

5^ο ΔΙΑΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΕΚΠΑΙΔΕΥΣΗΣ ΣΤΗ ΡΕΥΜΑΤΟΛΟΓΙΑ

Βασικές αρχές μη ειδικής ανοσίας (κύτταρα & μηχανισμοί) Cellular mechanisms of innate immunity



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Immune response

homeostasis



PROTECTION vs TISSUE DAMAGE

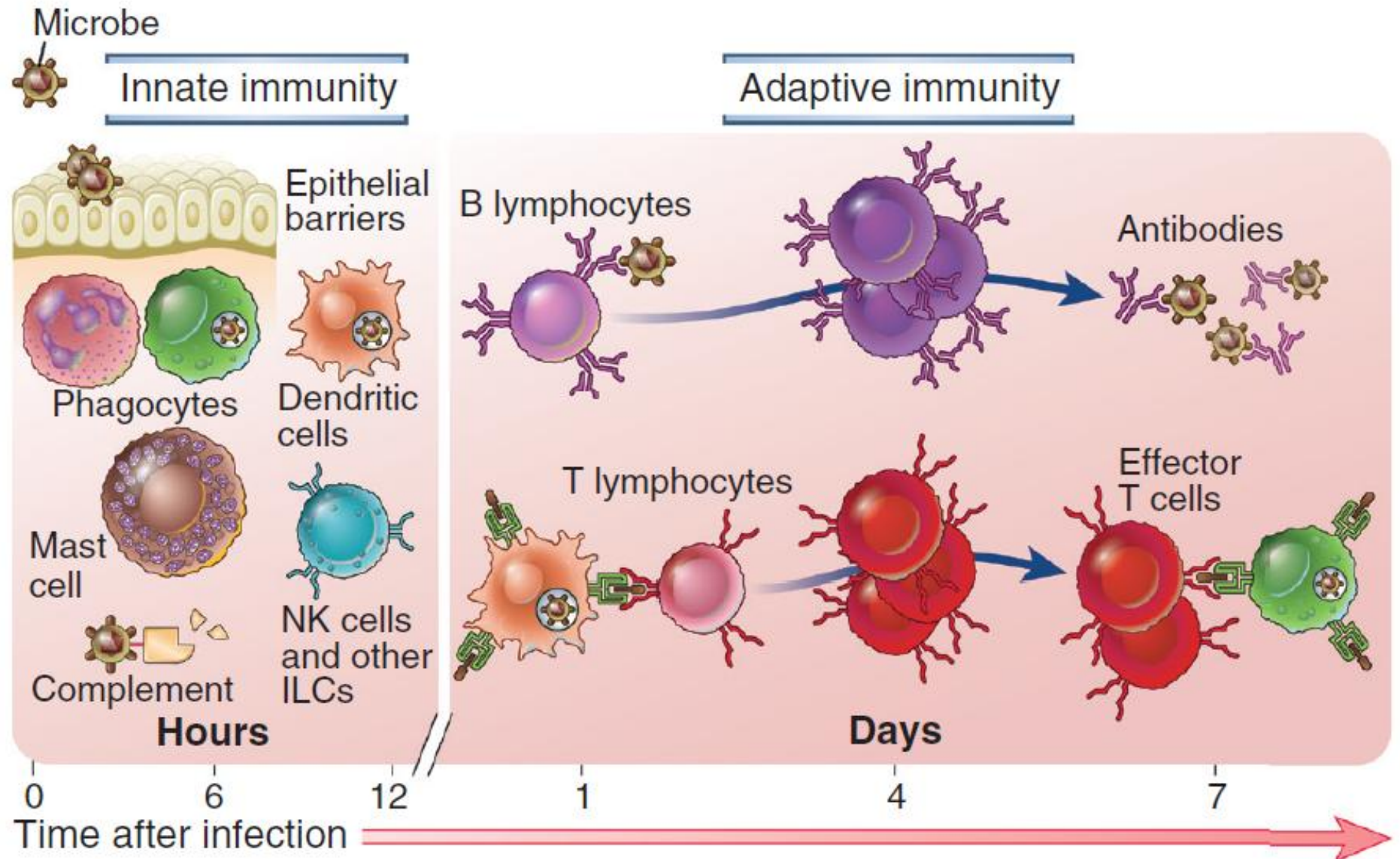
Infection overcome vs Sepsis/Septic shock

Δύο λειτουργικά σκέλη ανοσολογικής απόκρισης

- Μηχανισμοί φυσικής (innate)
/μη ειδικής ανοσίας/έμφυτης
- Μηχανισμοί επίκτητης (adaptive)
/ειδικής ανοσίας/προσαρμοσμένης

Φυσική και επίκτητη ανοσία

Οι μηχανισμοί της φυσικής ανοσίας ενεργοποιούνται αρχικά. Οι μηχανισμοί της επίκτητης ανοσίας αναπτύσσονται αργότερα και απαιτούν την ενεργοποίηση των λεμφοκυττάρων



Components (players) of innate immunity

- **physical and chemical barriers**

- epithelia (skin and the mucosal surfaces of the gastrointestinal, respiratory, and genitourinary tracts)
- antimicrobial substances produced at epithelial surfaces

- **cells**

neutrophils, macrophages, dendritic cells (DCs)

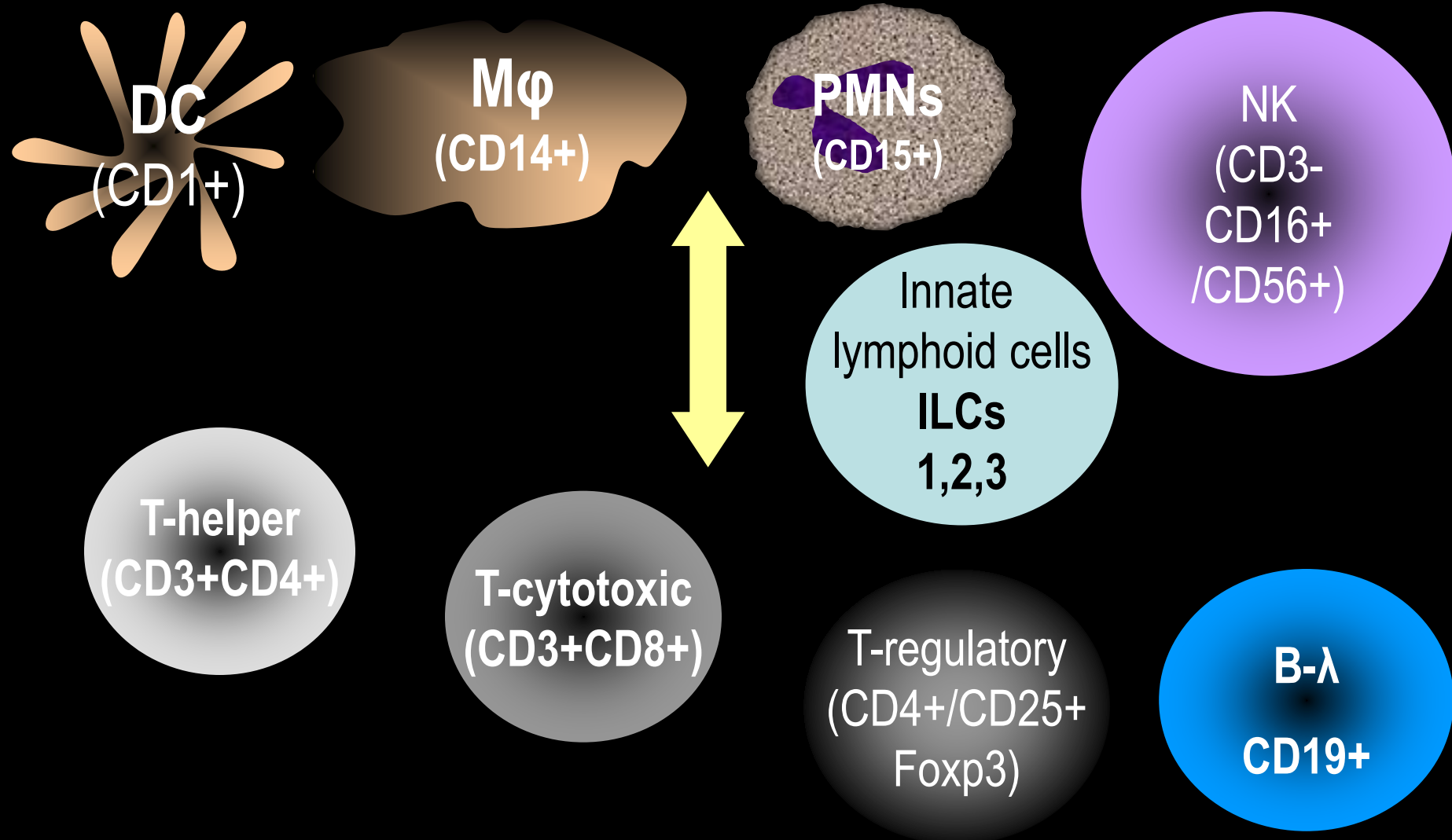
natural killer (NK) cells and other innate lymphoid cells (e.g. $\gamma\delta$ -T)

- **blood proteins/mediators of inflammation (soluble factors)**

- complement and coagulation systems
- cytokines, interferons, chemokines



Immune response **requires activation of both arms:** Innate and Adaptive Immunity



What remains remarkable conserved during evolution in humans???

Innate immune system (σύστημα έμφυτης/φυσικής ανοσίας)



Charles Janeway, Jr (1989)

Infectious-NonSelf Discrimination Model (INSD model)

- Janeway CA Jr. *Approaching the Asymptote? Evolution and Revolution in Immunology. Cold Spring Harbour Symposium Quant Biol* 1989;54:1-13.
- Janeway CA Jr. *The immune system evolved to discriminate infectious nonself from noninfectious self. Immunol Today* 1992;13:11-6.
- Medzhitov R, Janeway CA Jr. *Innate immunity: impact on the adaptive immune response. Curr Opin Immunol* 1997;9:4-9.
- Medzhitov R, Preston-Hurlburt P, Janeway CA Jr (1997) *A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. Nature* 388:394-397



PAMPs

(pathogen-associated molecular patterns)

evolutionary conserved structures/products,

no antigenic diversity,

essential for survival and virulence of the microbes

(infectious inflammation)

- lipopolysaccharide (LPS)
- peptidoglycan (PG)
- lipoproteins
- lipoteichoic acid (LTA)
- mannanes
- unmethylated CpG DNA sequences
- dsRNA, ssRNA

PAMP	pathogen	biologically active fragment
LPS	most Gram-negative bacteria	lipid A
lipoprotein, lipopeptide	eubacteria	di(three)Pam. Cys at N-term.
peptidoglycan	most bacteria	muropeptides
lipoteichoic acid	most Gram-positive bacteria	glycosidic link, glycolip. anch.
CpG	most pathogens	nonmethylated CpG ODN
lipoarabinomannan	mycobacteria	LAM, LM
N-formyl-Met	prokaryotes	amino-terminal N-formyl-Met
mannanes and mannoproteins	yeasts	unknown
dsRNA	viruses	dsRNA
flagellin	most bacteria	N and C-terminal
zymosan	fungi	β -glucan

Polly Matzinger (1994)

Danger Model

- Matzinger P (1994) *Tolerance, danger, and the extended family.*
Annu Rev Immunol 12:991-1045
- Matzinger P (1998) *An innate sense of danger.*
Semin Immunol 10:399-415



- Immune system recognizes **tissue damage** not only pathogens
- Activation by various **alert/danger signals** derived from damaged tissues

DAMPs

(damage/danger-associated molecular patterns)
sterile inflammation

- DNA, chromatin, HMGB1
- ATP
- crystals (monosodium urate, cholesterol)
- oxidized LDL (oxLDL)
- stress-derived proteins (eg heat-shock proteins, HSPs)
- immunocomplexes
- ????????

Τα Σήματα Συναγερμού: PAMPs & DAMPs

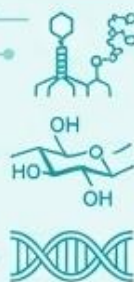


PAMPs
(Pathogen-Associated
Molecular Patterns)

Εξελικτικά διατηρημένες μικροβιακές δομές.
Ζωτικής σημασίας για τα παθογόνα.



Παραδείγματα:
LPS (Λιποπολυσακχαρίτης),
Πεπτιδογλυκάνη (PG),
Ιικό RNA/DNA (dsRNA, CpG).



DAMPs
(Damage/Danger-
Associated Molecular
Patterns)

Ενδογενή μόρια που απελευθερώνονται από κατεστραμμένους ιστούς
(Άσηπτη φλεγμονή).



Παραδείγματα:
Κυτταρικό DNA
Χρωματίνη (HMGB1)
ATP
Κρύσταλλοι (Ουρικό μονοάτριο,
Χοληστερόλη), oxLDL.



Φυσική vs. Επίκτητη Ανοσία

Φυσική Ανοσία



Ειδικότητα: Κοινές δομές ομάδων μικροβίων (PRRs).



Ποικιλομορφία: Περιορισμένη (germline-encoded).



Μνήμη: Καμία (παραδοσιακά).



Κύτταρα: Φαγοκύτταρα (Μακροφάγα, Ουδετερόφιλα), NK cells, Δενδριτικά.



Πρωτεΐνες: Συμπλήρωμα, Κυτταροκίνες.

Επίκτητη Ανοσία



Ειδικότητα: Ειδικά αντιγόνα μικροβίων.



Ποικιλομορφία: Τεράστια (σωματικός ανασυνδυασμός).



Μνήμη: Ναι.



Κύτταρα: Λεμφοκύτταρα (T και B).



Πρωτεΐνες: Αντισώματα.



Ώρες



Ημέρες

Table 1–2. Features of Innate and Adaptive Immunity

Innate		Adaptive
Characteristics		
Specificity	For structures shared by groups of related microbes	For antigens of microbes and for nonmicrobial antigens
Diversity	Limited; germline-encoded	Very large; receptors are produced by somatic recombination of gene segments
Memory	None	Yes
Nonreactivity to self	Yes	Yes
Components		
Physical and chemical barriers	Skin, mucosal epithelia; antimicrobial chemicals	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Blood proteins	Complement	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells	Lymphocytes

TABLE 1.2 Features of Innate and Adaptive Immunity

Innate		Adaptive
Characteristics		
Specificity	For molecules shared by groups of related microbes and molecules produced by damaged host cells	For microbial and nonmicrobial antigens
Diversity	Limited; recognition molecules encoded by inherited (germline) genes	Very large; receptor genes are formed by somatic recombination of gene segments in lymphocytes
Memory	None or limited	Yes
Nonreactivity to self	Yes	Yes
Components		
Cellular and chemical barriers	Skin, mucosal epithelia; antimicrobial molecules	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Blood proteins	Complement, various lectins and agglutinins	Antibodies
Cells	Phagocytes (macrophages, neutrophils), dendritic cells, natural killer cells, mast cells, innate lymphoid cells	Lymphocytes

TABLE 1.3 Features of Innate and Adaptive Immunity

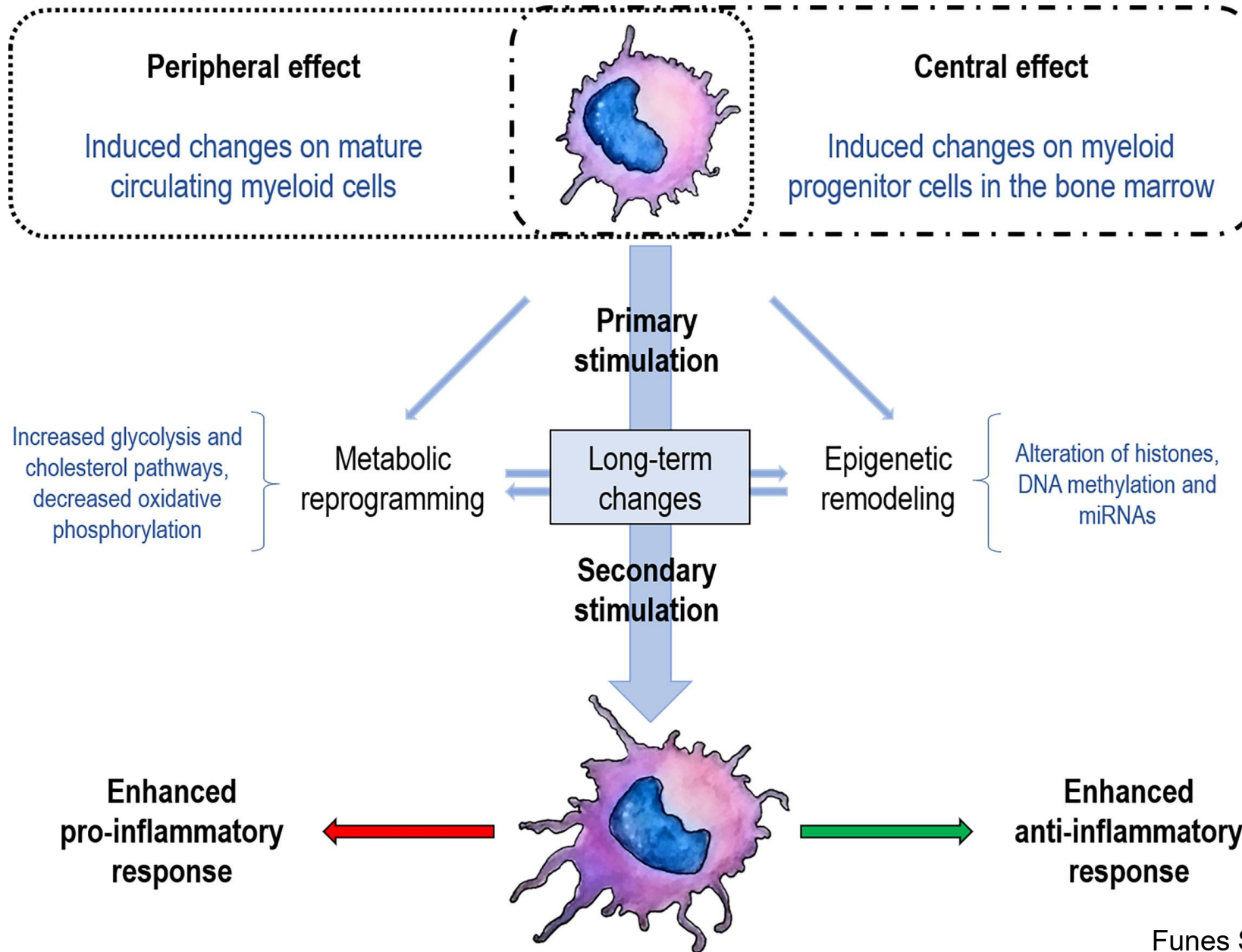
	Innate	Adaptive
Characteristics		
Specificity	For molecules shared by groups of related microbes and molecules produced by damaged host cells	For many different microbial and nonmicrobial antigens
Diversity	Low; recognition molecules encoded by inherited (germline) genes	Very high; antigen receptors are generated by somatic recombination of gene segments in lymphocytes
Memory	Limited	Yes
Nonreactivity to self	Yes	Yes
Components		
Cellular and chemical barriers	Skin, mucosal epithelia; antimicrobial molecules	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Secreted proteins	Complement, various lectins	Antibodies
Cells	Phagocytes (macrophages, neutrophils), dendritic cells, natural killer cells, mast cells, eosinophils, innate lymphoid cells	Lymphocytes (B and T)

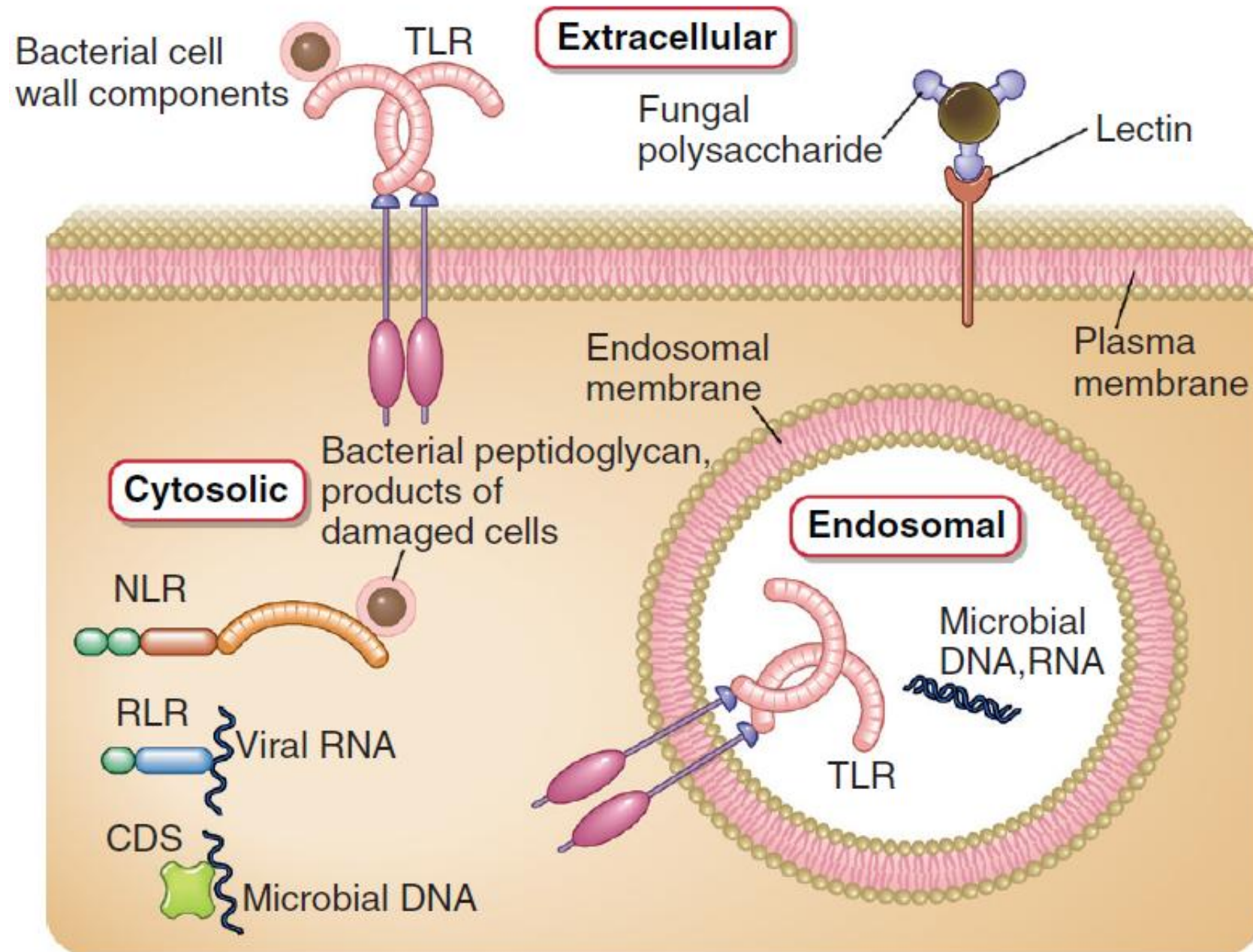
Characteristics of Trained Innate Immunity (innate Immune memory)

Cell Host & Microbe
Perspective

- Is induced **after a primary infection or vaccination**, and confers **protection against a secondary infection through mechanisms independent of T/B cell adaptive responses**.
- Increases resistance of the host to reinfection, but **is less specific than adaptive immunity** and thus may provide cross-protection to other infections.
- The mechanisms involve cells such as **macrophages** and **NK cells**, and entail improved pathogen recognition by PRRs and an **enhanced protective inflammatory response**.

Trained immunity concepts

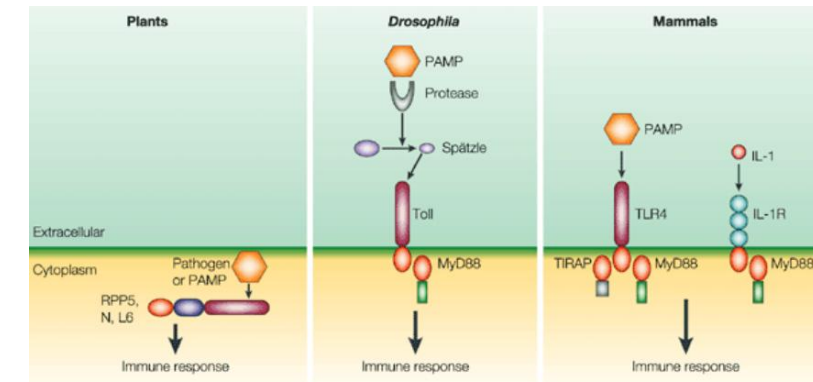
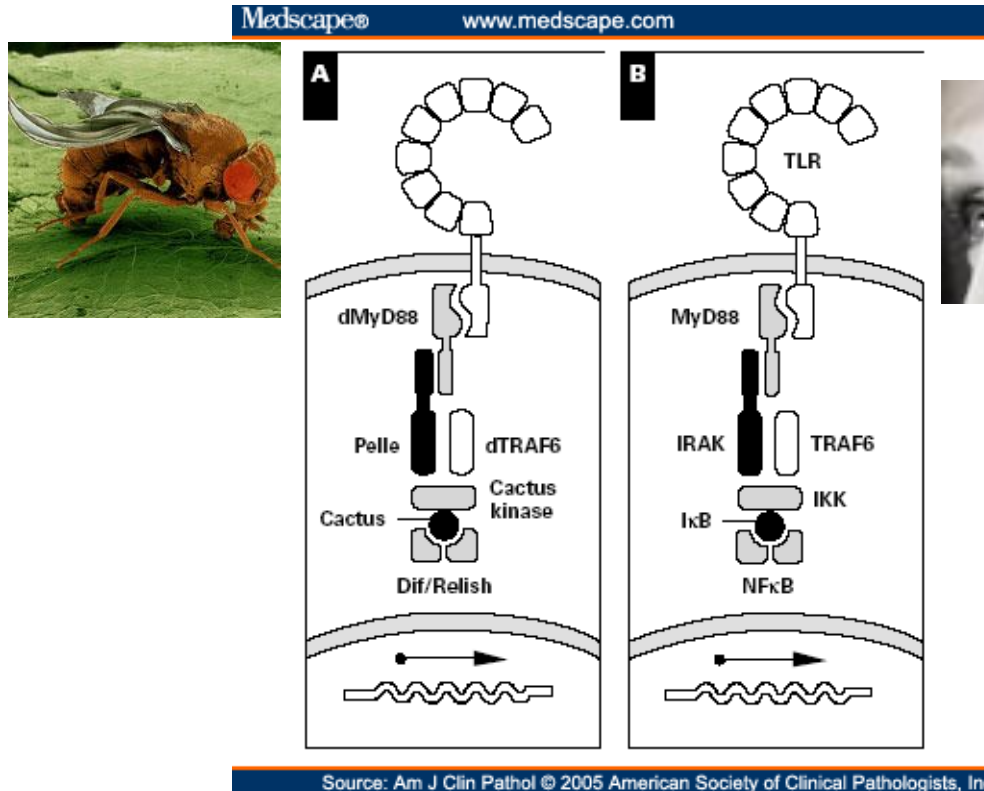




PRRs (pattern recognition receptors):
 οι υποδοχείς των
 κυττάρων της φυσικής
 ανοσίας (Μφ, Dcs, PMNs)

Toll Like Receptors (TLRs):

- ✓ περιγράφηκαν για πρώτη φορά στη Δροσόφιλα (Nuesslein-Volhard, 1985)
- ✓ ρόλος στην ανοσία της Δροσόφιλας (Hoffmann 1996)
- ✓ ενεργοποίηση επίκτητης ανοσίας (Medzhitov & Janeway 1997)
- ✓ στον άνθρωπο 11 TLRs
- ✓ πυροδοτούν κοινές και ξεχωριστές σηματοδοτικές οδούς



letters to nature

NATURE | VOL 388 | 24 JULY 1997

A human homologue of the *Drosophila* Toll protein signals activation of adaptive immunity

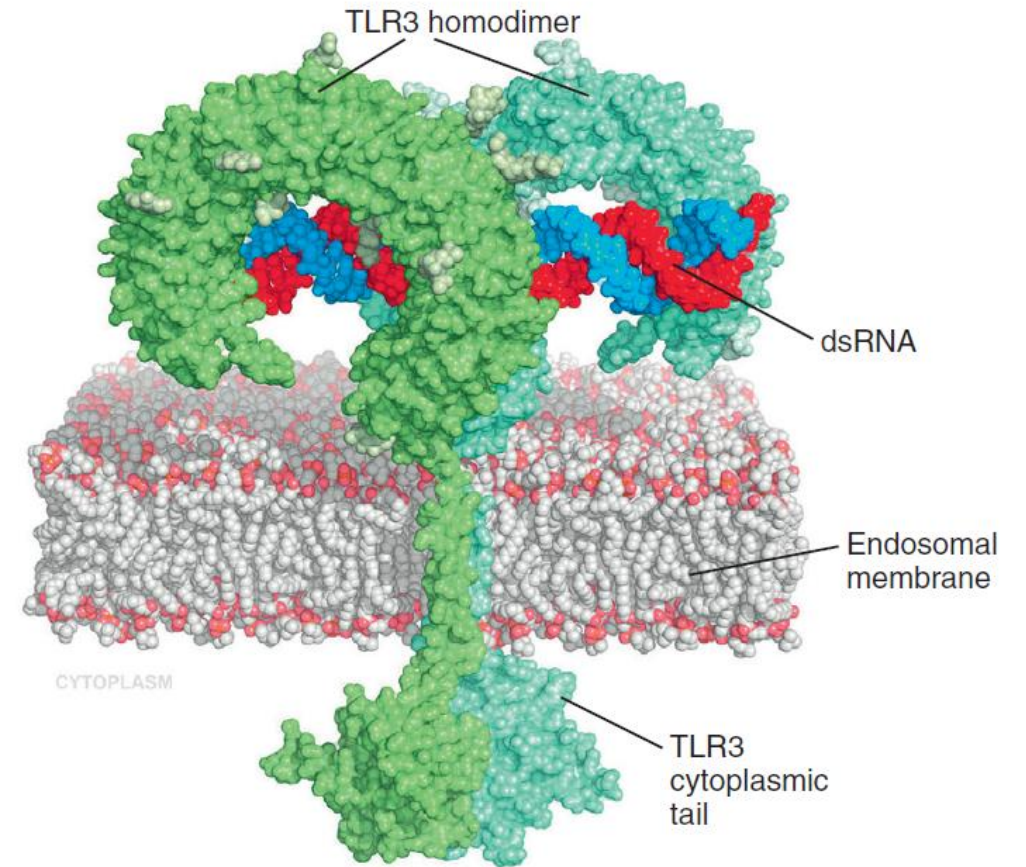
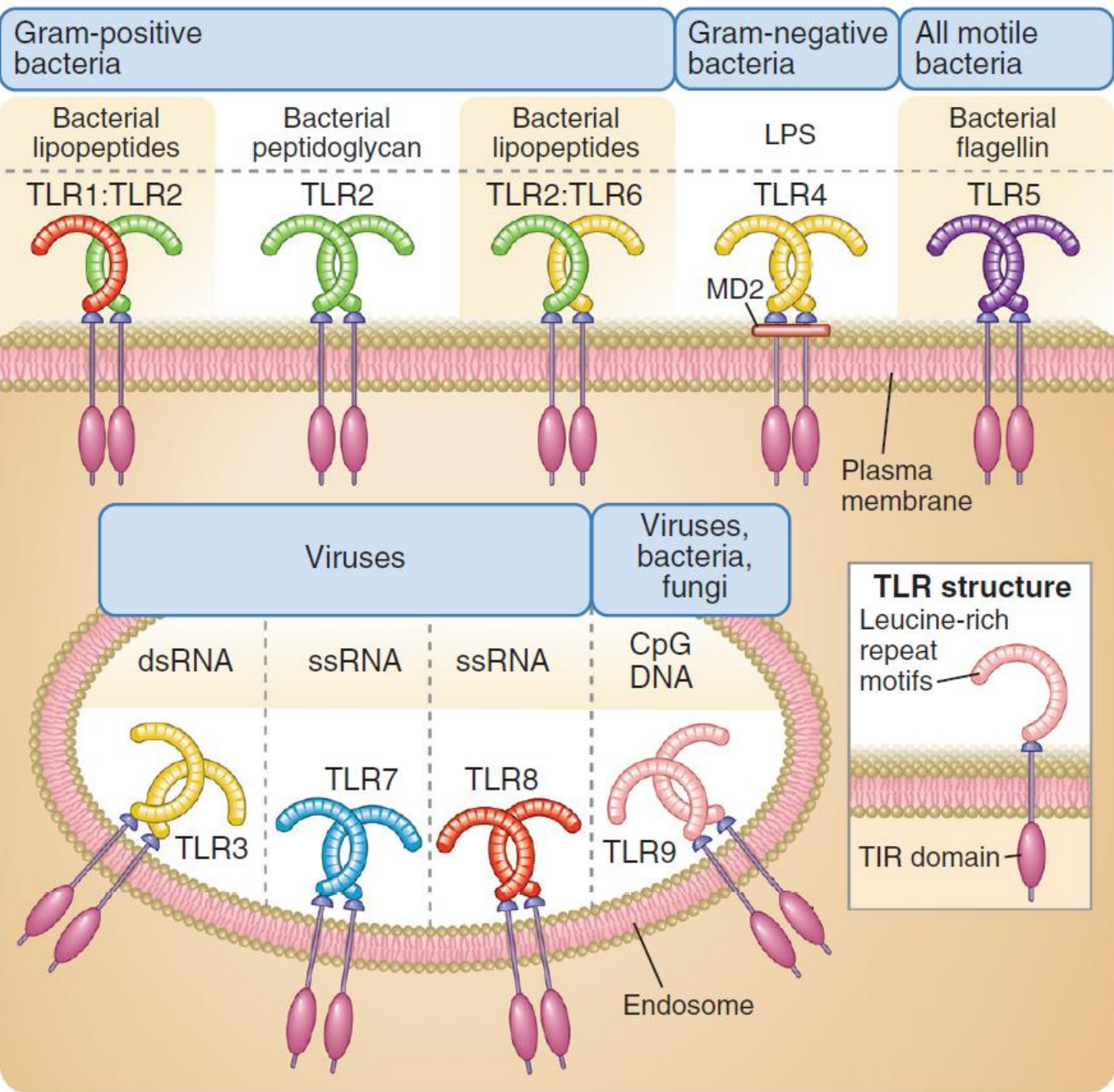
Ruslan Medzhitov*, Paula Preston-Hurlburt
& Charles A. Janeway Jr*

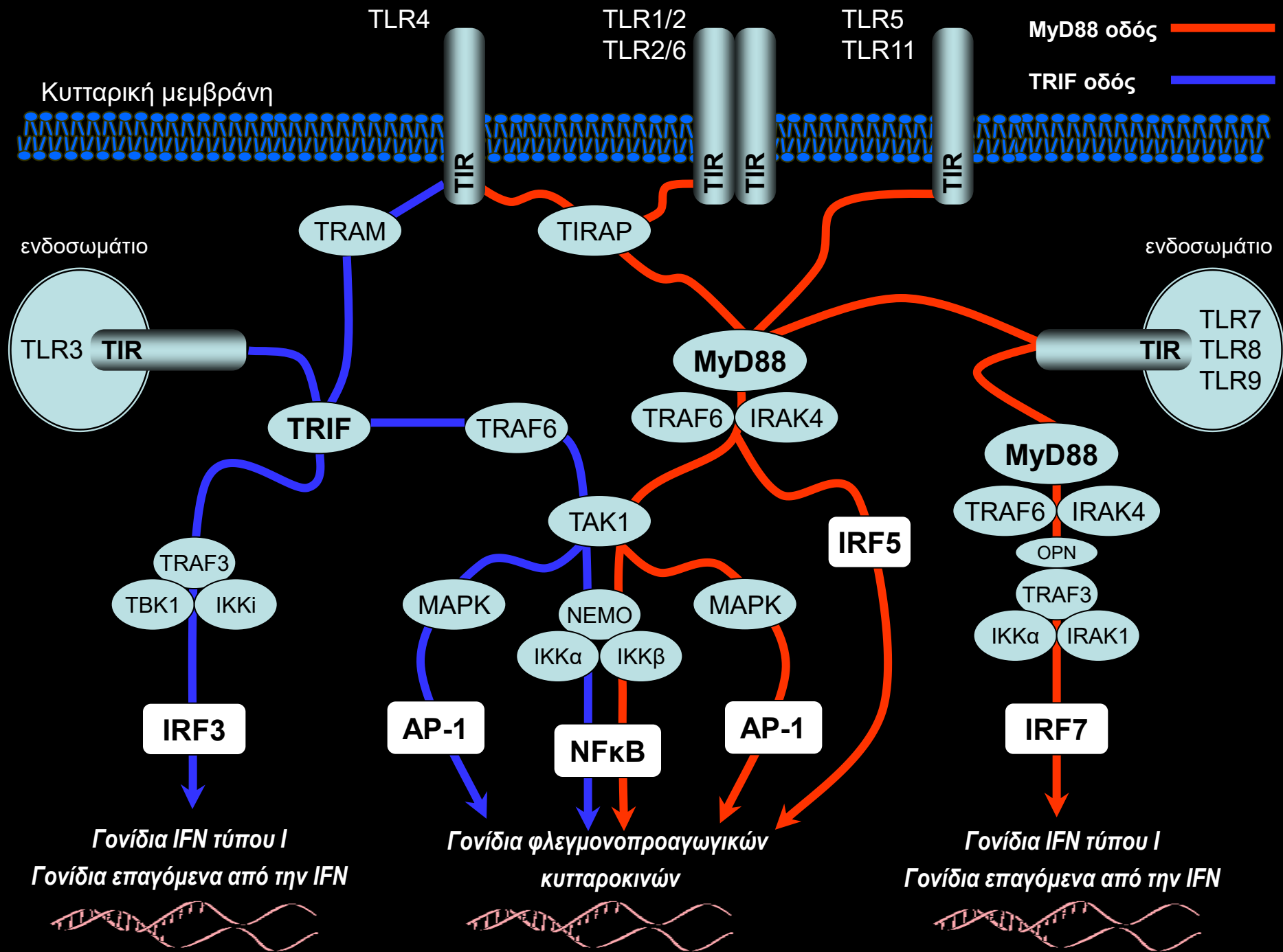
Section of Immunobiology, Yale University School of Medicine, and * Howard Hughes Medical Institute, New Haven, Connecticut 06520-8011, USA

TLR κυτταρική κατανομή

Υποδοχέας	Τύπος κυττάρου
TLR1	παντού
TLR2	ΔΚ, ΠΜΠ, και ΜΚ
TLR3	ΔΚ και ΝΚ, επάγεται στα επιθηλιακά και ενδοθηλιακά
TLR4	Μφ, ΠΜΠ, ΔΚ, ενδοθηλιακά
TLR5	ΜΚ, ανώριμα ΔΚ, επιθηλιακά, ΝΚ και Τ
TLR6	Υψηλή έκφραση στα Β, χαμηλή στα ΜΚ και ΝΚ
TLR7	Β, πλασματοκυτταροειδή ΔΚ
TLR8	ΜΚ, χαμηλή στα ΝΚ και Τ
TLR9	πλασματοκυτταροειδή ΔΚ, Β, Μφ, ΠΜΠ, ΝΚ, και μικρογλοιακά
TLR10	Β, πλασματοκυτταροειδή ΔΚ
TLR11	ΜΚ/Μφ, ηπαρ, νεφρός, ουροθήλιο

Οι περισσότεροι ιστοί εκφράζουν τουλάχιστον έναν TLR





Οδός Σηματοδότησης TLR: Δύο Κύριοι Άξονες



Identification of the “inflammasome”: a major breakthrough in the field of innate immunity & autoinflammation

Molecular Cell, Vol. 10, 417–426, August, 2002, Copyright ©2002 by Cell Press

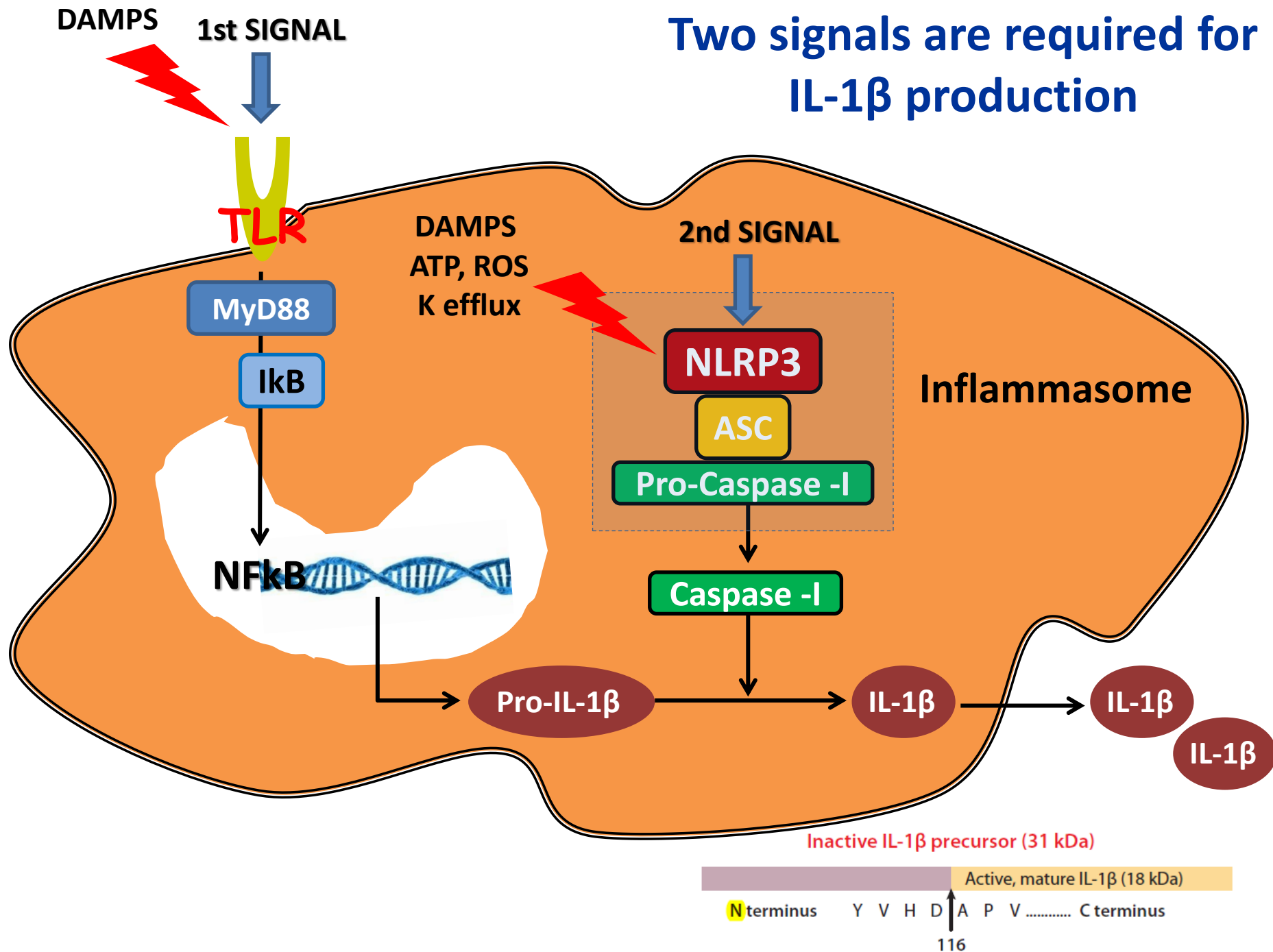


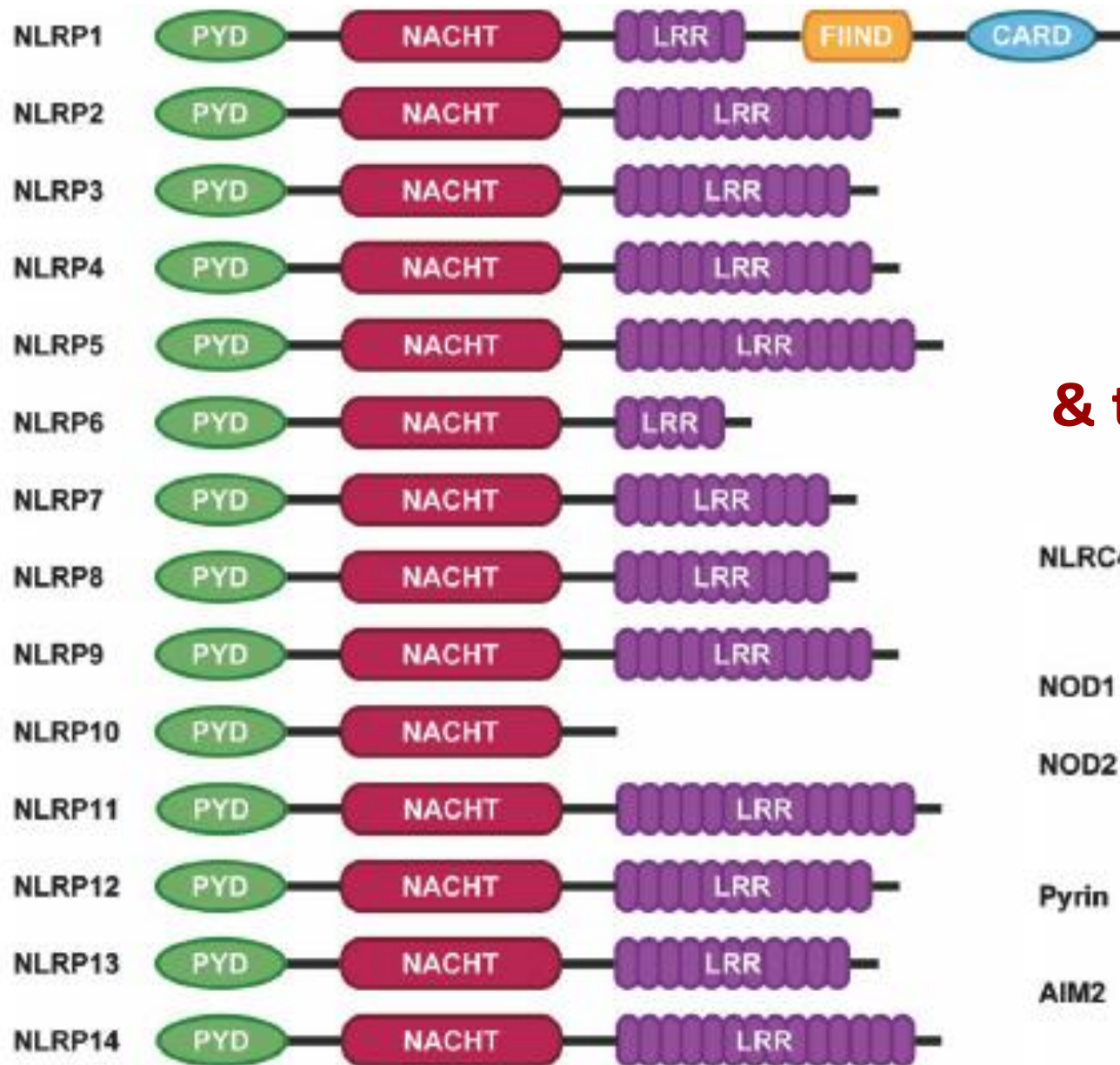
The Inflammasome: A Molecular Platform Triggering Activation of Inflammatory Caspases and Processing of proIL- β

Fabio Martinon, Kimberly Burns,
and Jürg Tschopp¹
Institute of Biochemistry
University of Lausanne
BIL Biomedical Research Center
Chemin des Boveresses 155
CH-1066 Epalinges
Switzerland

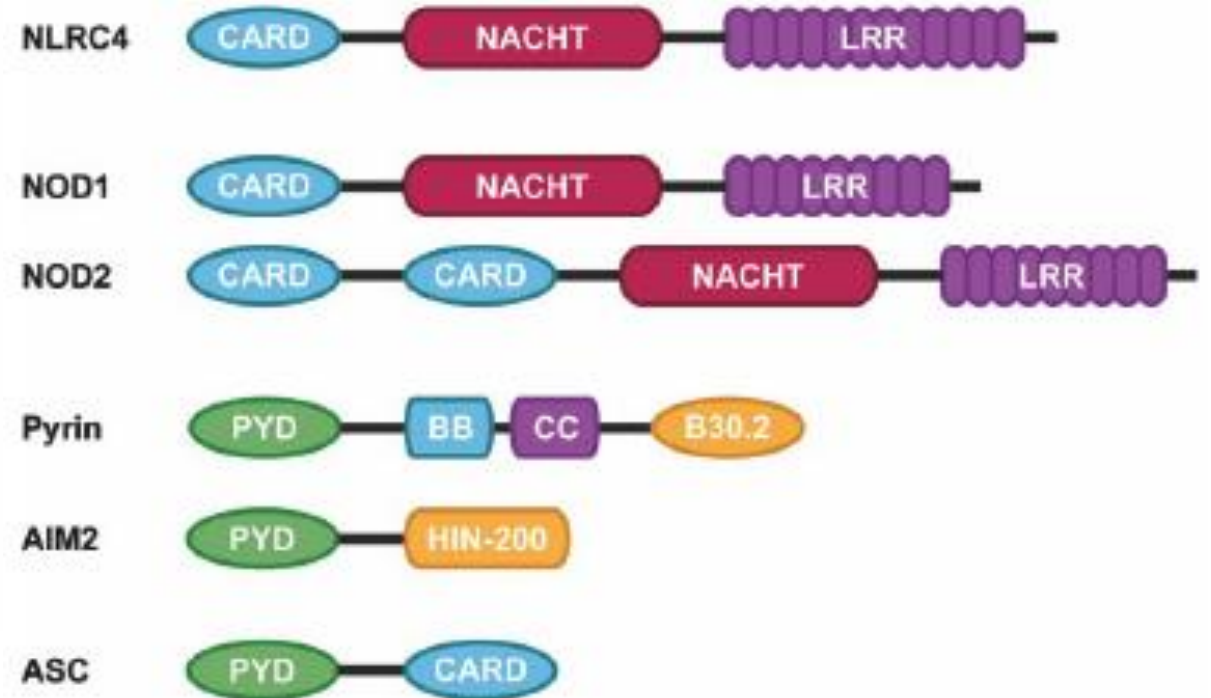
that they possess several distinct protein/protein interaction domains which are used to assemble large multi-component complexes. Apaf-1, for example, contains an N-terminal CARD followed by a NBS/self-oligomerization domain and a C-terminal WD-40 repeat (Jaroszewski et al., 2000; Koonin and Aravind, 2000; van der Biezen and Jones, 1998) (Figure 1A). Via these domains, Apaf-1 assembles a complex (called the apoptosome)

Two signals are required for IL-1 β production





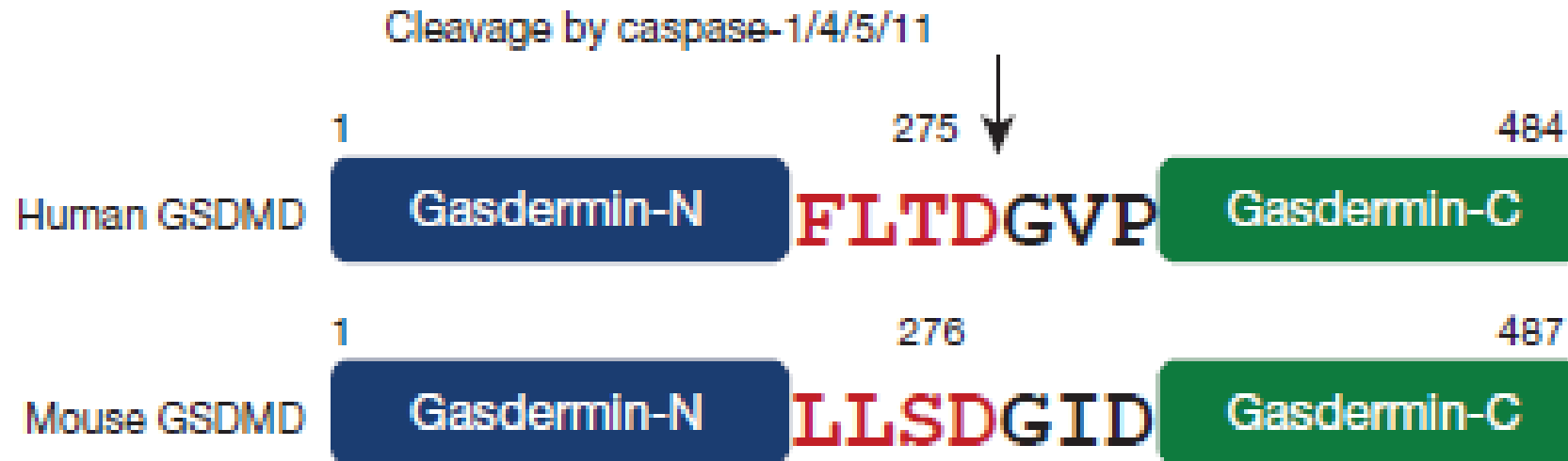
NOD-like Receptors, AIM2, & the Adaptor Protein ASC



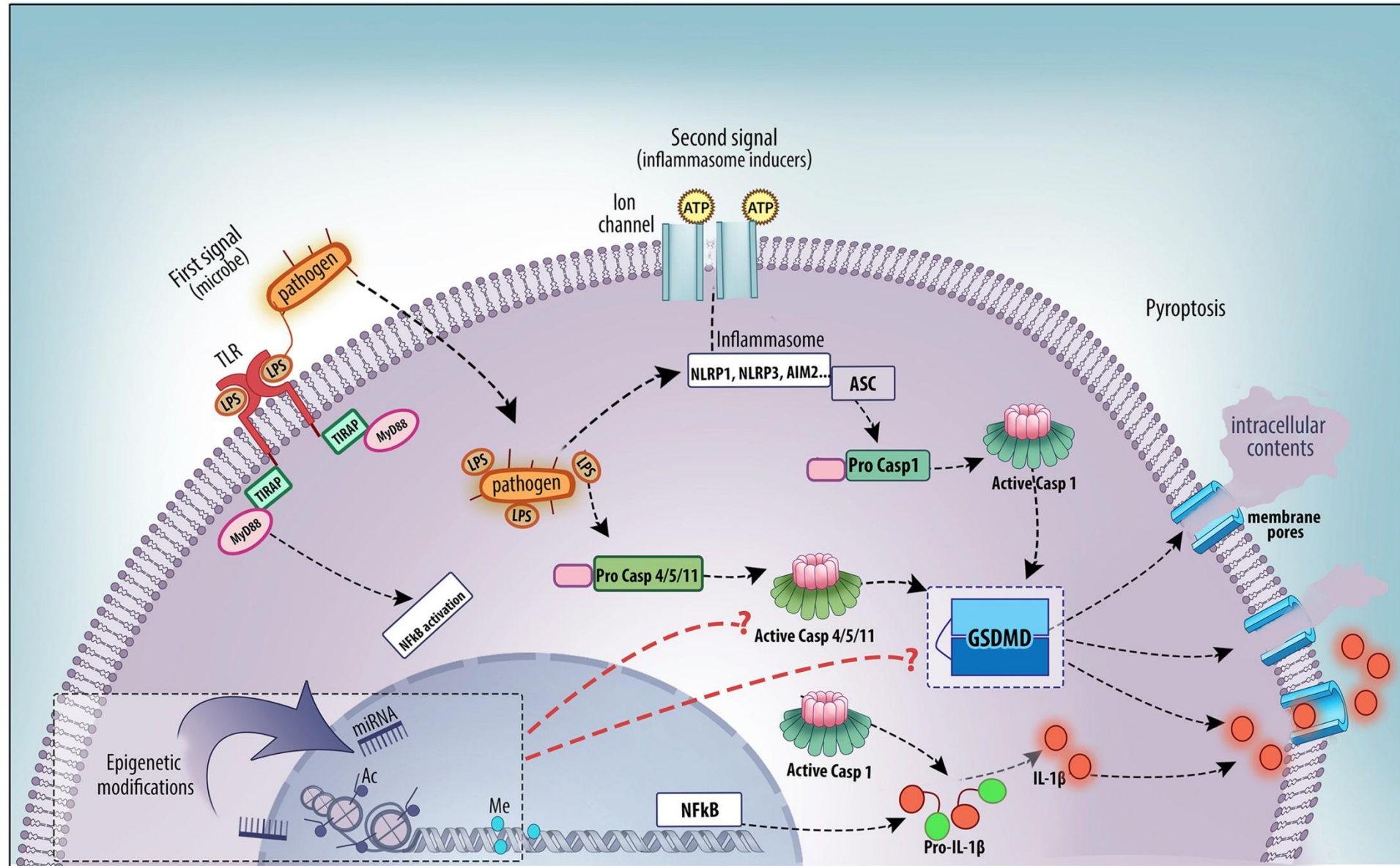
Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death

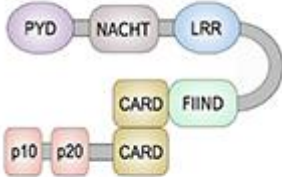
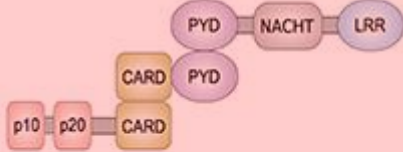
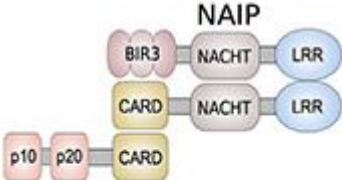
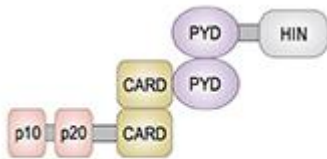
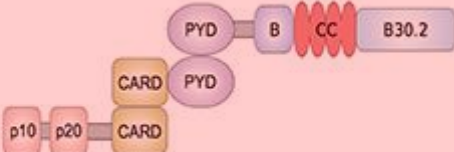
Jianjin Shi^{1,2*}, Yue Zhao^{2*}, Kun Wang², Xuyan Shi², Yue Wang², Huanwei Huang², Yinghua Zhuang², Tao Cai², Fengchao Wang² & Feng Shao^{2,3,4}

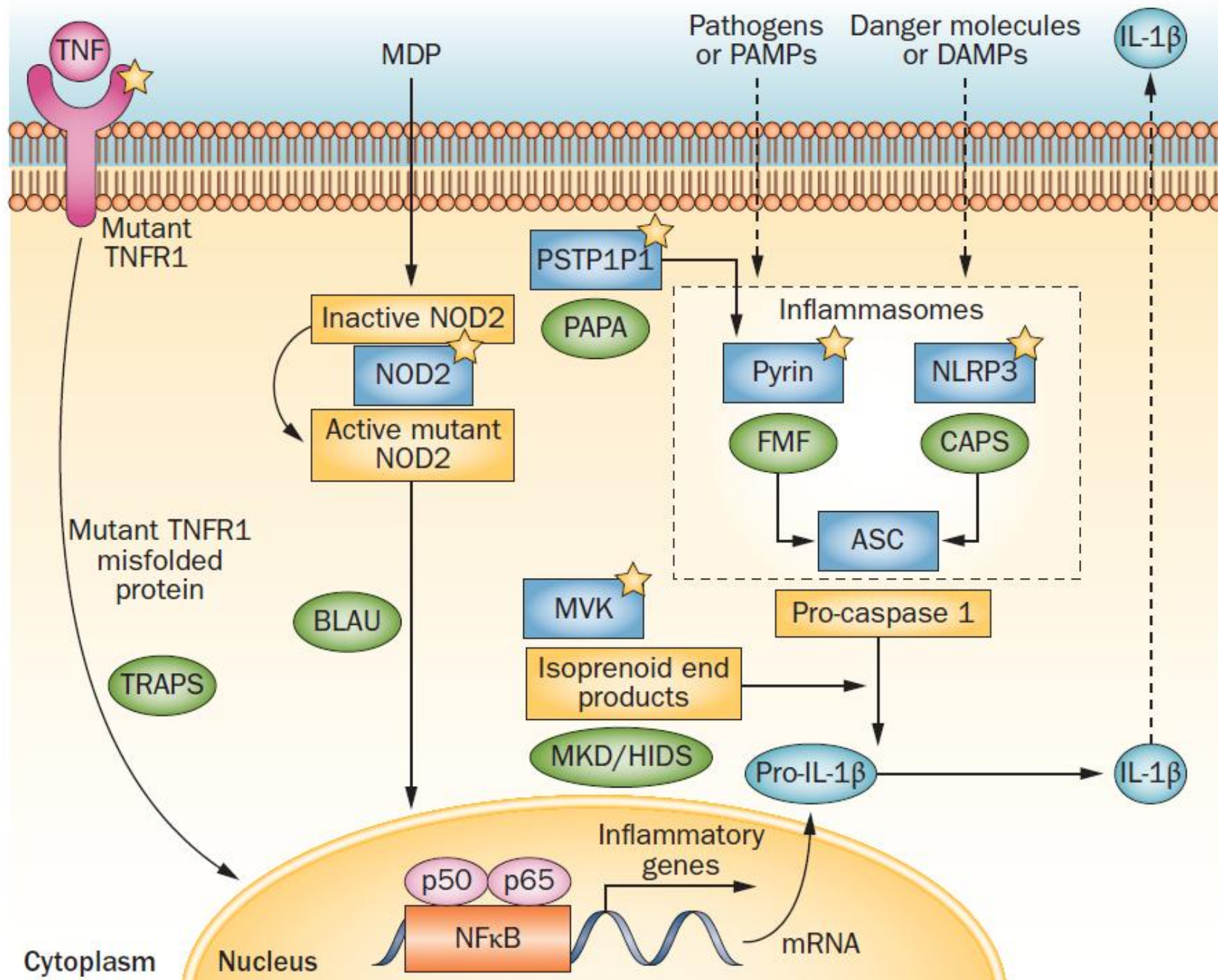
NATURE | VOL 526 | 29 OCTOBER 2015



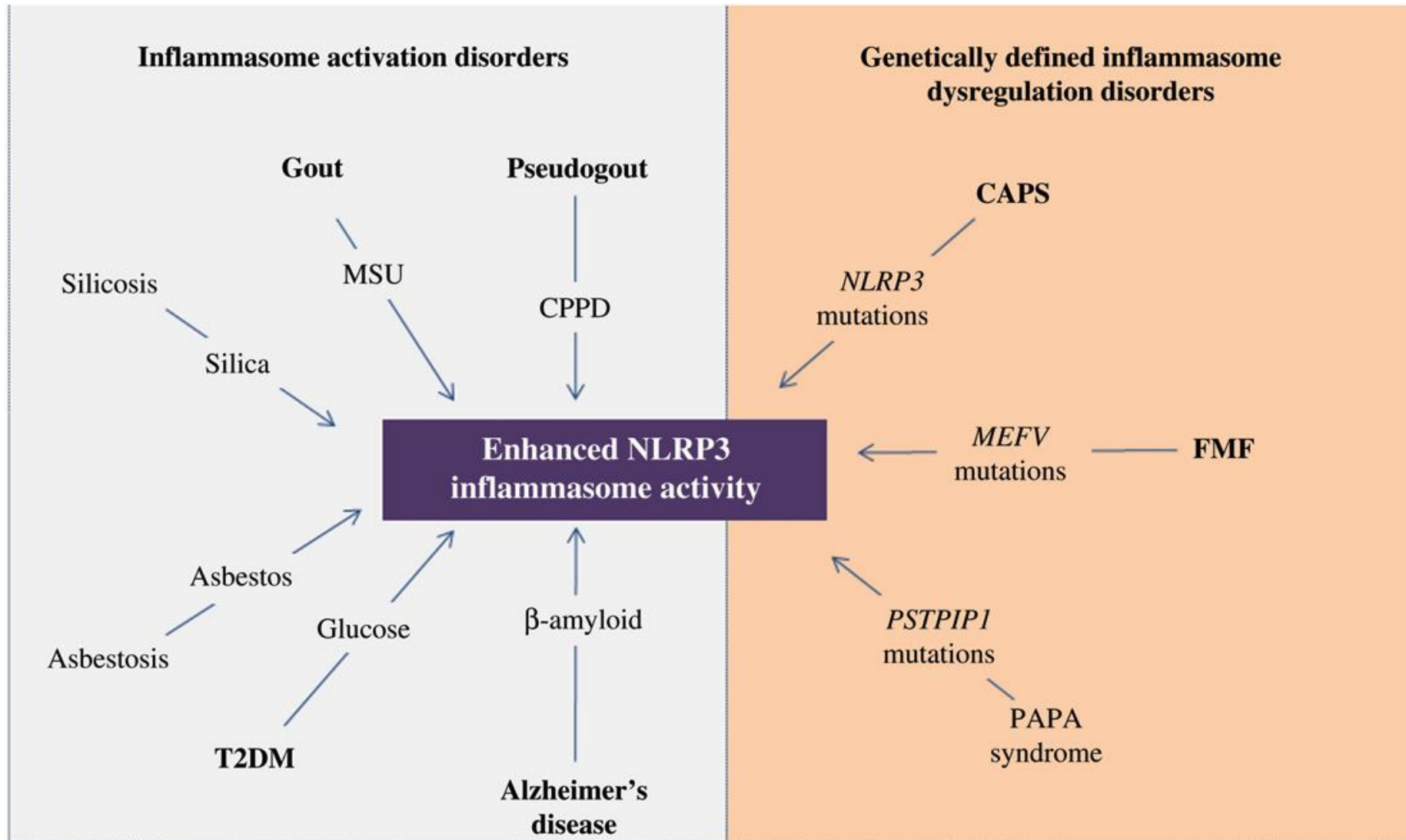
Gasdermin D (GSDMD): A new player to the inflammasome



Inflammasome	Structure	Stimulation signal	Downstream signal	Monogenic associated disorders
NLRP1		Bacterial toxins, (i.e. <i>Bacillus anthracis</i> toxin), intracellular ATP depletion, muramyl dipeptide	Auto-cleavage of FIIND	NLRP1-associated autoinflammation with arthritis and dyskeratosis Crohn's disease (NAIAD); familial keratosis lichenoides chronica (FKLC); multiple self-healing palmoplantar carcinoma (MSCP)
NLRP3		Extracellular ATP, Pore forming toxins (i.e. Nigericin), Crystalline, Particulate structures (silica, alum, asbestos, amyloid-β)	ROS, K ⁺ efflux, intracellular Ca ²⁺ , cAMP, phagosomal rupture	Cryopyrin-associated periodic syndromes (CAPS); familial cold autoinflammatory syndrome (FACS); Muckle-Wells syndrome (MWS); neonatal-onset multisystem inflammatory disease (NOMID/CINCA)
NLRC4		Cytosolic flagellin (i.e. <i>Salmonella typhimurium</i>), Type III secretion system components (i.e. <i>Escherichia coli</i>)	Phosphorylation (Pkc δ kinase)	Syndrome of enterocolitis and autoinflammation associated with mutation in NLRC4 (SCAN4); macrophage activation syndrome (MAS)
AIM2		Cytosolic dsDNA from DNA viruses or cytosolic bacteria (i.e. papillomavirus, <i>Mycobacterium tuberculosis</i>)	Direct recognition of dsDNA, Pyroptosis	
Pyrin		RhoA-GTPase inactivation (i.e. <i>Bordetella pertussis</i> (pertussis toxin), <i>Burkholderia cenocepacia</i> (TecA), <i>Clostridium botulinum</i> (C3 toxin), <i>Clostridium difficile</i> (TcdB), <i>Histophilus somni</i> (IbpA), <i>Vibrio parahaemolyticus</i> (VopS), <i>Yersinia pestis</i> (Yops))	PKN1/2 inactivation, reduced pyrin 14-3-3 interaction	Familial Mediterranean fever (FMF); pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND); mevalonate kinase deficiency (MKD)/hyperimmunoglobulinemia D syndrome (HIDS); pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome; WDR1 deficiency/PFIT



Disorders that are associated with dysregulation of NLRP3 inflammasome and increased production of IL-1 β



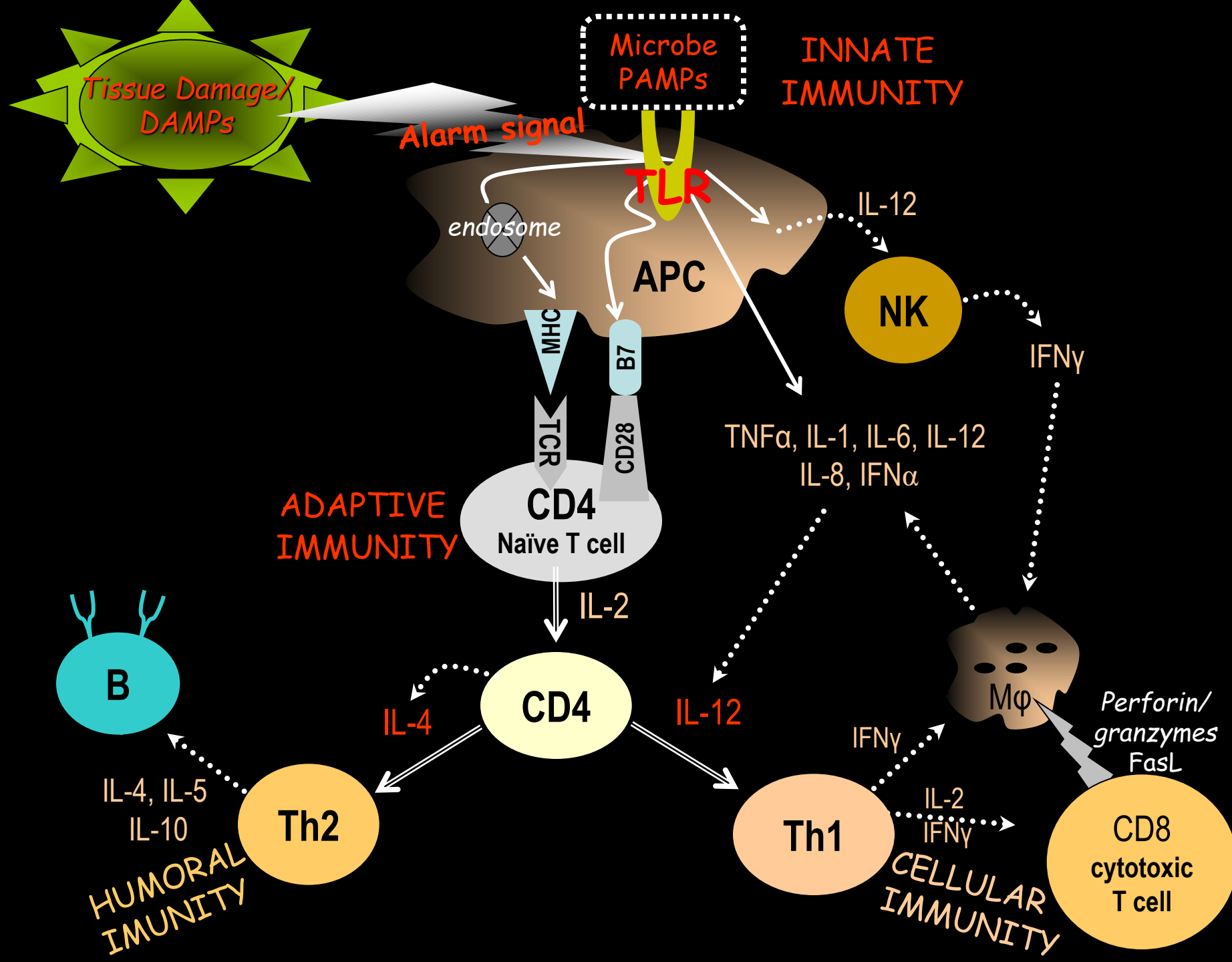
Innate immunity:

Influence the **nature and type** (Th1,Th2)
of adaptive immune response

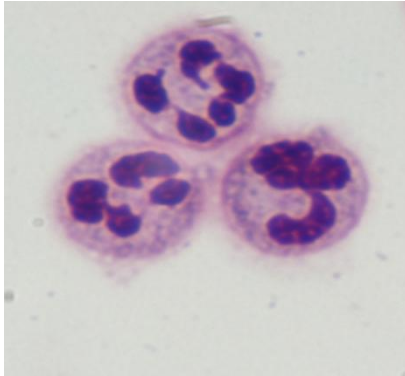
Toll-like receptors control activation of adaptive immune responses

Markus Schnare^{1,2,*}, Gregory M. Barton^{1,2,*}, Agnieszka Czopik Holt¹, Kiyoshi Takeda³, Shizuo Akira³ and Ruslan Medzhitov^{1,2}

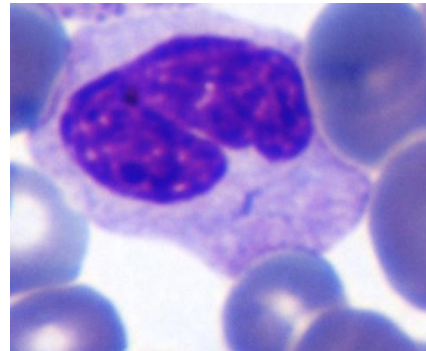
Nature Immunology 2:947 (2001)



Cells of innate immunity

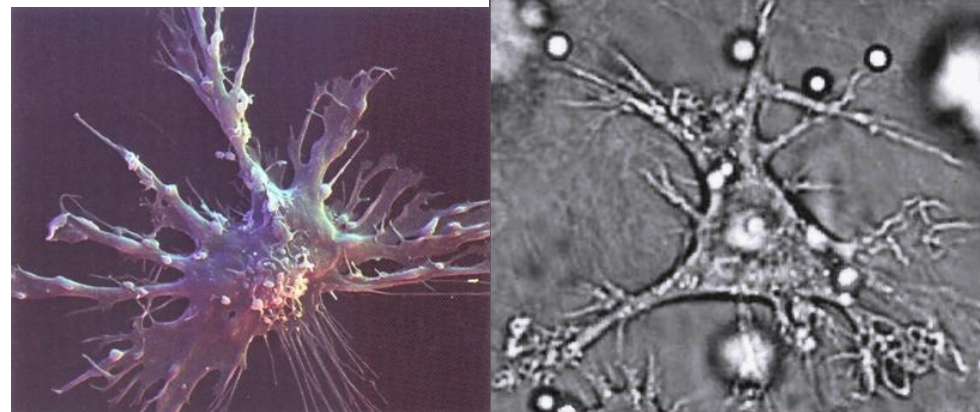
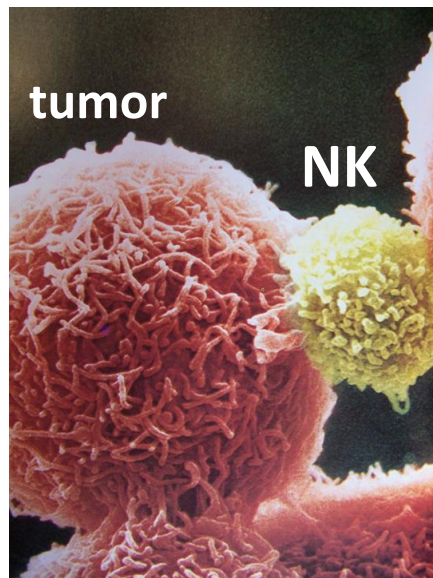


Neutrophils

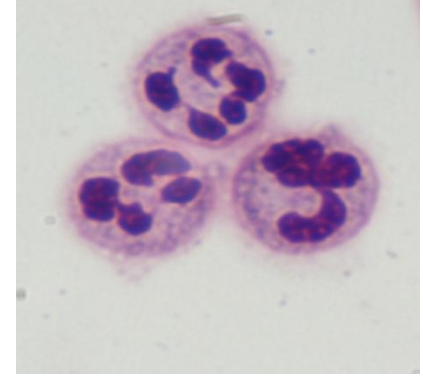


Monocytes/macrophages

Dendritics



Neutrophils (PMNs)



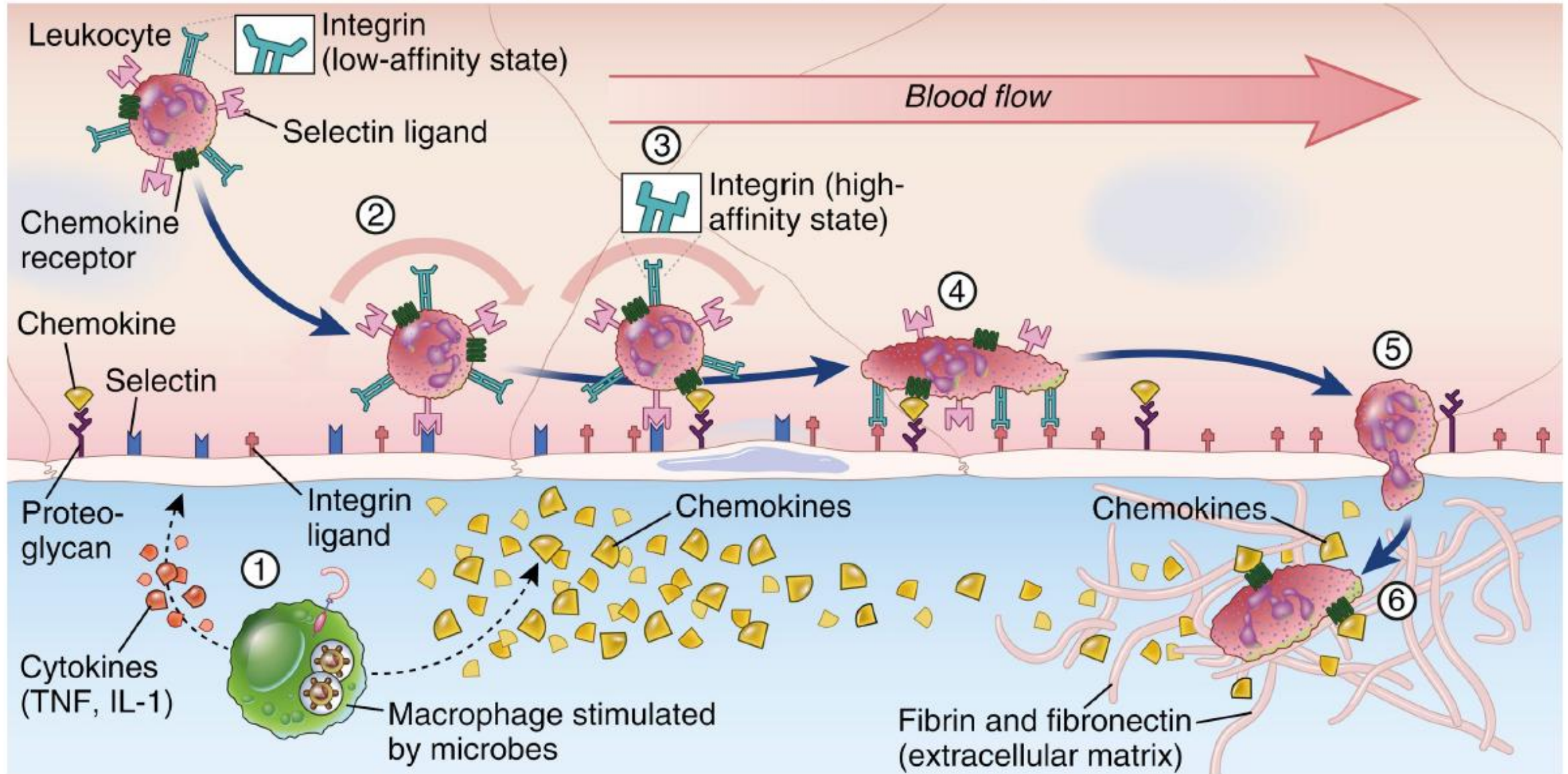
- the most abundant (50-70%) of circulating white blood cells
- Short life-span (18 hours to 4 days)
- arrive first at the site of inflammation
- migrate via chemotaxis (**C5a, IL-8**) toward site of inflammation
- **IL-17 (Th17)** promotes neutrophil action

Rolling

Integrin activation
by chemokines

Stable
adhesion

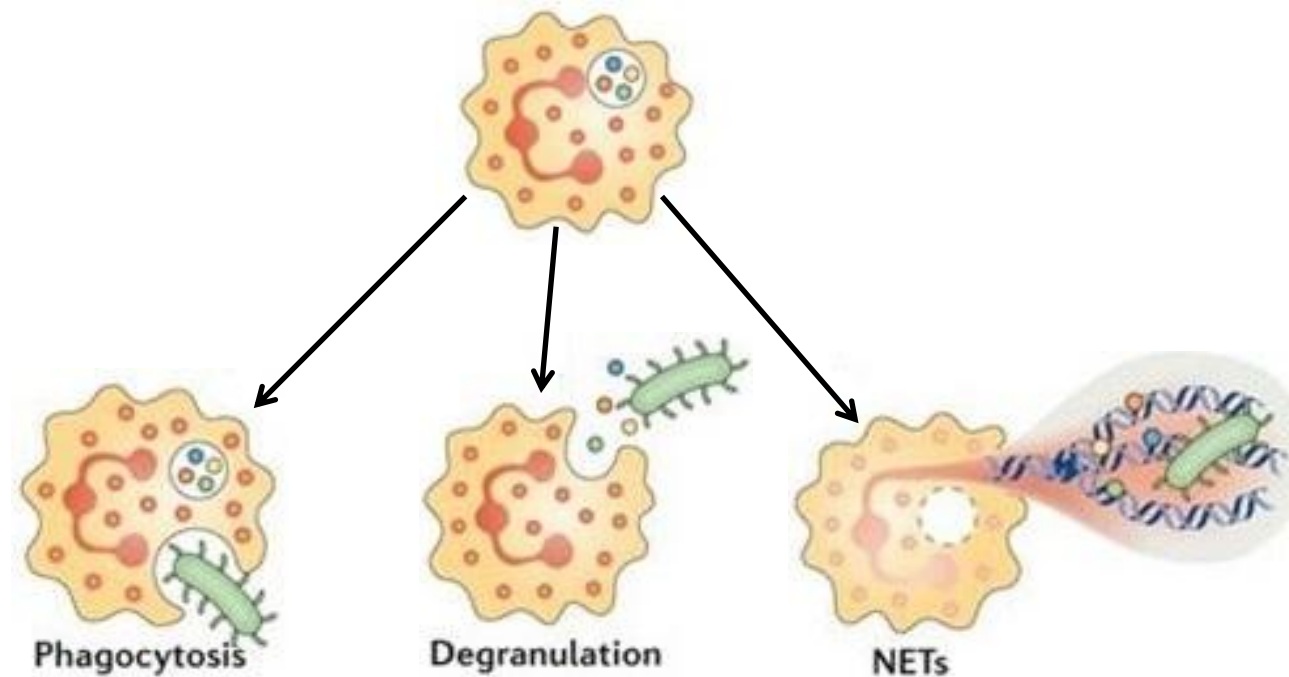
Migration through
endothelium



Granules of neutrophils

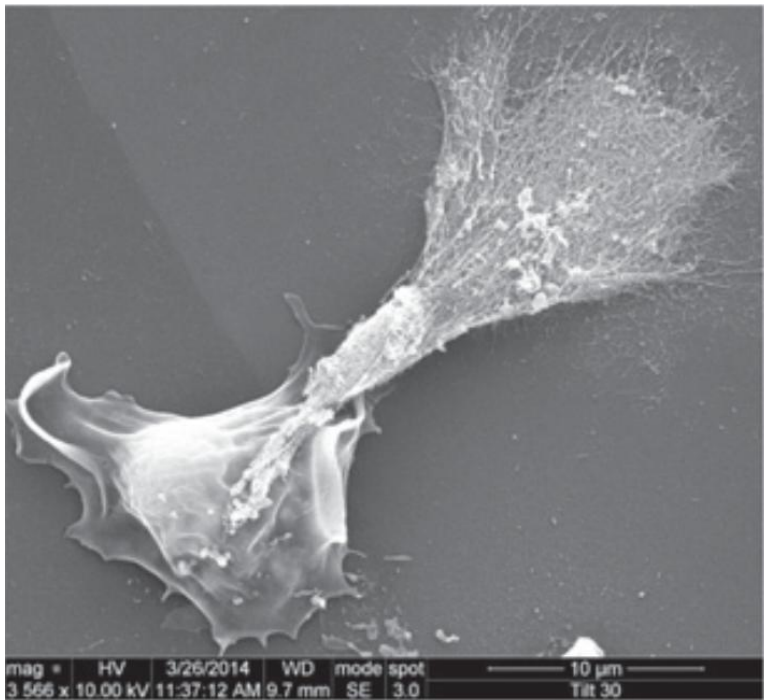
Granule type	Protein
azurophilic granules (or "primary granules")	Myeloperoxidase (MPO) Bactericidal/permeability-increasing protein Defensins Serine proteases neutrophil (elastase, cathepsin G)
specific granules (or "secondary granules")	Alkaline phosphatase Lysozyme NADPH oxidase Collagenase Lactoferrin Cathelicidin (LL-37)
tertiary granules	Cathepsin , gelatinase

Neutrophils employ three strategies to contain and clear the infection

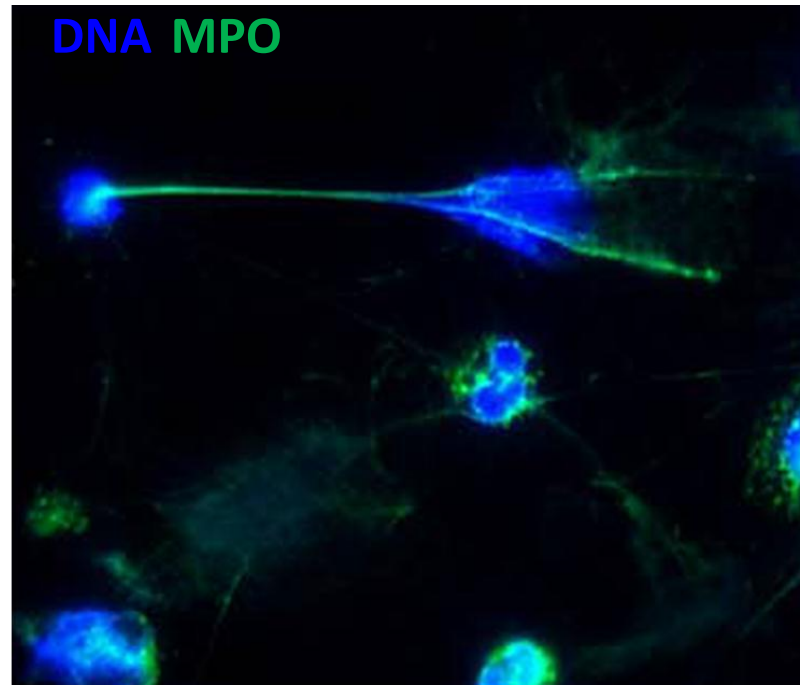


- i. **Phagocytosis:** Involves the engulfment and subsequent elimination of microbes in specialized phagolysosome compartments.
- ii. **Degranulation:** Releases antimicrobial molecules in the vicinity of infection.
- iii. **Neutrophil Extracellular Traps (NETs):** NETs are extracellular neutrophil-derived DNA fibers that trap and kill invading pathogens.

- NETs are composed of **citrullinated chromatin** and **granule constituents** (myeloperoxidase, elastase, defensins etc)
- NETs are released by neutrophils undergoing **phagocytosis** or after activation **by autophagy ROS and various inflammatory mediators**
- Implicated in several disorders including **infections/sepsis, thrombosis, SLE, RA, ANCA+ vasculitis, FMF, gout, psoriasis....**

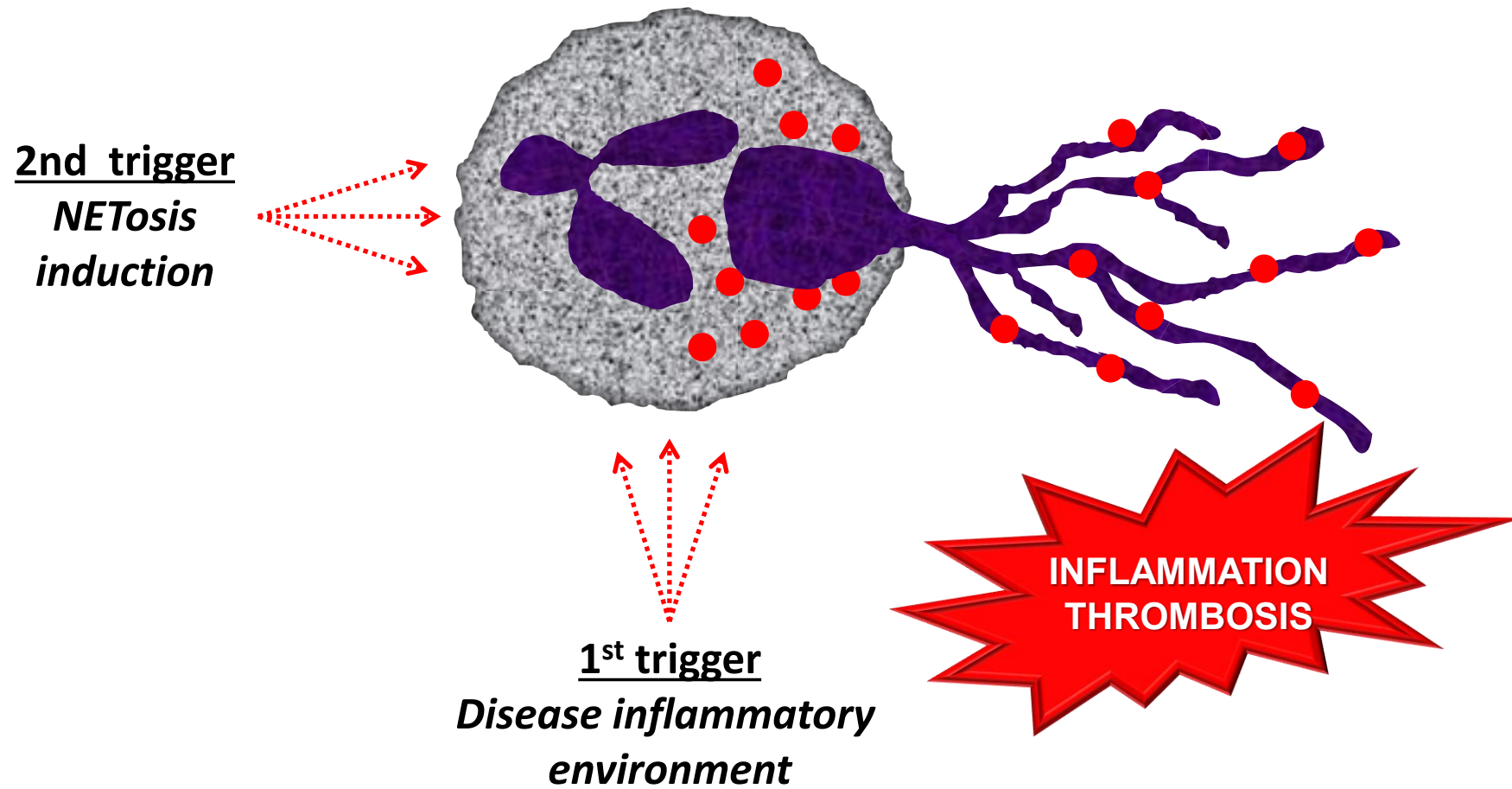


Barnado A et al. J. Leukoc. Biol. 2016



Laboratory of Molecular Hematology,
DUTH, Alexandroupolis, Greece

NET release (NETosis) “Two hits model”



Excess NET formation can drive a variety of severe pathologies

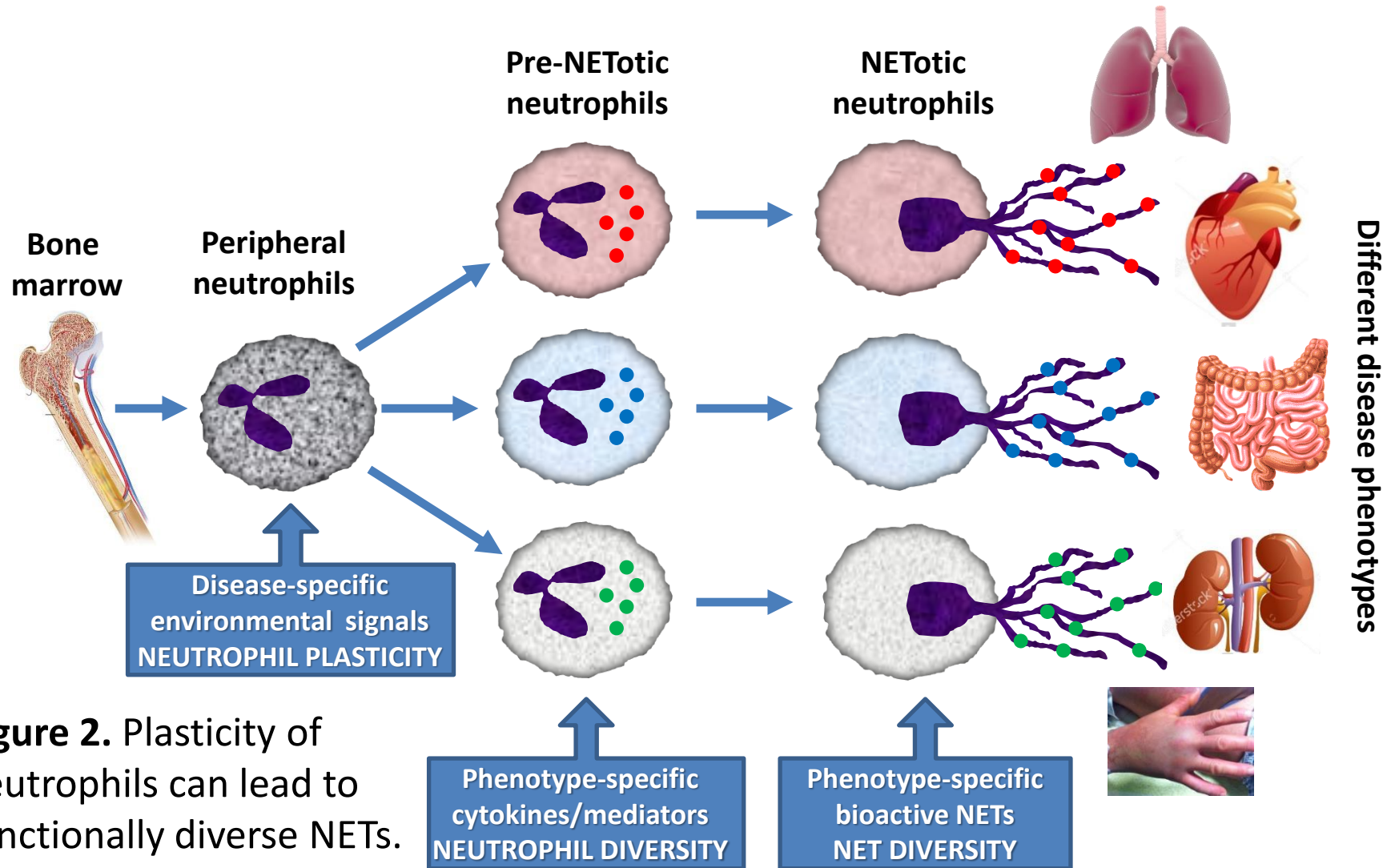
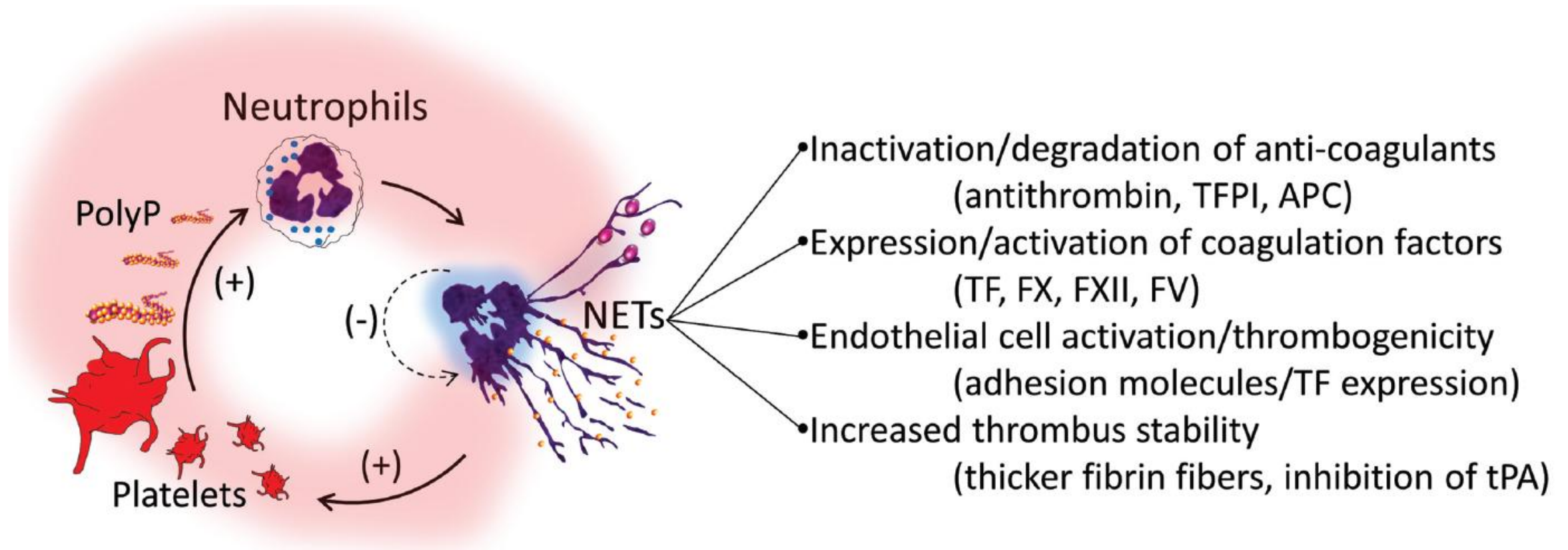


Figure 2. Plasticity of neutrophils can lead to functionally diverse NETs.

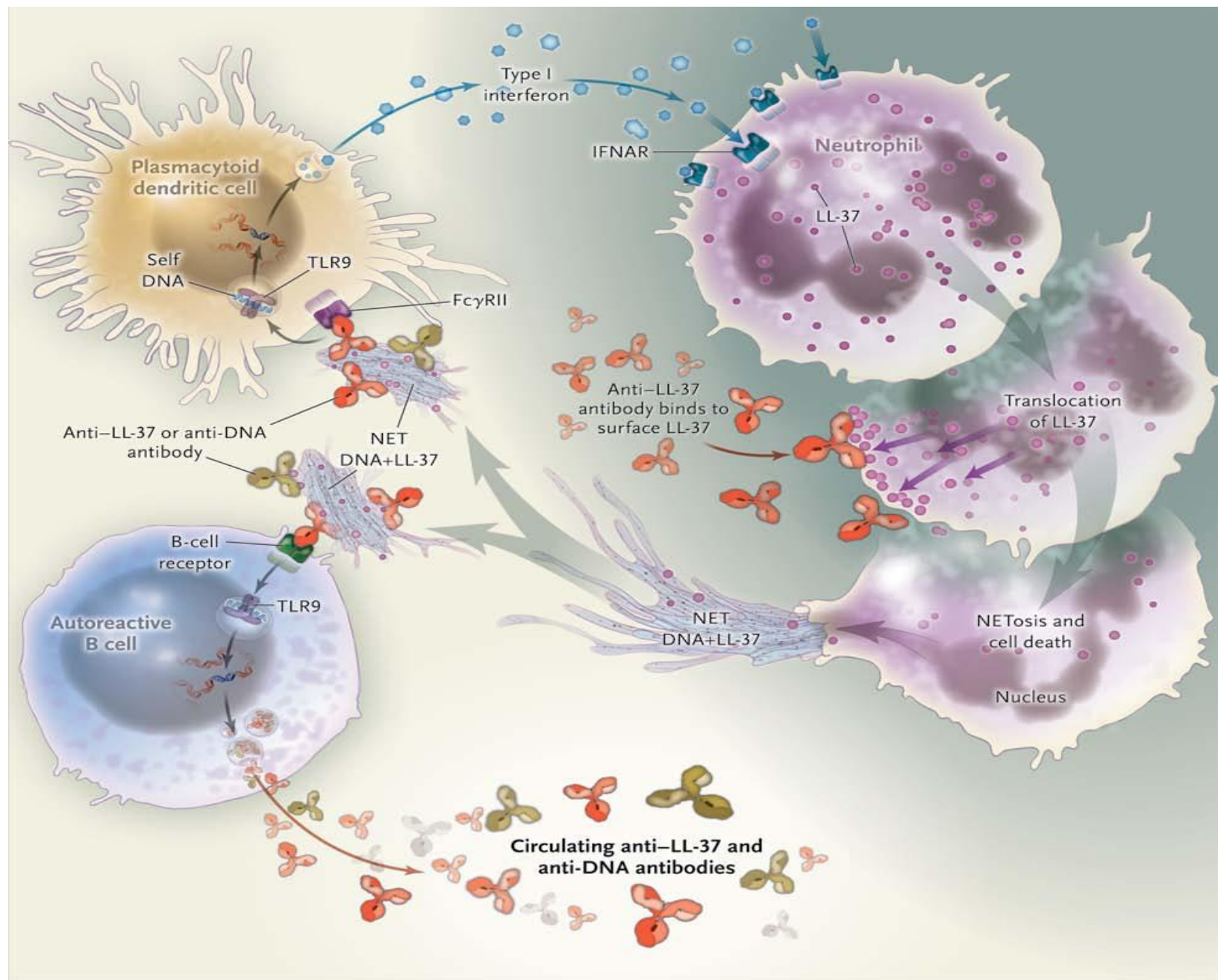
Mechanisms of neutrophil extracellular trap (NET) thrombogenicity



Proteins derived from NETs may serve as self-antigens and mediate organ damage in autoimmune diseases

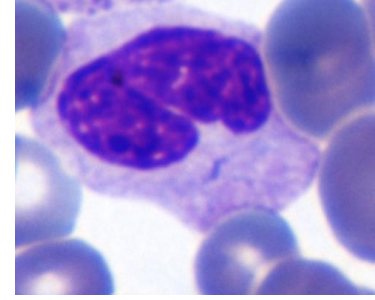
Table 1 | NET proteins with potential roles in autoimmunity.

Protein	Present in disease-specific NETs (by IF)	Present in PMA-induced NETs (by proteomics*)	AutoAbs	Role(s) in auto-immunity
Histones	All (by definition)	Yes	SLE, Felty's	AutoAg in SLE and Felty's; pro-thrombotic
MPO	SLE, psoriasis, SVV, gout	Yes	SVV, SLE	AutoAg in SVV; oxidative stress?
Proteinase 3	SVV	Yes	SVV, SLE	AutoAg in SVV
LL37	SLE	No	SLE	Binds ICs to activate pDCs
HNP/ α -defensins	SLE	Yes	SLE	Binds ICs; predisposes to CVD?
HMGB1	SLE, gout	No	Unknown	Binds ICs; pro-inflammatory
IL-17	SLE, psoriasis	No	SLE, psoriasis	Pro-inflammatory
C1q	SLE	No	SLE	Activates complement; protects from degradation?
Elastase	SLE, psoriasis	Yes	SLE	Unknown
Lactoferrin	Unknown	Yes	SLE	Unknown
Cathespin G	Unknown	Yes	SLE	Unknown
Calprotectin	Unknown	Yes	Unknown	Unknown
α -enolase	Unknown	Yes	SLE	Unknown
Catalase	Unknown	Yes	SLE	Oxidative stress?

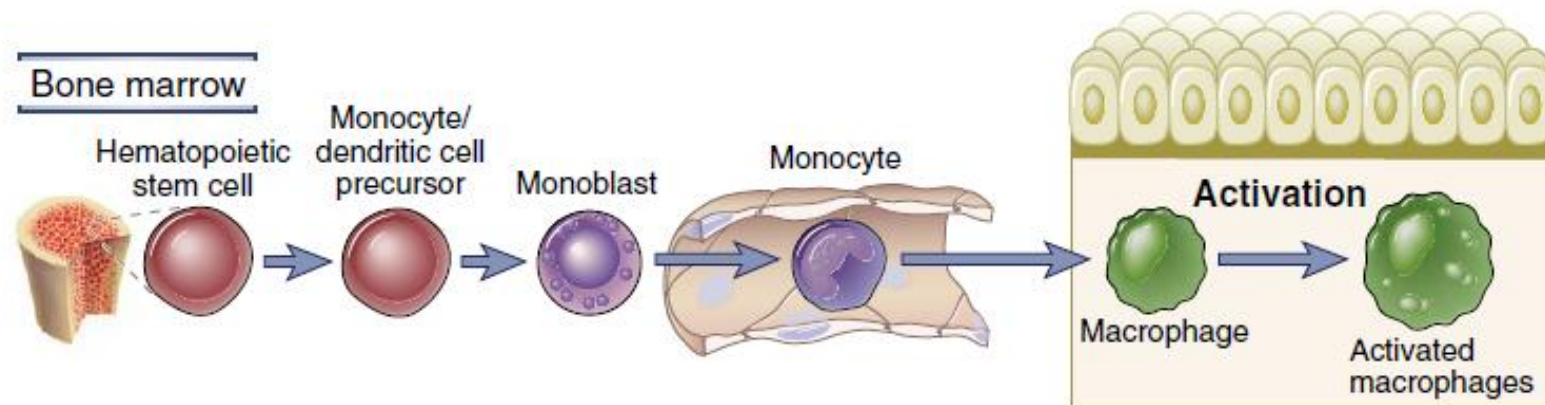


NETs in Lupus, N Eng J Med 2011

Monocytes-Macrophages (Mφ)

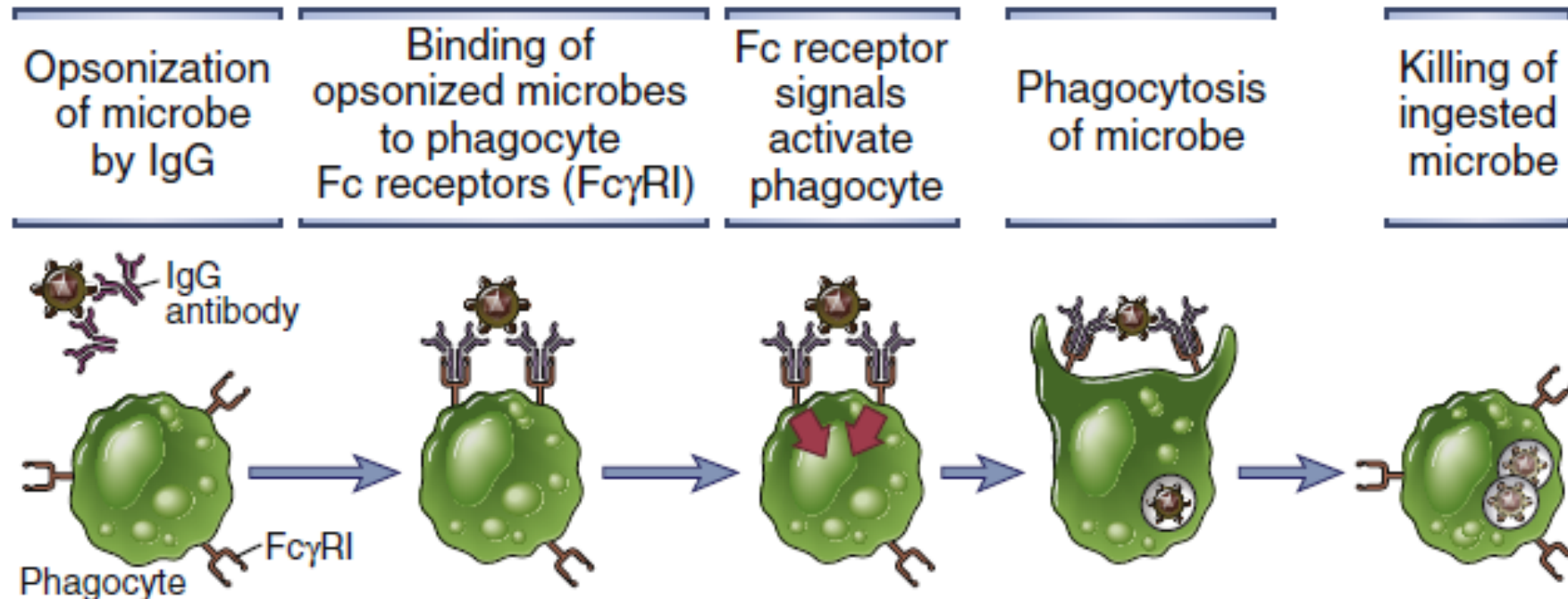


- **Monocytes** arise from the myeloid lineage in the bone marrow
- Circulate in the blood, and are recruited into tissues in inflammatory reactions, where they mature into **macrophages**
- **Phagocytosis**
- **Antigen presentation** (APC: antigen-presenting cell)

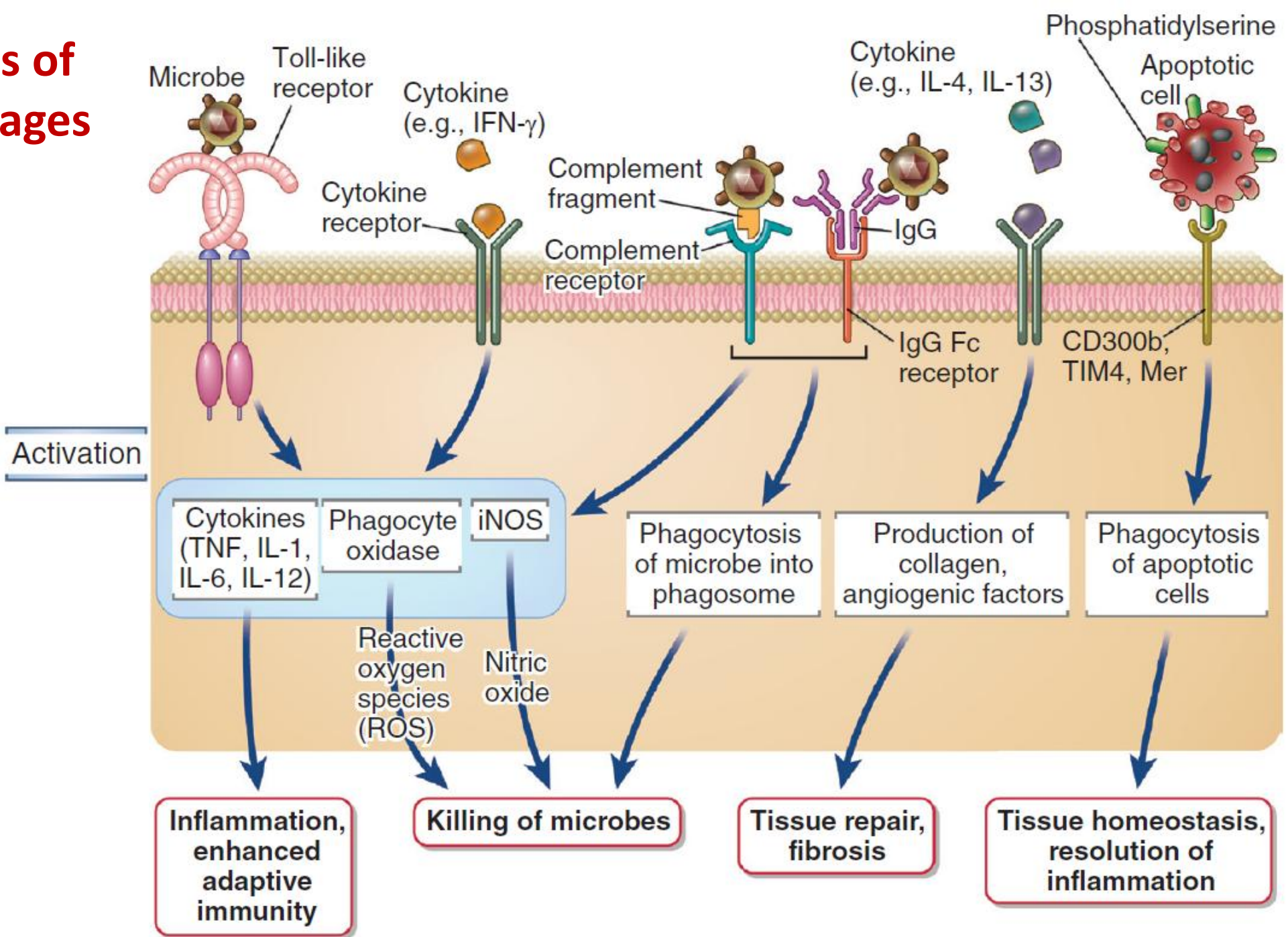


Opsonization

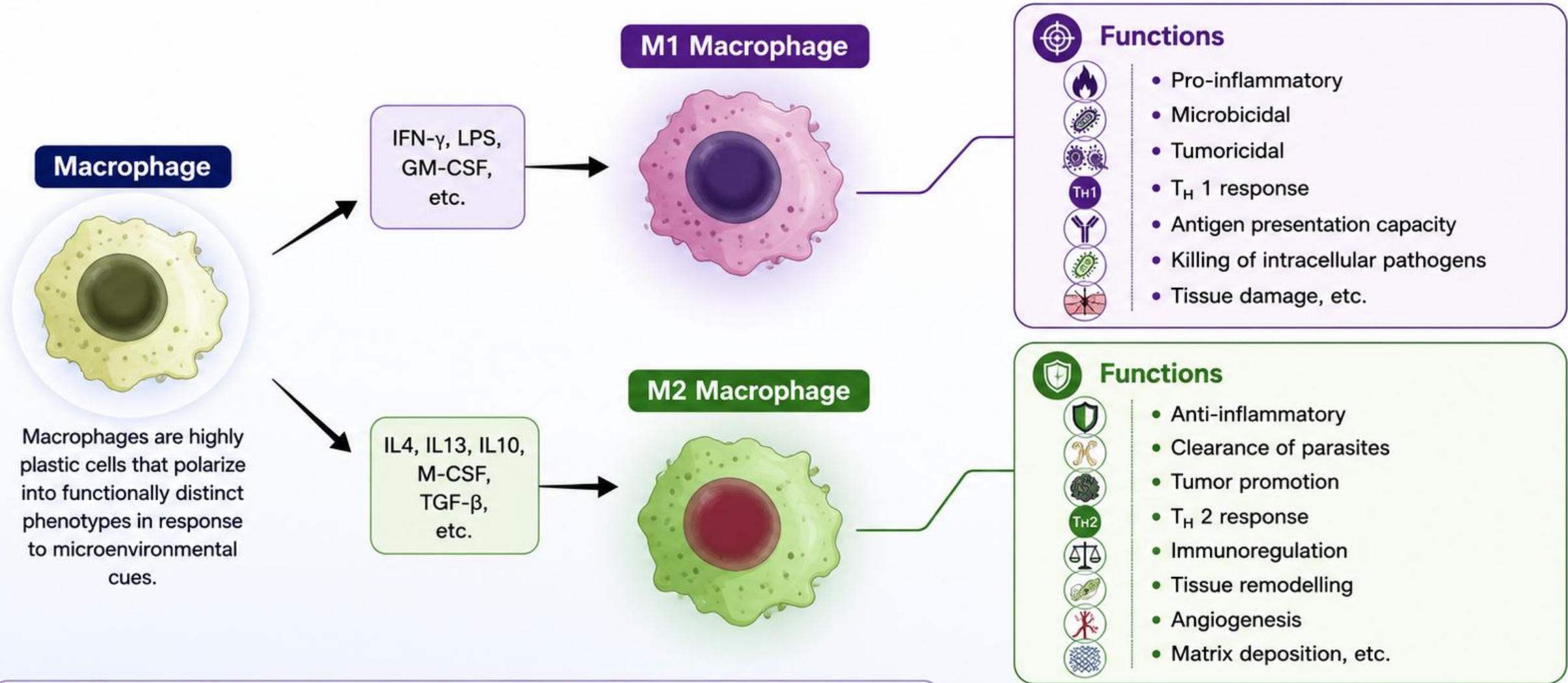
- Robust phagocytosis requires opsonization
- The process of coating particles to promote phagocytosis
- Substances that perform this function (opsonins), including **antibodies (IgG)** and **complement (C3b)**
- **Fcγ** και **CR1** receptors, respectively



Functions of macrophages



Macrophage Polarization and Specific Functions of M1 and M2 Macrophages



Macrophages adapt to environmental cues and polarize into M1 or M2 phenotypes. M1 macrophages drive inflammation and host defense, whereas M2 macrophages promote resolution, repair, and tissue homeostasis.

Ουδετερόφιλα εναντίον Μακροφάγων: Οι Φύλακες του Ανοσοποιητικού

Σύγκριση των δύο βασικών τύπων φαγοκυττάρων: Κατανόηση των διακριτών ρόλων στην ανοσολογική απόκριση.

Ουδετερόφιλα: Βραχύβιοι & Ακαριαίοι

Βιολογικό Προφίλ



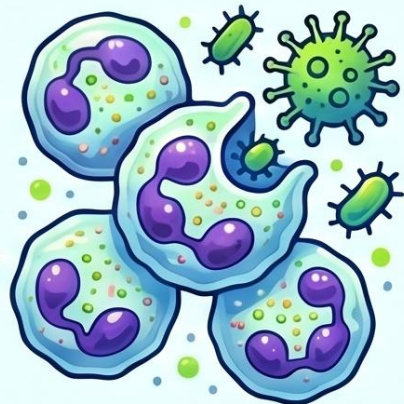
Βραχύβια Δράση (1-2 Ημέρες)

Τα ουδετερόφιλα ζουν μόλις 1-2 ημέρες.



Προέλευση: Μυελός των Οστών

Τα ουδετερόφιλα προέρχονται από το μυελό των οστών.



Λειτουργική Απόκριση



Ακαριαία Δράση

Δρουν ακαριαία με έτοιμα ένζυμα.



Μοναδικός Μηχανισμός: Εξωκυττάρια Δίκτυα (NETs)

Μόνο τα ουδετερόφιλα σχηματίζουν εξωκυττάρια δίκτυα (NETs) για την παγίδευση μικροβίων.



Χαμηλά Επίπεδα Κυτταροκινών

Περιορισμένη παραγωγή σημάτων.

Μακροφάγα: Μακρόβιοι & Στρατηγικοί

Βιολογικό Προφίλ



Μακροχρόνια Επιβίωση (Ετη)

Τα μακροφάγα των ιστών επιβιώνουν για χρόνια.



Προέλευση: Μυελός & Εμβρυϊκές Δομές

Τα μακροφάγα προέρχονται από το μυελό και εμβρυϊκές δομές.



Λειτουργική Απόκριση



Προγραμματισμένη Δράση

Απαιτούν χρόνο για μεταγραφή γονιδίων.



Εργοστάσια Παραγωγής Κυτταροκινών

Αποτελούν κύρια πηγή παραγωγής κυτταροκινών και σημάτων.



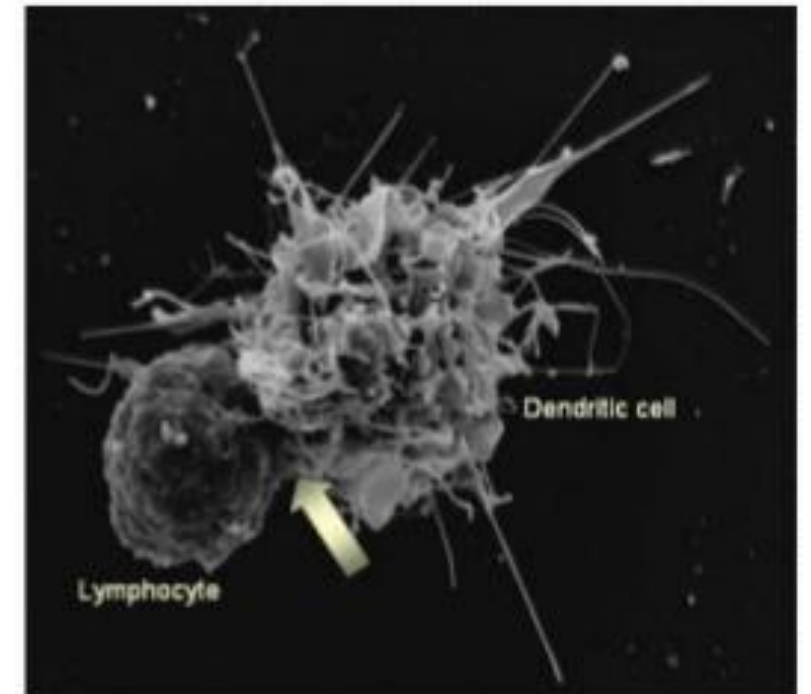
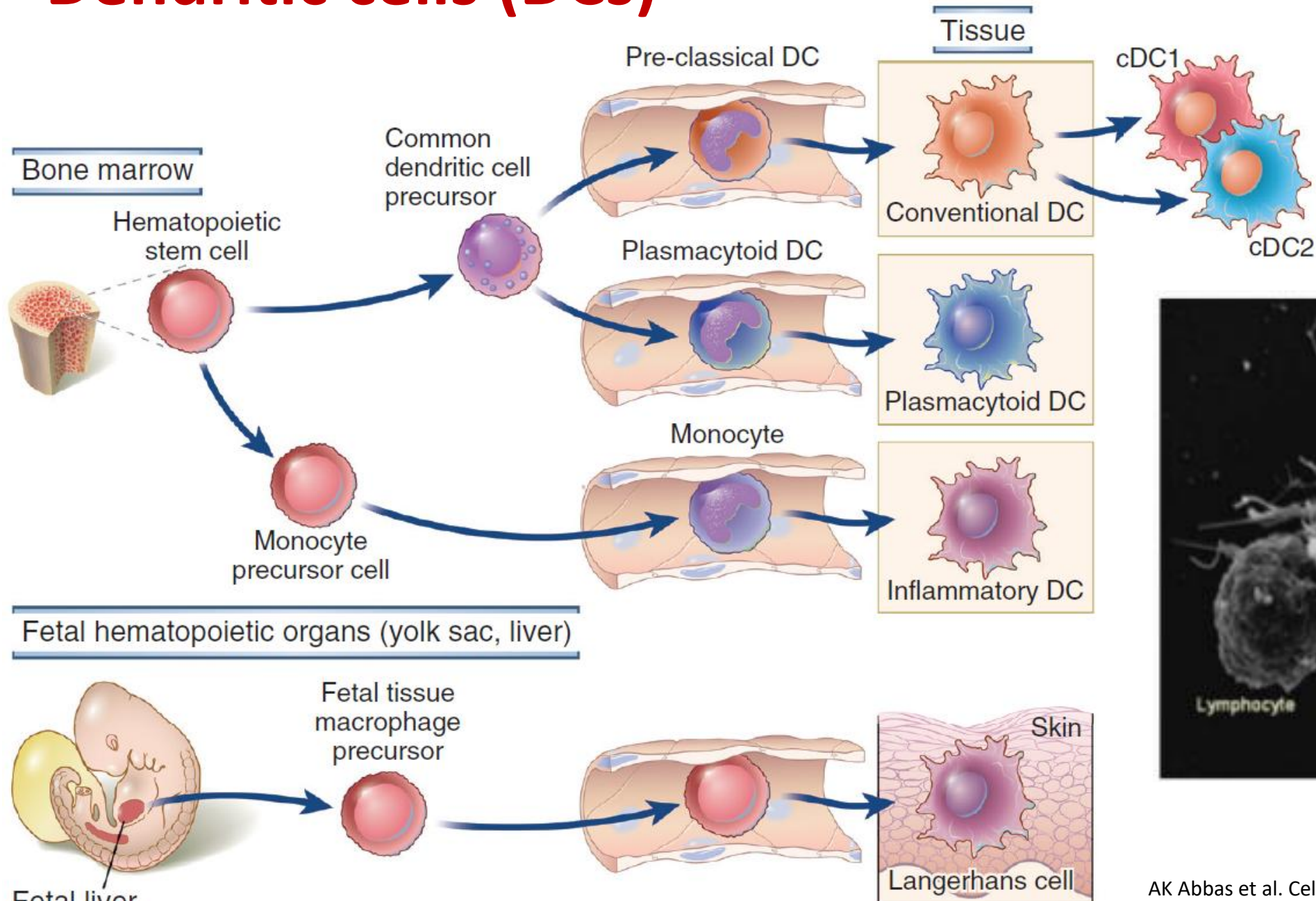
Παρατεταμένη Ικανότητα Καθαρισμού

Συνεχής και μακροχρόνια φαγοκυττάρωση.

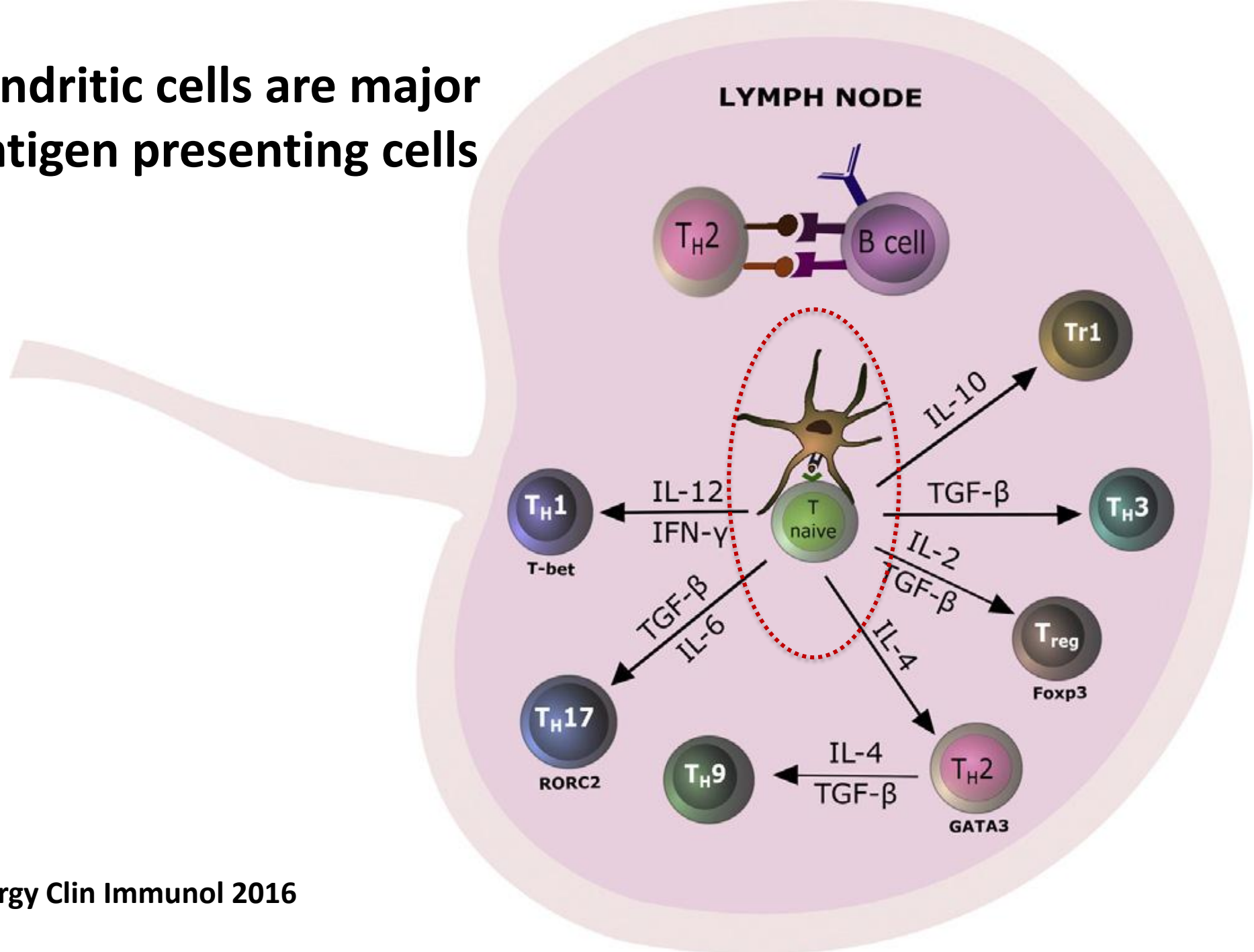
Σύνοψη Κυριότερων Λειτουργικών Διαφορών

Χαρακτηριστικό	Ουδετερόφιλα	Μακροφάγα
 Φαγοκυττάρωση	Ταχεία κατάποση μικροβίων	Παρατεταμένη ικανότητα καθαρισμού
 Δραστικές Μορφές Οξυγόνου	Πολύ έντονη παραγωγή	Λιγότερο εμφανής
 Σχηματισμός NET	Ναι (Ταχεία επαγωγή)	Όχι

Dendritic cells (DCs)

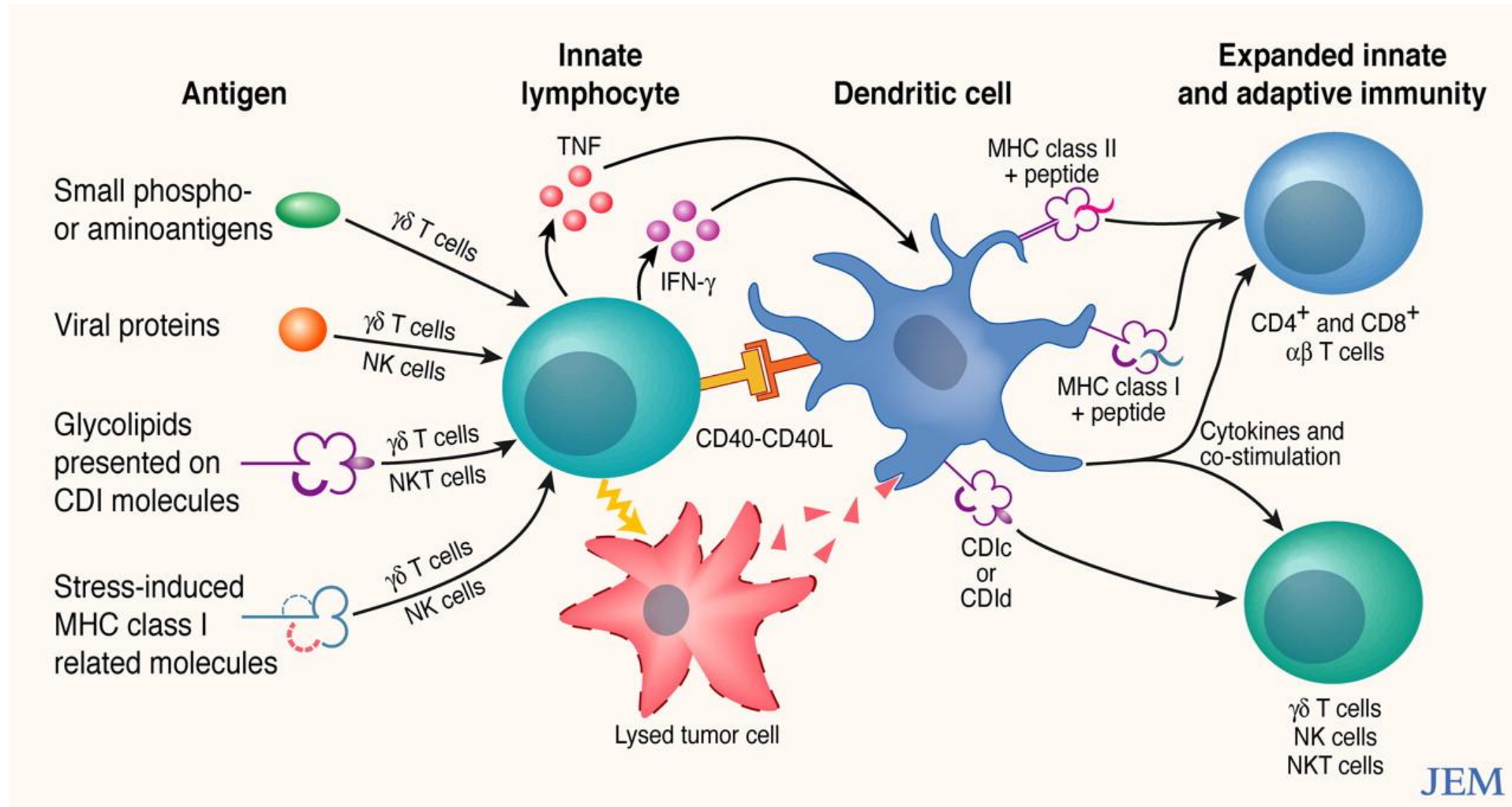


Dendritic cells are major antigen presenting cells



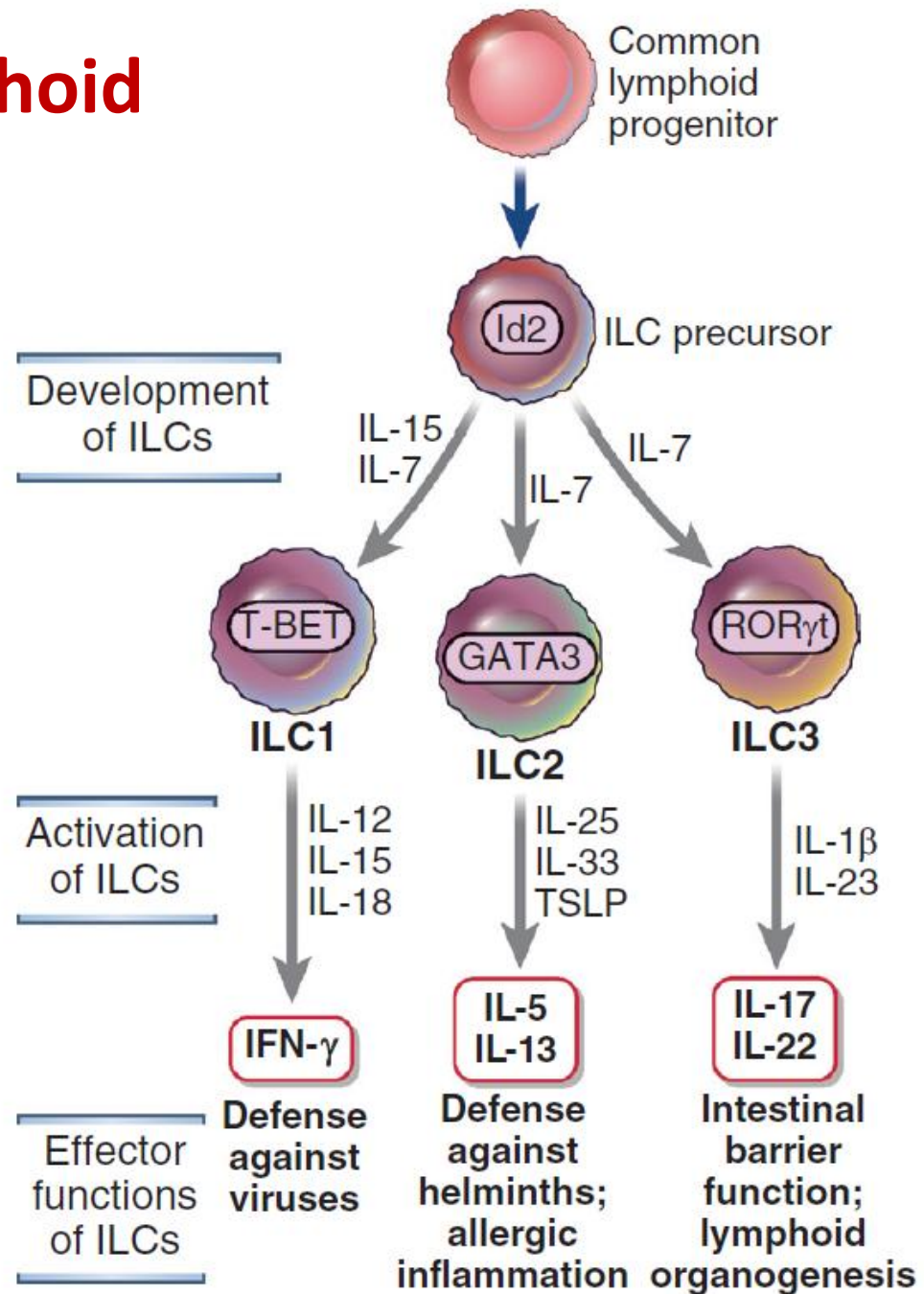
Innate lymphocytes

(Innate immunity lymphocytes, NK, NKT, $\gamma\delta$ T)

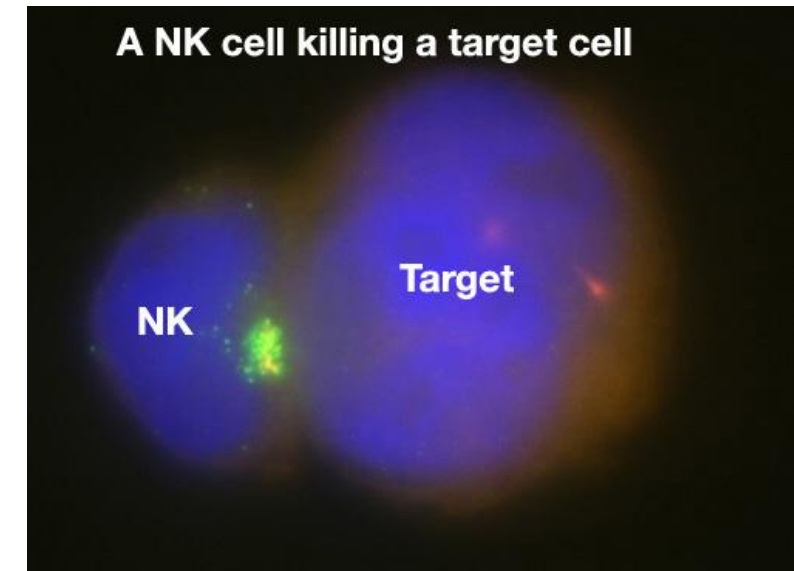


Münz C et al. J Exp Med 2005;202:203-207

Innate lymphoid cells (ILCs)



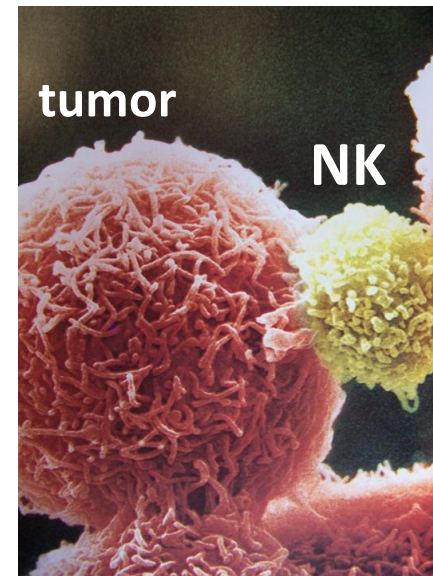
Natural Killers cells, NK (cytotoxic cells)



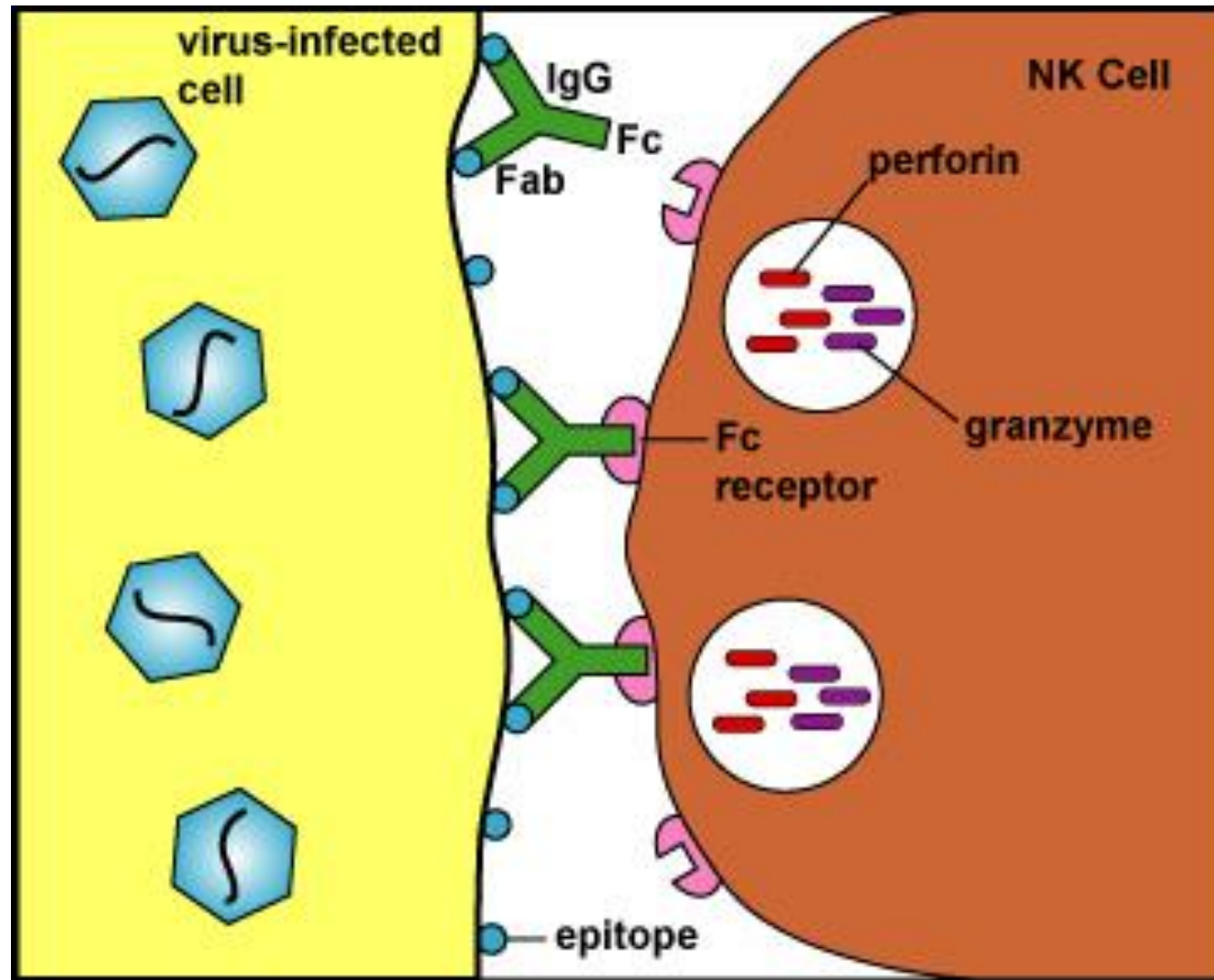
- **Antiviral immunity**

*recognize infected cells early in the course of infection,
before adaptive immune responses have developed*

- **Anti- tumor immunity**



NK cells: Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)

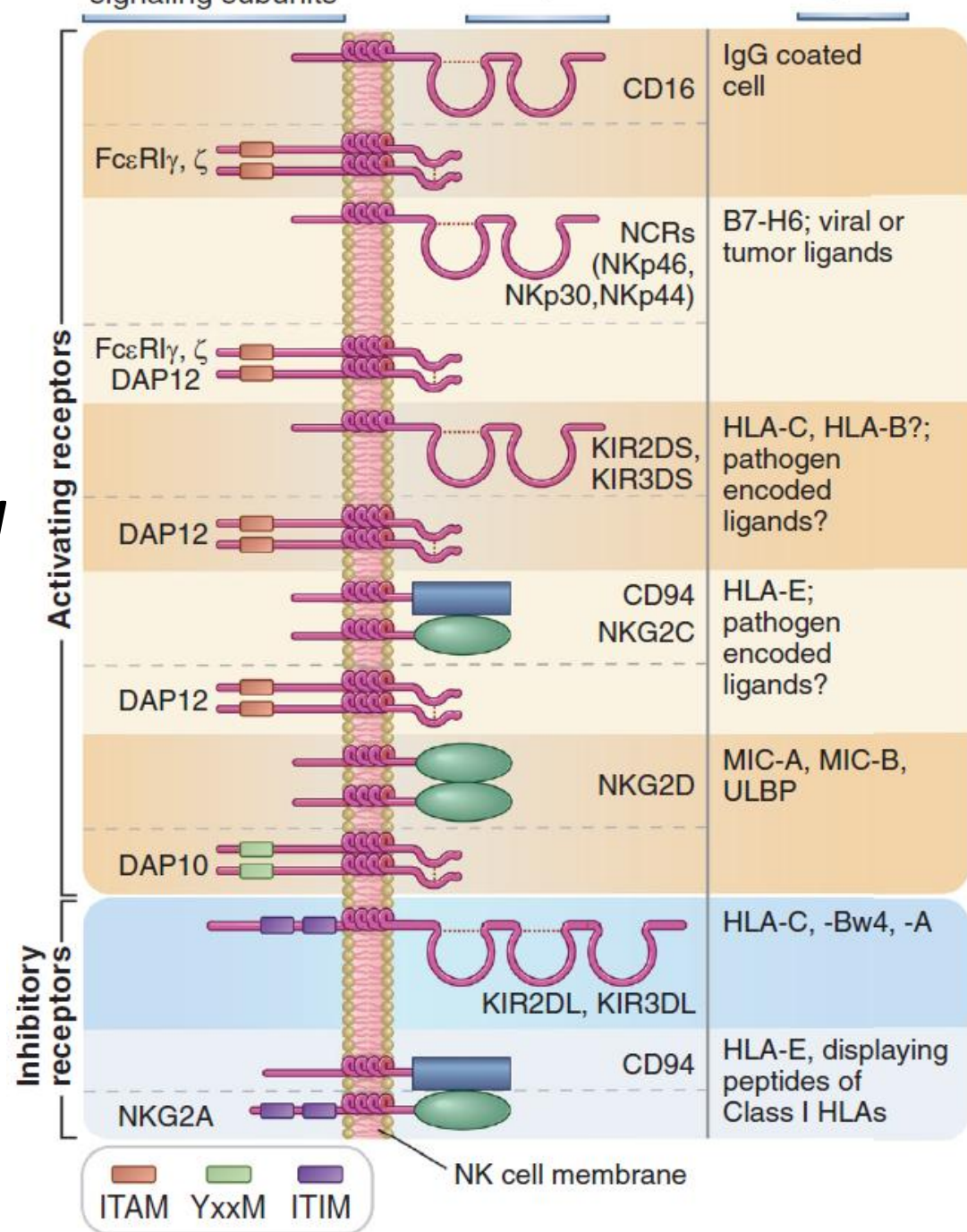


NK receptors

activating

NK cells distinguish **infected** and **stressed** cells from healthy cells, and NK cell function is regulated by a **balance** between signals that are generated by activating and inhibitory receptors

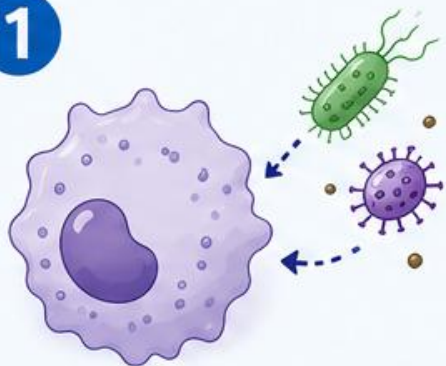
inhibitory



Έμφυτο ανοσοποιητικό σύστημα – Λειτουργίες

Η πρώτη γραμμή άμυνας του οργανισμού

1



Αναγνωρίζει μοριακές δομές

Αναγνωρίζει μοριακές δομές που παράγονται από **μικροβιακούς παθογόνους** ή από **κατεστραμμένα κύτταρα** χρησιμοποιώντας:



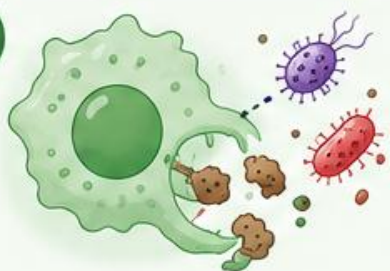
PRRs (π.χ. TLRs)

Υποδοχείς αναγνώρισης προτύπων



Συμπλήρωμα και άλλοι διαλυτοί μεσολαβητές (π.χ. CRP)

2



Εξουδετέρωση μικροβίων και κατεστραμμένων κυττάρων

Εξουδετέρωση μικροβίων και κατεστραμμένων κυττάρων και έναρξη της διαδικασίας **επιδιόρθωσης των ιστών**.



3

Ενεργοποίηση φλεγμονής και άλλων μηχανισμών άμυνας

Επαγωγή φλεγμονής, ενεργοποίηση του συμπληρώματος και της πήξης, **οφωνινοποίηση** και φαγοκυττάρωση.



Φλεγμονή



Συμπλήρωμα



Πήξη



Οφωνινοποίηση



Φαγοκυττάρωση

4

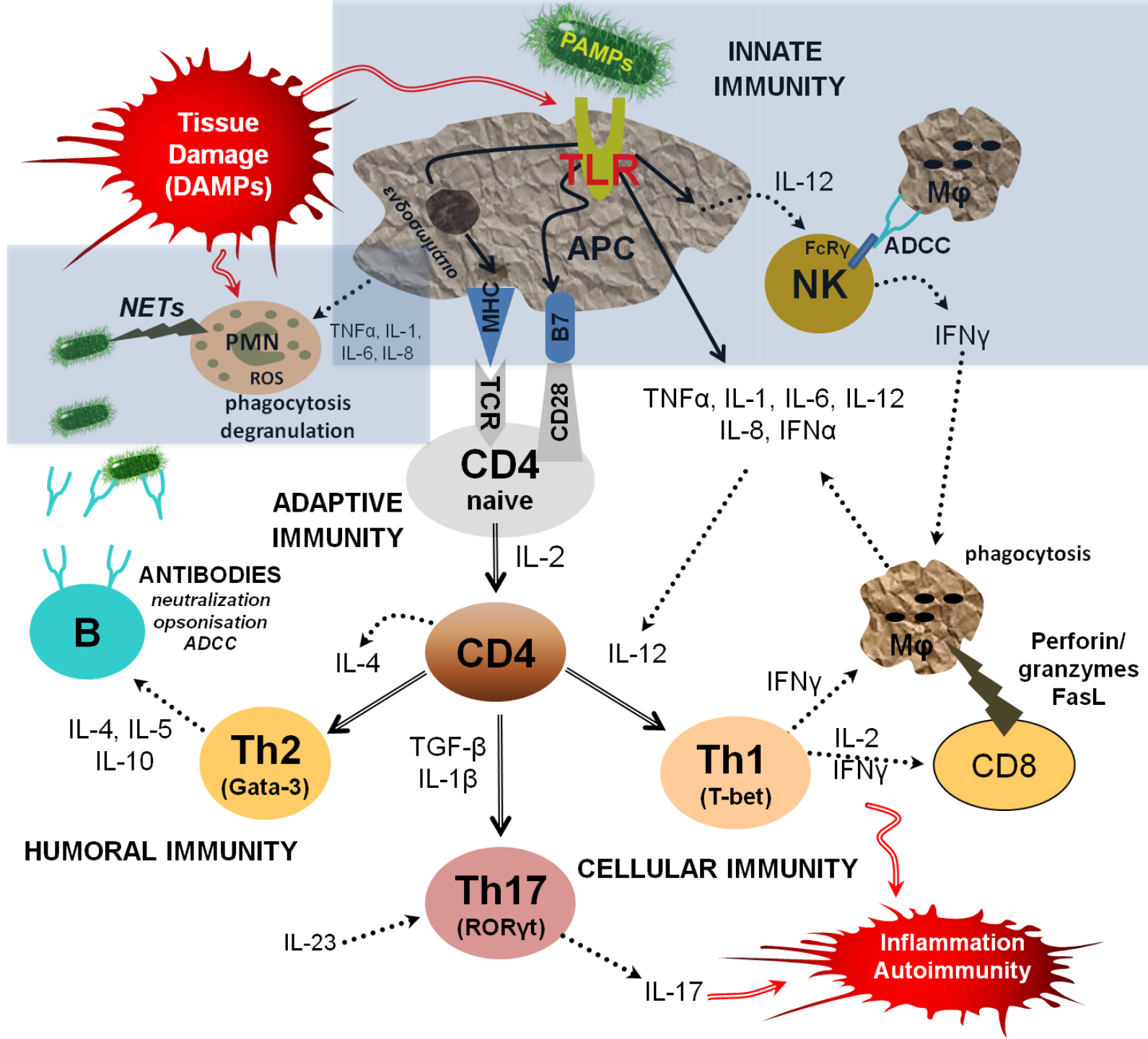
Παρέχει σήματα κινδύνου στην προσαρμοστική (επίκτητη/ειδική) ανοσία

Παρέχει σήματα κινδύνου στην προσαρμοστική (επίκτητη/ειδική) ανοσία για την τόνωση των προσαρμοστικών ανοσολογικών αποκρίσεων και



Κύρια σήματα:

- MHC-II
- B7 (CD80)





“...go forth, you young people, and tackle the really difficult problems in health.....you have all the tools, now we need individuals who have the will to work...”

Charles Alderson Janeway, Jr. (1943 – 2003)