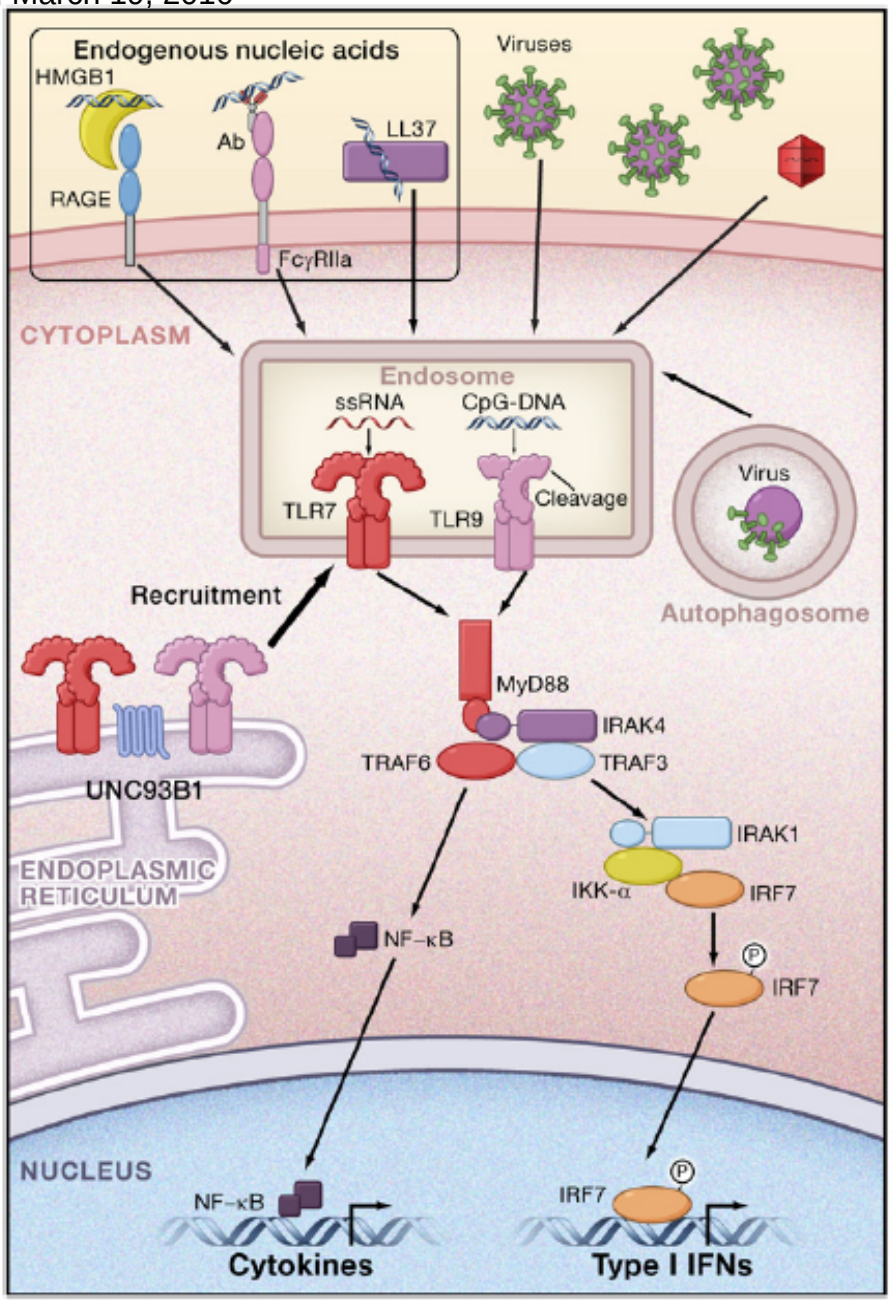


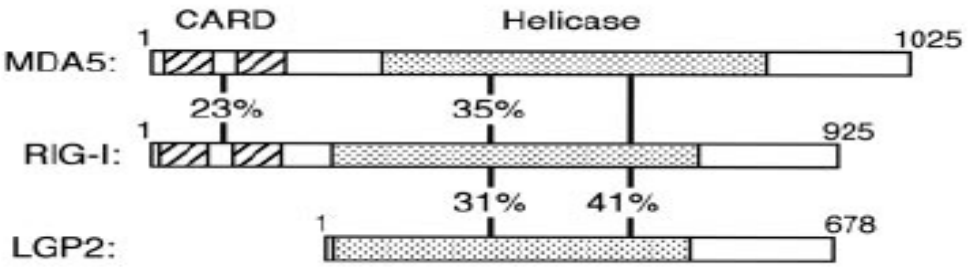
Figure 2. Nucleic Acid Sensing by TLR7 and TLR9

非TLR识别途径

RLR途径：RIG-1，MDA5

NLR途径：Nod1，Nod2

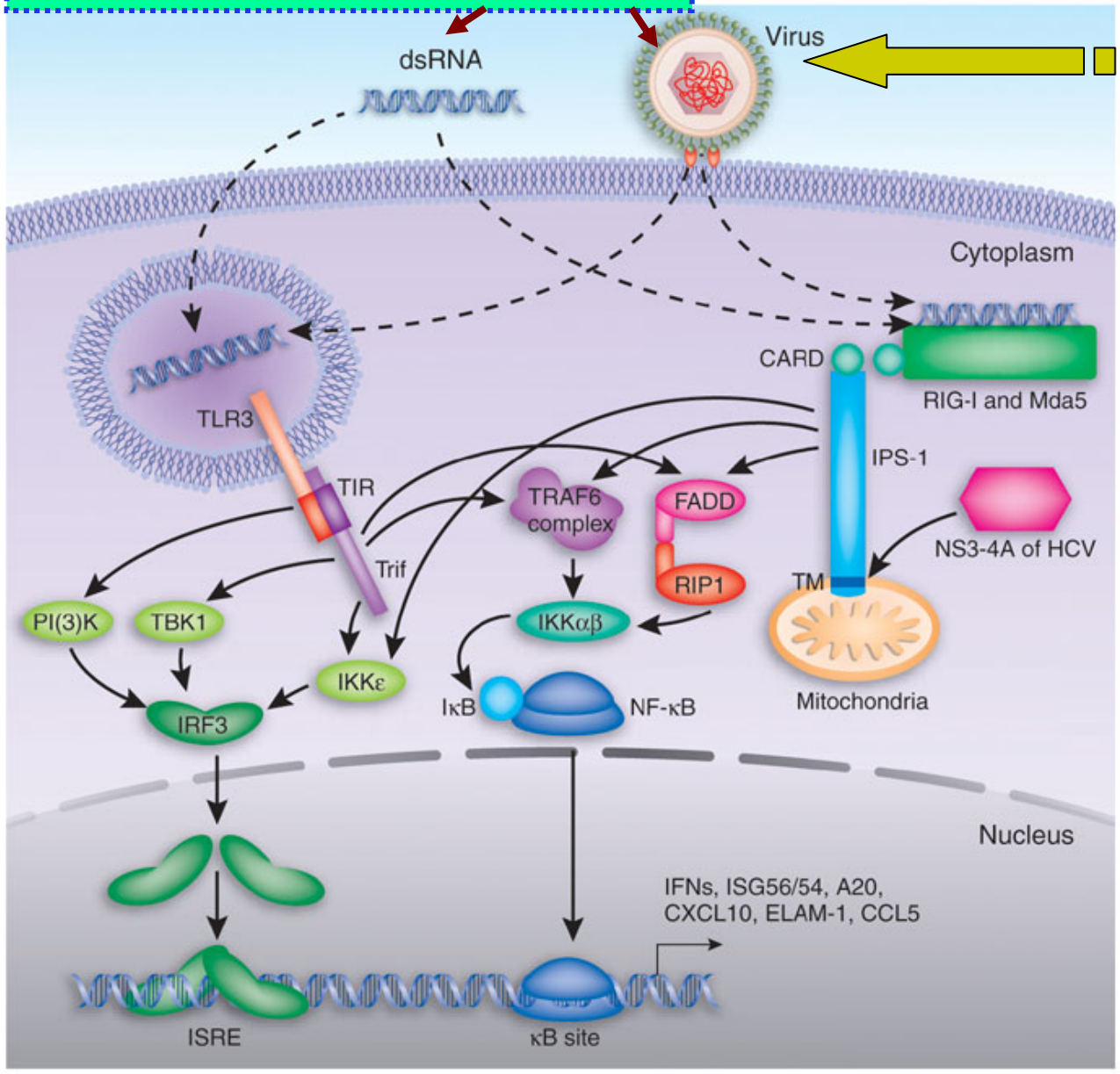
Siglec-H



Nature Immunology **6**, 1074 - 1076 (2005)

RIG-1 and MDA5

RNA病毒的两条识别途径：TLR 和 RIG-I



MDA5 recognizes poly(I:C)

RIG-I detects in vitro transcribed dsRNAs.

RIG-I is essential for the production of interferons in response to RNA viruses including paramyxoviruses, influenza virus and Japanese encephalitis virus

MDA5 is critical for picornavirus detection.

----Nature. 2006 May 4;441(7089):101-5

Signaling pathways activated by RNA viruses and dsRNA.

Exogenous or viral dsRNA can signal either through RIG-I present in the cytoplasm (right) or through TLR3 present mostly in endosomal membranes (left). Through its Toll–interleukin 1 receptor (TIR) domain, TLR3 interacts with Trif, leading to activation of the IRF3 kinase TBK1. TBK1 phosphorylates IRF3, causing its dimerization, nuclear translocation and transcriptional activation. Phosphatidylinositol-3-OH kinase (PI(3)K), via protein kinase B, is important in the complete activation of IRF3. Trif also causes NF- B activation via the IKK pathway. Another dsRNA- or virus-mediated gene induction pathway is the RIG-I pathway. RIG-I presumably binds dsRNA through its C-terminal helicase domain and signals through its N-terminal CARD. The N-terminal CARD of IPS-1 interacts with the CARD of RIG-I and causes activation of the IRF3 kinase IKK . IPS-1 uses either the TRAF6 adaptor complex or the FADD-RIP1 adaptor complex, depending on the cell type, to activate IKK , causing NF- B release, translocation and gene induction. The C-terminal of IPS-1 contains a small transmembrane region (TM) that localizes the protein to the outer mitochondrial membrane. This localization is required for its function, and proteolytic cleavage of this part by the HCV protein NS3-4A inactivates IPS-1.

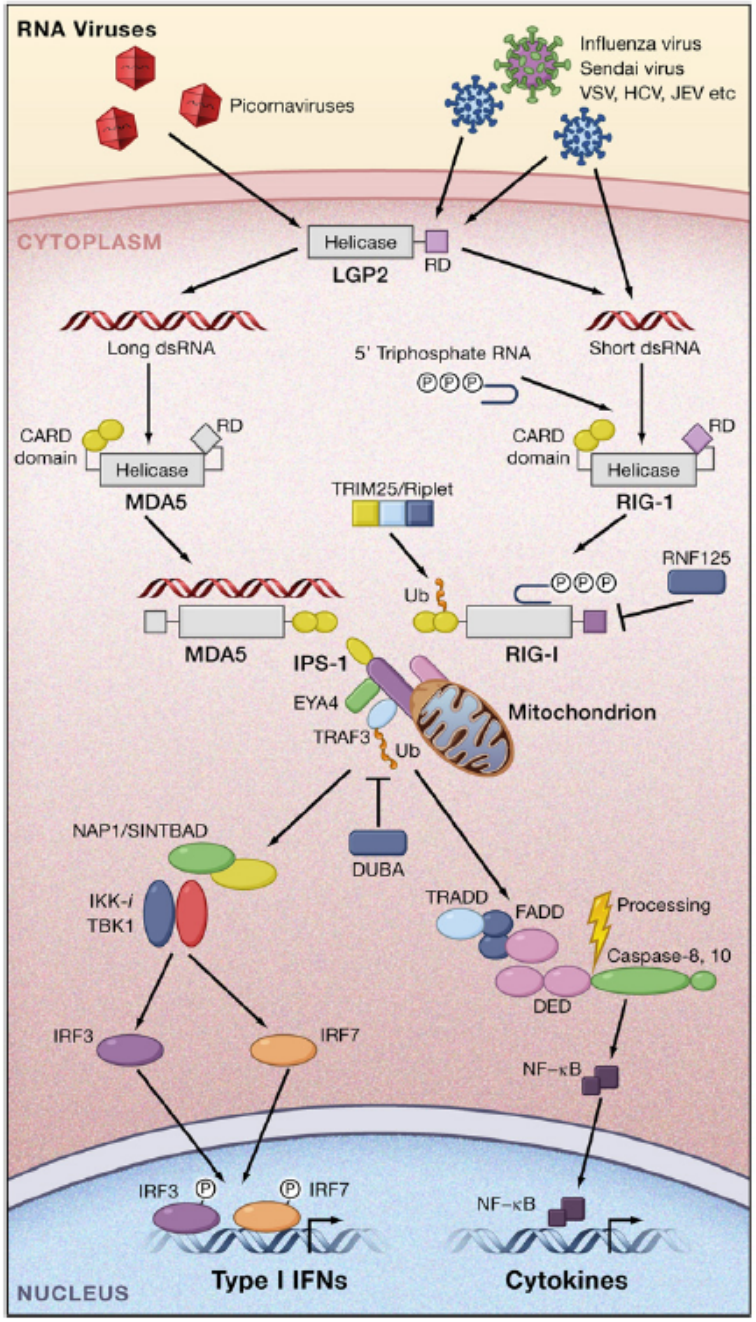


Figure 3. Recognition of RNA Viruses by RLRs

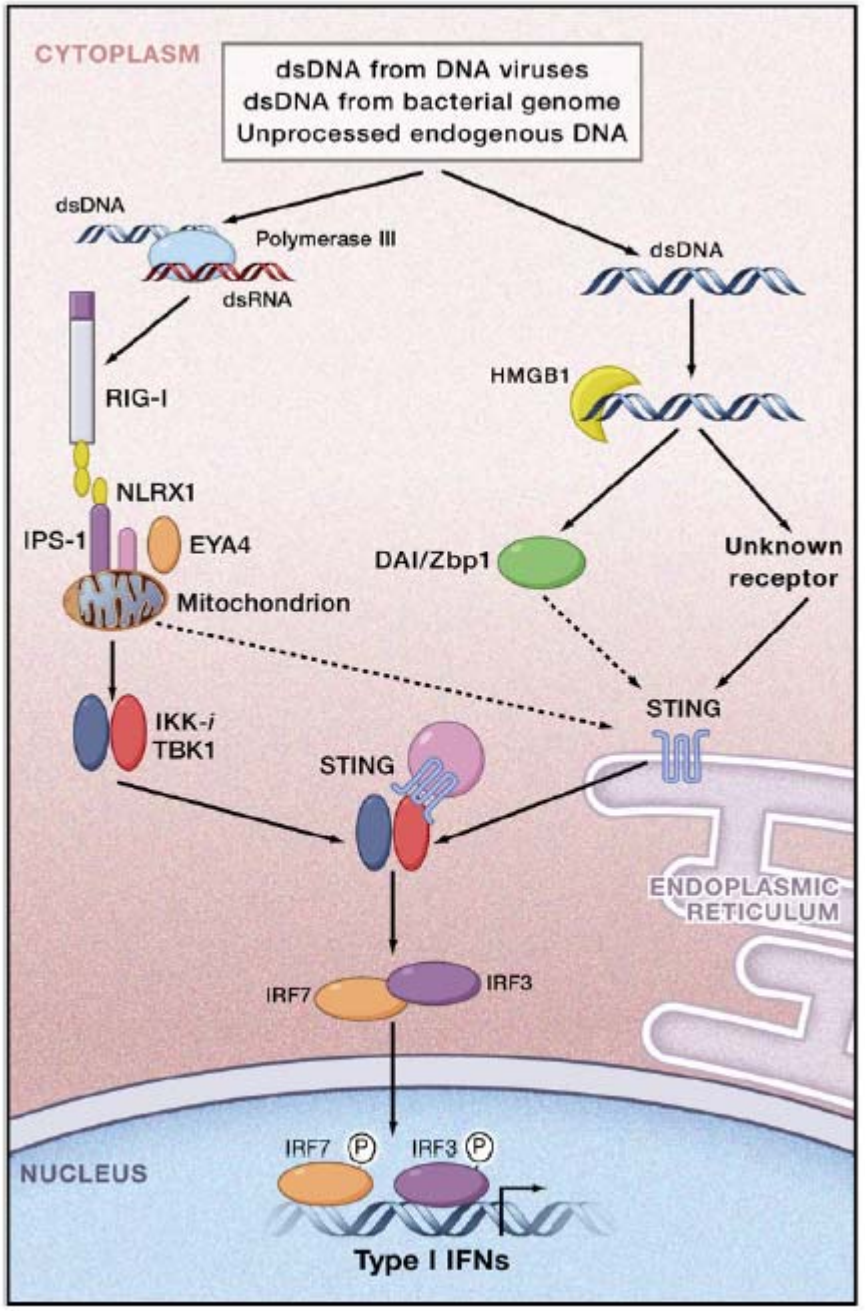
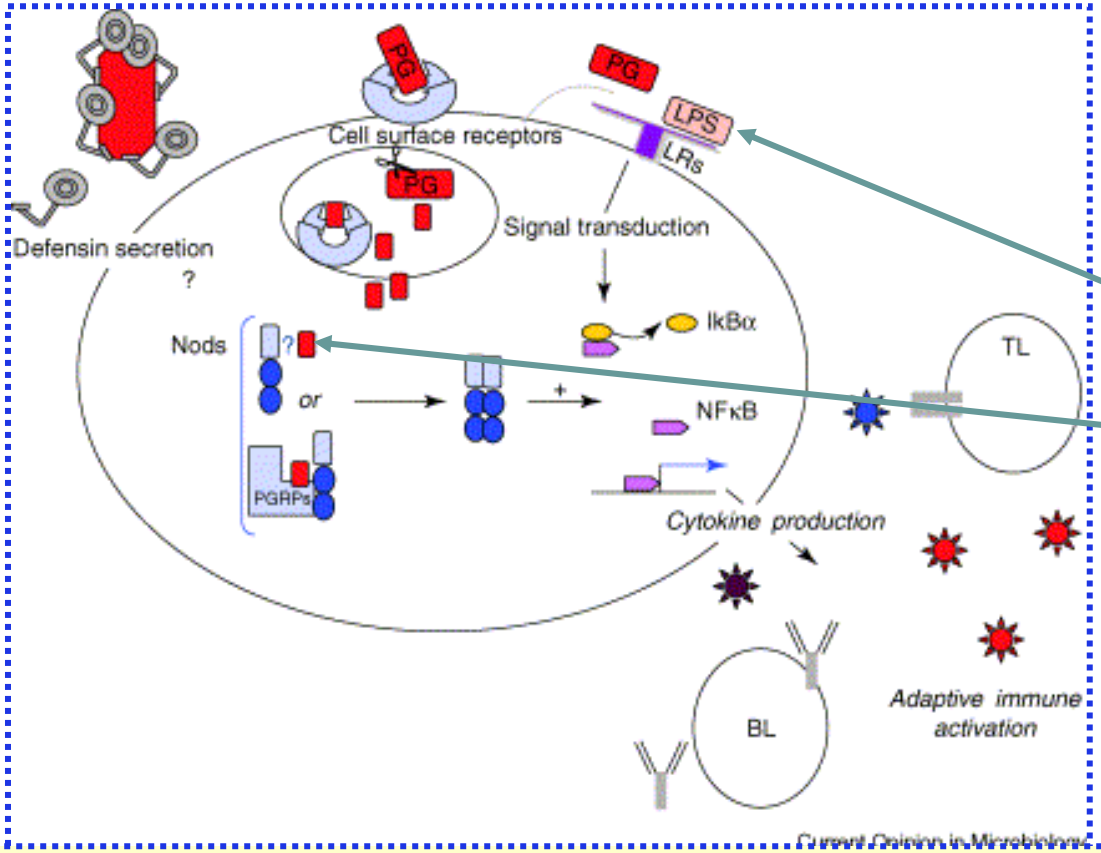


Figure 4. Recognition of Cytoplasmic DNA and IFN Production

Curr Opin Microbiol. 2004 Feb;7(1):25-32

Dana J. Philpott, Univ. of Toronto, Nod *proteins in bacterial detection*

Nods

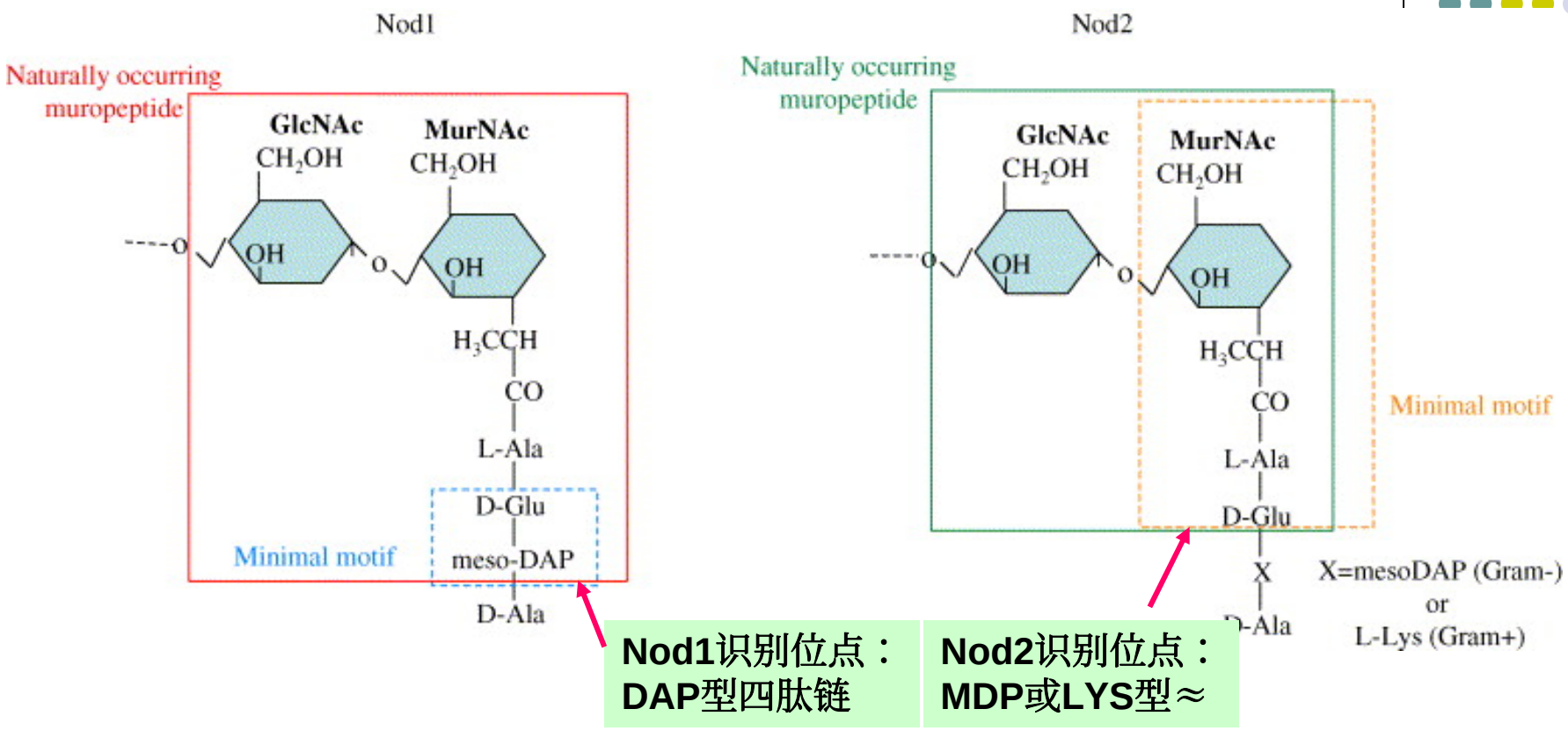


TLR作为细胞表面受体
识别LPS和PG
Nod识别内化的PG

Extracellular and intracellular sensing of bacterial products. TLRs, with their extracellular leucine-rich (LR) domains, act as cell surface receptors for PAMPs, including LPS and PG, leading to NF κ B activation and cytokine production. Intracellular recognition and/or sensing is carried out by Nod1 and Nod2 after PG internalization, perhaps by cell surface receptors, and processing by enzymes such as lysozyme and amidases present within specialized compartments. Interaction of Nods with PG motifs, either directly or indirectly through intermediary molecules, results in similar proinflammatory responses to those induced by TLRs. Production and/or secretion of antimicrobial defensin molecules may also be triggered by Nod induction. Cytokine production and upregulation of co-stimulatory molecules resulting from TLR and Nod activation is a prerequisite for the triggering of the adaptive immune response, through B and T lymphocytes (BL and TL), which enables a tailored defense response against a particular pathogen. Much remains to be discovered in order to determine the nature of the interaction between Nods/TLRs and their bacterial ligands and also to determine whether these pathways interact to produce an efficient defense response.

Mol Immunol. 2004 Nov;41(11):1099-108
Dana J. Philpott, Univ. of Toronto, **Nod *proteins in bacterial detection***

Nods



Naturally occurring and minimal peptidoglycan motifs sensed by Nod1 and Nod2. For Nod1, the minimal naturally occurring peptidoglycan (PGN) motif that is detected is the sugar backbone of *N*-acetylglucosamine (GlcNAc) and *N*-acetylmuramic acid (MurNAc) linked to a stem peptide consisting of L-Ala- ɣ -D-Glu-*meso*-DAP (GM-triDAP; outlined in red square). The minimal PGN structure detected by Nod1 is the dipeptide D-Glu-*meso*-DAP, in which *meso*-DAP amino acid is in the terminal position (outlined in blue). Nod2 detects GlcNAc-MurNAc linked to L-Ala- ɣ -D-Glu as the naturally occurring PGN motif (outlined in green) whereas the minimal motif consists of MurNAc-L-Ala- ɣ -D-Glu (MDP; outlined in orange).

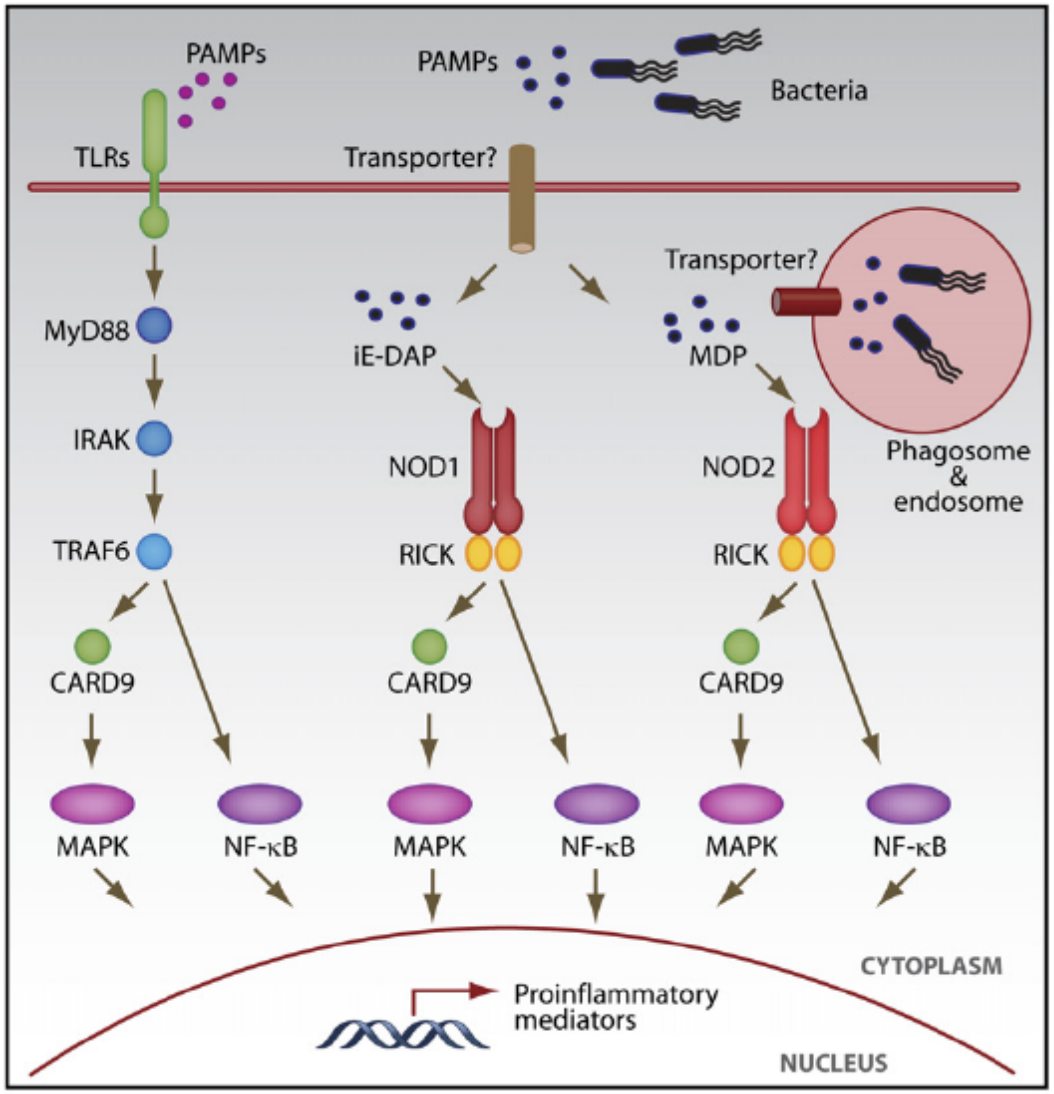
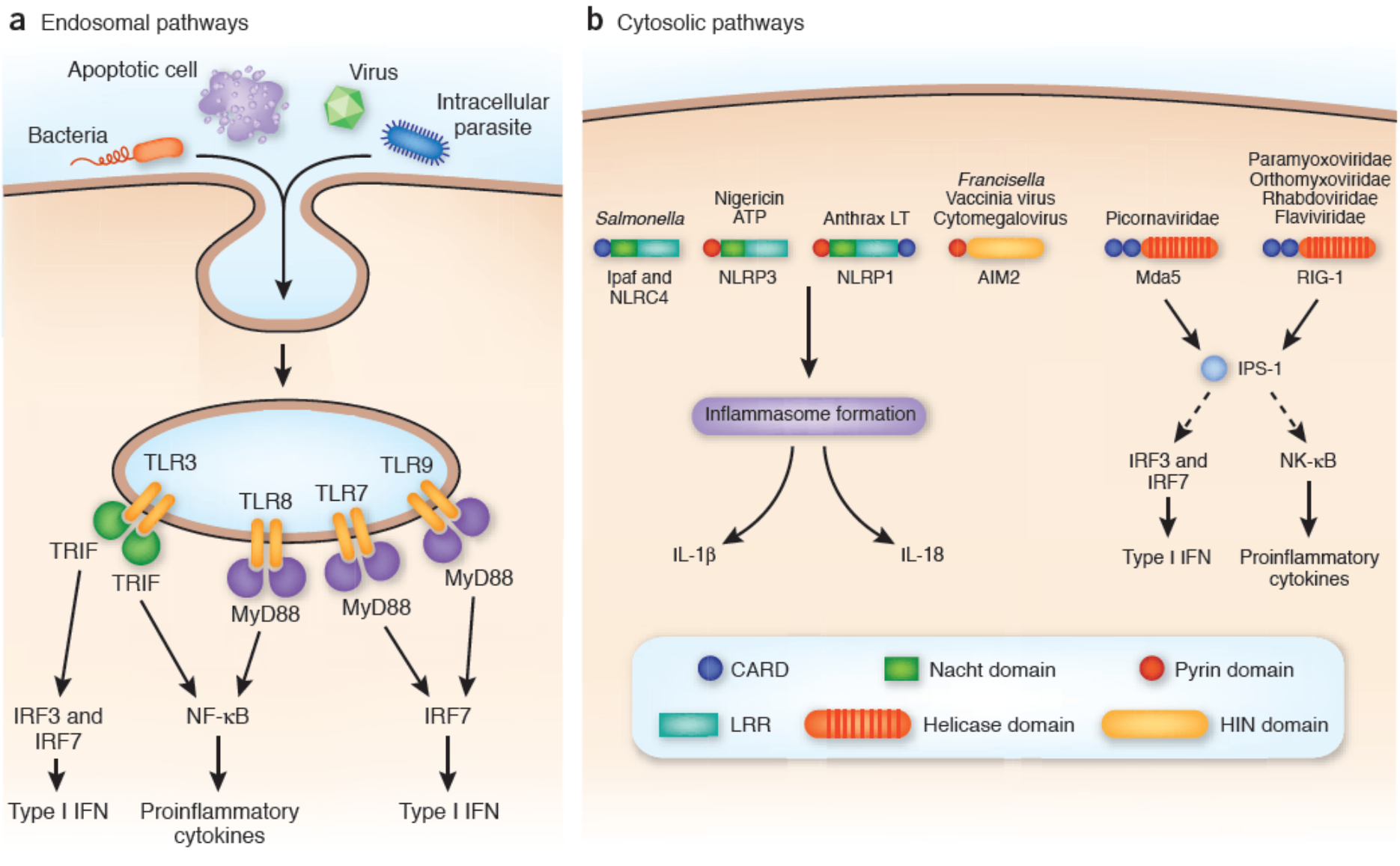


Figure 1. Model for PGN Recognition by NOD1 and NOD2

The NLR proteins NOD1 and NOD2 sense intracellular iE-DAP and MDP, respectively, leading to recruitment of the adaptor proteins RICK and CARD9. Extracellular PAMPs are recognized by TLRs, which signals through MyD88, IRAK proteins, and TRAF members. For clarity, the TLR pathway has been simplified. The subsequent activation of NF-κB and MAP kinases results in the transcriptional upregulation of proinflammatory genes.

Immunity 27, October 2007
549-559



Endosomal and cytosolic pathways for pathogen detection.

Nat Immunol,May 2010, Volume 11 No 5 p367

Although this description risks oversimplification, the innate immune system detects pathogens through specific receptors located on the cell surface (for example, some TLRs; not shown); in endosomal compartments (TLR homodimers specialized for RNA and DNA binding; **a**); and in the cytoplasm (RLRs, NLRs and AIM2; **b**). The RLRs RIG-I and Mda5 share a common structure, with two caspase-recruitment domains (CARD) and a helicase domain, but they are activated by different viral RNA structures. RIG-I is activated by certain RNA structures that contain a 5′ triphosphate, whereas Mda5 is thought to be activated by dsRNA, but the structures have not yet been well characterized.Because of these different substrate specificities, these RLRs differ in the viral infections to which they respond, by signaling through MAVS (IPS-1), which leads to the induction of interferon and cytokine synthesis (**b**). Three families of NLRs have been described, each of which contains a Nacht domain and a leucine-rich repeat (LRR) domain, but which have distinct combinations of caspase-recruitment and pyrin domains (**b**). These different structures also confer distinct substrate specificities, but all lead to inflammasome formation. AIM2 has a unique structure, with a HIN-200 domain and a pyrin domain, and forms an inflammasome after detecting dsDNA.

免疫识别途径

Table 1. PRRs and Their Ligands

PRRs	Localization	Ligand	Origin of the Ligand
TLR			
TLR1	Plasma membrane	Triacyl lipoprotein	Bacteria
TLR2	Plasma membrane	Lipoprotein	Bacteria, viruses, parasites, self
TLR3	Endolysosome	dsRNA	Virus
TLR4	Plasma membrane	LPS	Bacteria, viruses, self
TLR5	Plasma membrane	Flagellin	Bacteria
TLR6	Plasma membrane	Diacyl lipoprotein	Bacteria, viruses
TLR7 (human TLR8)	Endolysosome	ssRNA	Virus, bacteria, self
TLR9	Endolysosome	CpG-DNA	Virus, bacteria, protozoa, self
TLR10	Endolysosome	Unknown	Unknown
TLR11	Plasma membrane	Profilin-like molecule	Protozoa
RLR			
RIG-I	Cytoplasm	Short dsRNA, 5′triphosphate dsRNA	RNA viruses, DNA virus
MDA5	Cytoplasm	Long dsRNA	RNA viruses (Picornaviridae)
LGP2	Cytoplasm	Unknown	RNA viruses
NLR			
NOD1	Cytoplasm	iE-DAP	Bacteria
NOD2	Cytoplasm	MDP	Bacteria
CLR			
Dectin-1	Plasma membrane	β-Glucan	Fungi
Dectin-2	Plasma membrane	β-Glucan	Fungi
MINCLE	Plasma membrane	SAP130	Self, fungi

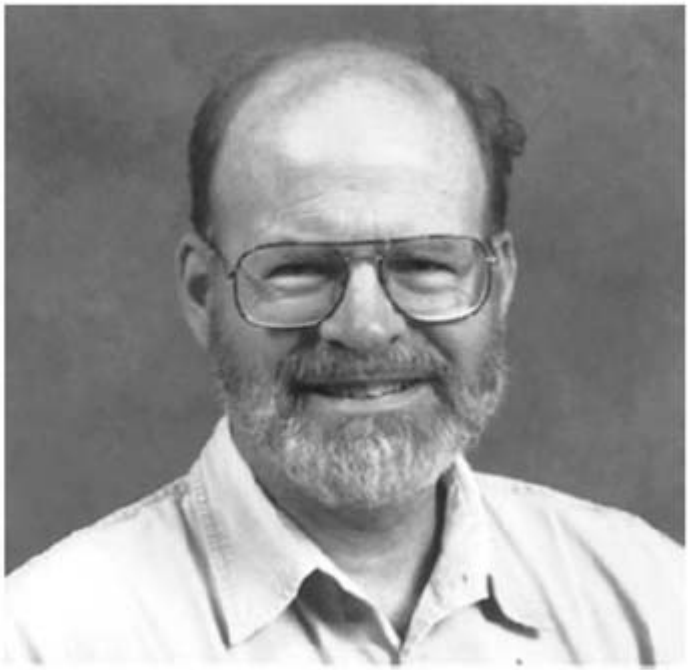
Cell 140, 805–820, March 19, 2010


The End

Presidential Address to The American Association of Immunologists

The Road Less Traveled by: The Role of Innate Immunity in the Adaptive Immune Response[1,2]

Charles A. Janeway, Jr.



Charles A. Janeway, Jr.

Presented at the Annual Meeting of The American Association of Immunologists, April 18–22, 1998, San Francisco, CA.

J Immunol. 1998 Jul 15;161(2):539-44

FIGURE 1. Photographs of my forbears: Edward Gamaliael Janeway (*left*), Theodore Caldwell Janeway (*center*), and Charles A. Janeway (*right*).

His great-grandfather, Edward Gamaliel Janeway, was the health commisioner of the City of New York and a professor of medicine and pathology at Bellvue Hospital on Roosevelt Island. Here he is standing beside a patient, but we don't know if the patient is alive or dead, as he took care of live patients and their corpses! Note the formal dress of the medical students in the audience;I would like to see a class at Yale with such dignity!

His grandfather, Theodore Caldwell Janeway ,was a professor of medicine with interests in cardiology and infectious disease. He first worked at Columbia's College of Physicians and Surgeons, and later at John's Hopkins University School of Medicine. In late 1917 he was asked by the United States Army to visit the encampments of soldiers, as the rate of mortality in these camps was very high. He did this, contracted the same pneumococcal pneumonia that accounted for the high mortality rate among the troops, and died within a week in December 1917; my father was 8 at the time.

My father, Charles A. Janeway (Fig. 1, *right*), was a professor of pediatrics and department chairman for about 30 years at the Children's Hospital Medical Center in Boston. During the World War II, he worked with Dr. Edwin Cohn on the fractionation of human plasma into various protein solutions. He used injections of pooled γ globulin to treat these patients, which protected them from infection; this treatment is still used today.

Presidential Address to The American Association of Immunologists

The Road Less Traveled by: The Role of Innate Immunity in the Adaptive Immune Response[1,2]

Charles A. Janeway, Jr.

The Road Not Taken

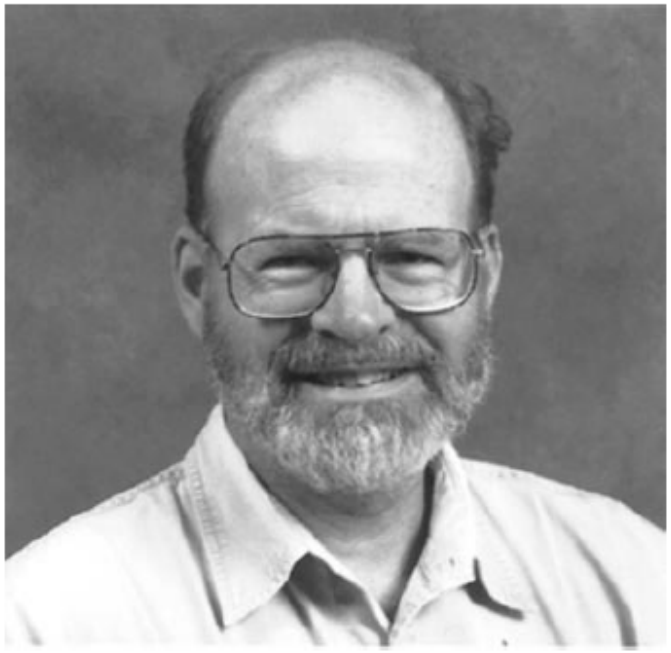
Two roads diverged in a yellow wood,
And sorry I could not travel both
And be one traveler, long I stood
And looked down one as far as I could
To where it bent in the undergrowth;

Then took the other, as just as fair,
And having perhaps the better claim,
Because it was grassy and wanted wear;
Though as for that the passing there
Had worn them really about the same.

And both that morning equally lay
In leaves no step had trodden black.
Oh, I kept the first for another day!
Yet knowing how way leads on to way,
I doubted if I should ever come back.

I shall be telling this with a sigh,
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.

—Robert Frost



Charles A. Janeway, Jr.

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Presidential Address to The America of Immunologists

The Road Less Traveled by: The Role of Innat Immune Response[1,2]

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And that has made all the difference.

—Robert Frost

My g
was the
fessor of
Island. H

未选择的路

森林叶黄 分出岔路两行
可惜我 不能同时前往
我在那路口久久伫立
向着一条路极目远望

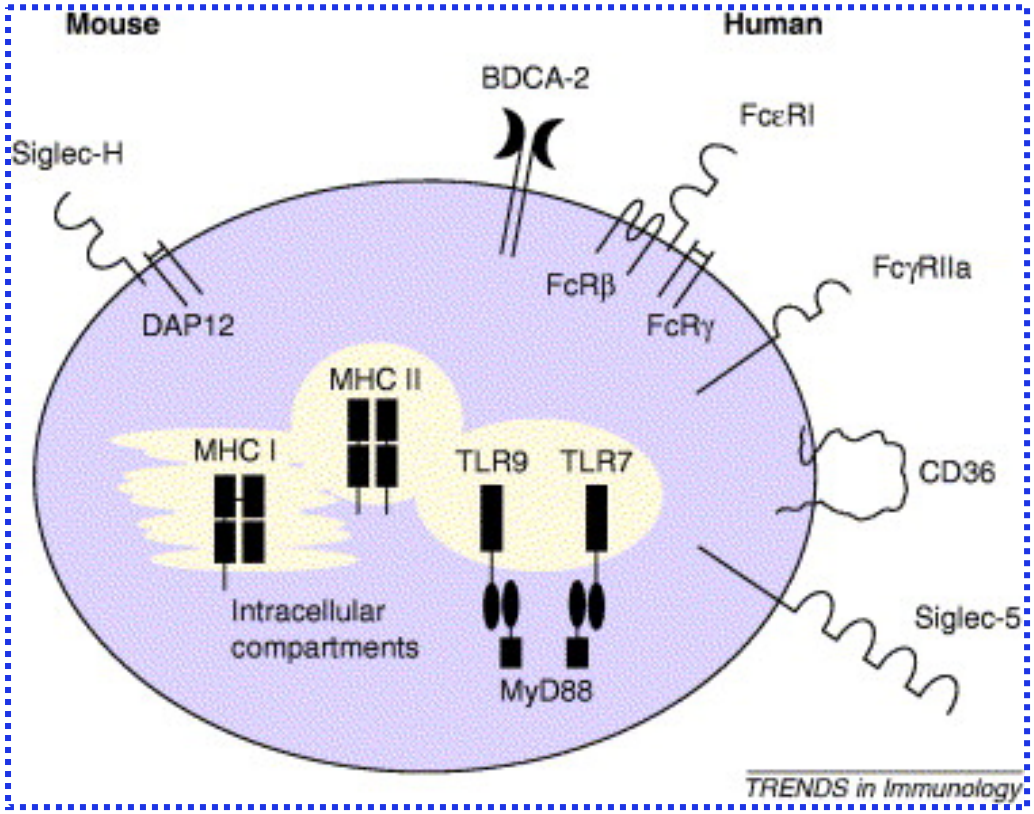
但我却选择了另外一条
它荒草萋萋，十分幽长
但它更诱人，更令人遐想
虽然在这条小路上
很少见到旅人踏荒

那天清晨落叶满地
落叶上也无脚踩的痕伤
呵，留下一条路待他日寻访
虽然我知道路径延绵无尽头
重游此地许是痴想

也许多少年后在某一个地方
我将轻声叹息把往事回想
一片森林里曾分出两条路
而我却选择了人迹更少的一条
从此决定了我一生不同的方向

Siglec-H

Marco Colonna: Plasmacytoid dendritic cells in immune responses
Trends Immunol. 2006 May 5;



Antigen-capturing molecules on human and mouse pDCs. Human pDCs (right hand side) uniquely express the C-type lectin BDCA-2. Additionally, they express the Fc receptors Fc ɣ RIIa and Fc ε RI, CD36 and Siglec-5, which are also present on other cells. Mouse pDCs express Siglec-H. These receptors could mediate pathogen uptake and delivery to intracellular compartments for TLR stimulation and presentation on MHC.

Siglec-H

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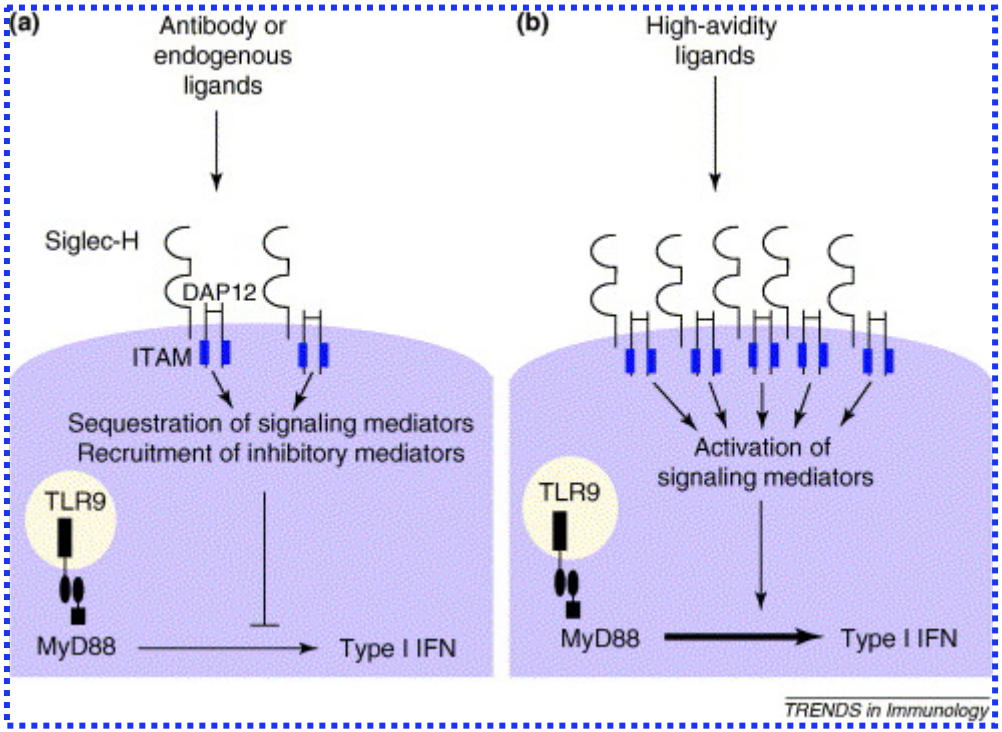

The avidity model of Siglec-H–DAP12 signaling in pDCs. **(a)** The TLR9–MyD88 pathway stimulates the secretion of type I IFN by pDCs. Siglec-H can mediate inhibition of this pathway when engaged by antibody or low-avidity endogenous ligands, which induce suboptimal receptor clustering. **(b)** By contrast, high-avidity ligands for Siglec-H optimally engage the receptor, resulting in multivalent clustering, activation of signaling mediators and cytokine secretion

Siglec-H与低亲和力配体结合后出现负调节功能
Siglec-H与高亲和力配体结合后出现正调节功能

Siglec-H

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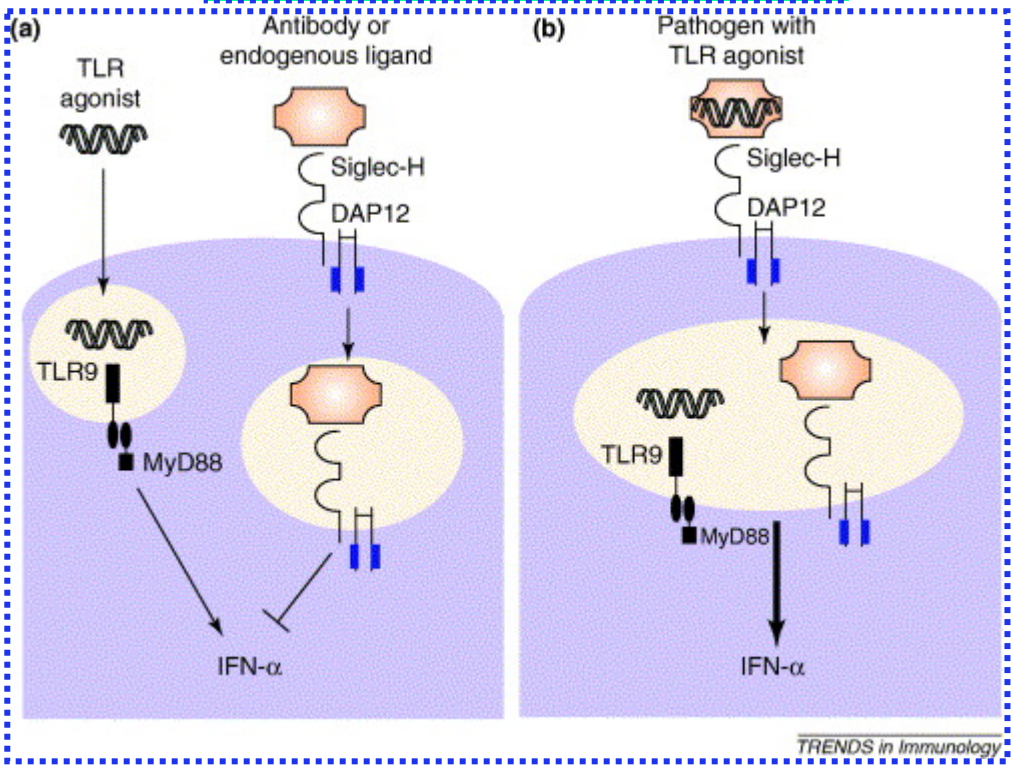
无病原体 有病原体



The compartmentalization model of Siglec-H–DAP12 signaling in pDCs. **(a)** When engaged by an endogenous ligand lacking TLR agonists, such as mAb 440c, Siglec-H–DAP12 and its cargo are internalized in endosomes devoid of TLR signaling. DAP12 in these endosomes can compete for signaling mediators with TLR in other compartments, resulting in the inhibition of IFN-α secretion. **(b)** By contrast, when engaged by a pathogen containing TLR agonists, Siglec-H is internalized and delivered to a TLR compartment, where DAP12 signaling synergizes with TLR signaling in activating IFN-α secretion.