Breakfast Seminar

Inflammasome and Allergic Diseases

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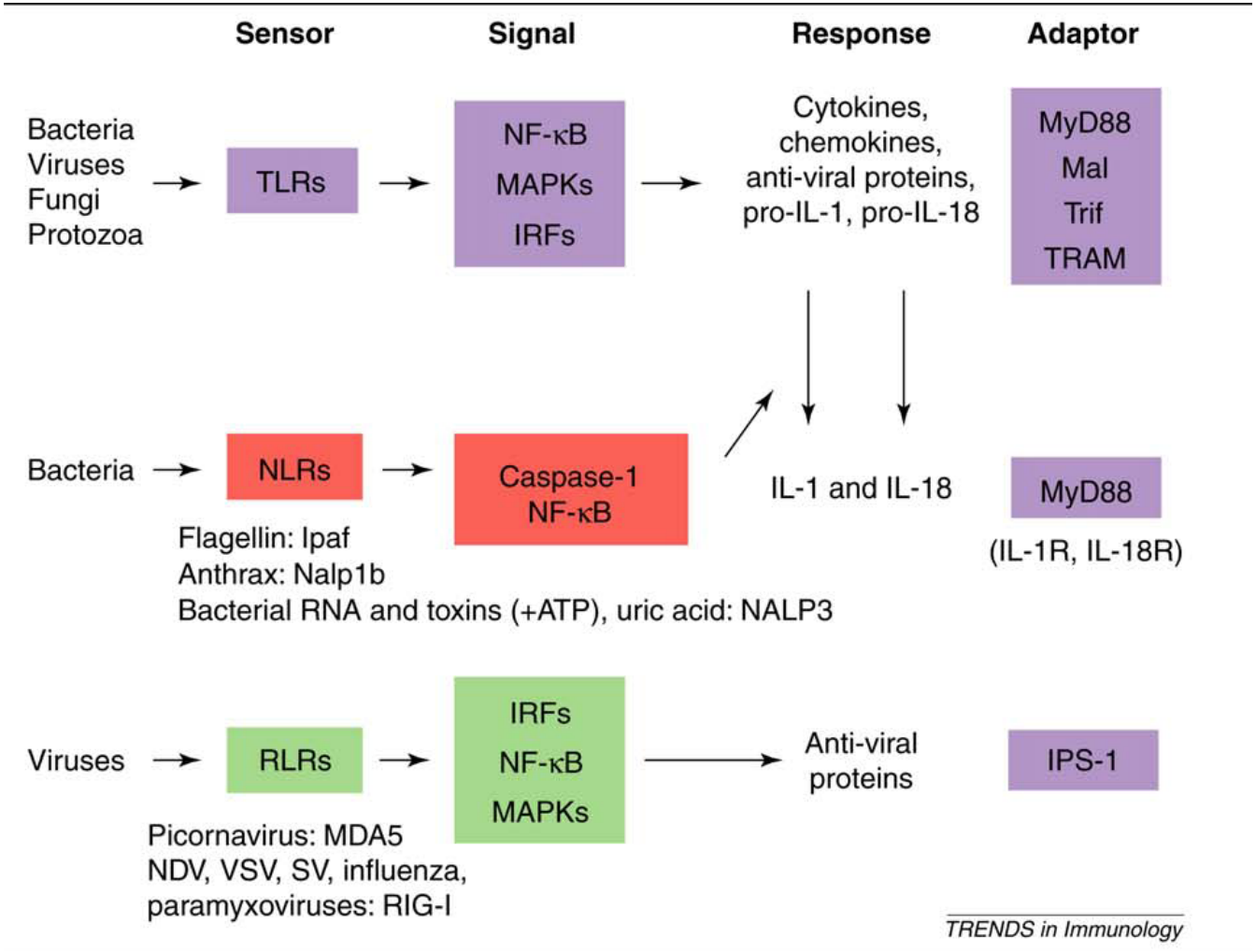
World Allergy Congresss , Cancun, Mexico
December 4, 2011

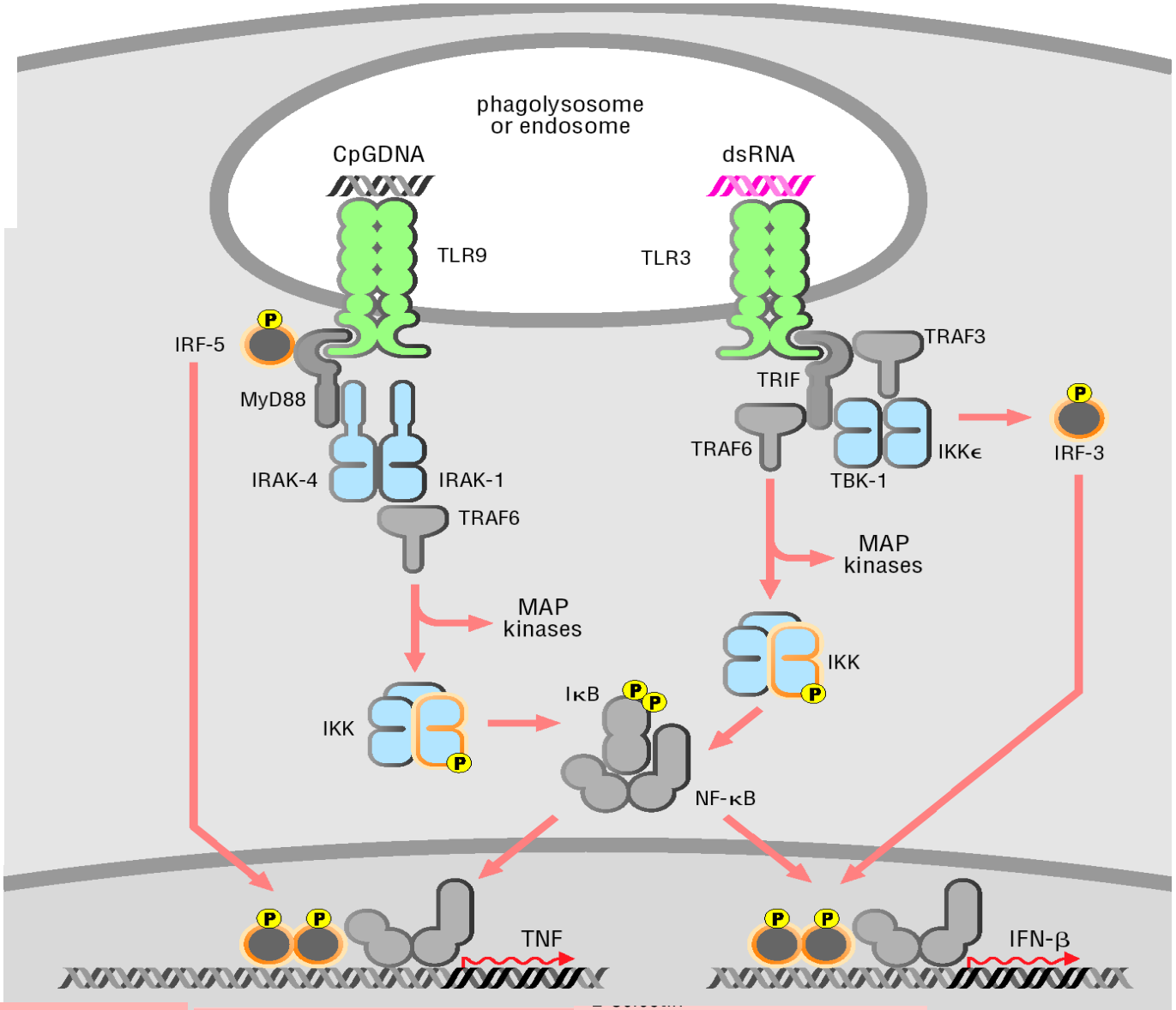
A Trinity of Pathogen Sensors: Team work in Innate Immunity



Creagh & O'Neil 27:352

TLR signaling pathways

- Ligand induced dimerization of TLR--> induced assembly with TIR-domain containing adaptors
- MyD88 pathway and TRIF pathway;
- Activate Transcription factors and MAP kinases
- NFKb upregulates ~350 proinflammatory genes.



Inflammatory cytokines	Chemokines	Adhesion molecules	Immune effector molecules	Pro-survival
TNF	IL-8	ICAM-1	FasL	Bcl-XL
IL-1	MIP-1a	VCAM-1	iNOS	A1
IL-6	MCP	E-selectin	COX-2	c-IAP1, 2
IL-12	RANTES		β-defensins	
Lymphotoxin α/β	Eotaxin			
GM-CSF				
IFN-β				

NOD1 & NOD2 recognize peptidoglycan substructures and promote innate immune responses

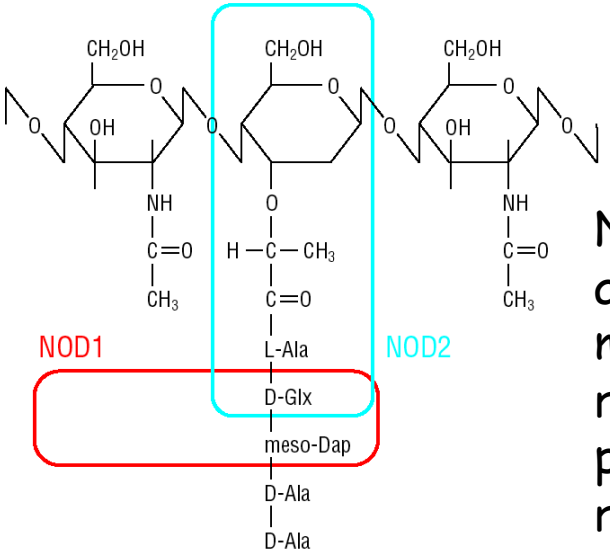
Table 1. The NLR Family

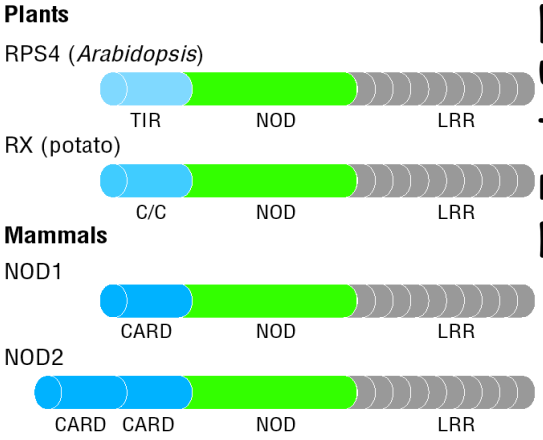
Subfamily	Human	Mouse	N Terminus	Other Names
NLRA				
	CIITA		CARD	NLRA;MHCIITA;C2TA
		CIIta	CARD	*Nlra; MHCIITA;C2ta*
NLRB				
	NAIP		BIR	BIRC1;CLR5.1
		Naip1-7	BIR	*Birc1a-g*
NLRC				
	NOD1		CARD	NLRC1;CARD4;CLR7.1
		Nod1	CARD	*Nlrc1;Card4*
	NOD2		CARD	NLRC2;CARD15;CD;BLAU;IBD1;PSORAS1; CLR16.3
		Nod2	CARD	*Nlrc2;Card15*
	NLRC3		CARD[a]	NOD3;CLR16.2
		Nlrc3	CARD[a]	*Clr16.2*
	NLRC4		CARD	IPAF;CARD12;CLAN;CLR2.1
		Nlrc4	CARD	*Ipaf;Card12;CLAN*
	NLRC5		CARD[a]	NOD27;NOD4;CLR16.1
		Nlrc5	CARD[a]	
NLRP				
	NLRP1		PYD	NALP1;CARD7;NAC;DEFCAP;CLR17.1
		Nlrp1a-c	PYD	*Nalp1a-c*
	NLRP2		PYD	NALP2;PYPAF2;NBS1;PAN1;CLR19.9
		Nlrp2	PYD	*Nalp2;Pypaf2;Nbs1;Pan1*
	NLRP3		PYD	NALP3;Cryopyrin;CIAS1;PYPAF1;CLR1.1
		Nlrp3	PYD	*Nalp3;Cryopyrin;Cias1;Pypaf1;Mmig1*
	NLRP4		PYD	NALP4;PYPAF4;PAN2;RNH2;CLR19.5
		Nlrp4a	PYD	*Nalp4a;Nalp-eta;Nalp0D*
		Nlrp4b	PYD	*Nalp4b;Nalp-gamma;Nalp9E*
		Nlrp4c	PYD	*Nalp4c;Nalp-alpha;RNH2*
		Nlrp4d	PYD	*Nalp4d;Nalp-beta*
		Nlrp4e	PYD	*Nalp4e;Nalp-epsilon*
		Nlrp4f	PYD	*Nalp4f;Nalp-kappa;Nalp9F*
		Nlrp4g	PYD	*Nalp4g*
	NLRP5		PYD	NALP5;PYPAF8;MATER;PAN11;CLR19.8
		Nlrp5	PYD	*Mater;Op1*
	NLRP6		PYD	NALP6;PYPAF5;PAN3;CLR11.4
		Nlrp6	PYD	*Nalp6*
	NLRP7		PYD	NALP7;PYPAF3;NOD12;PAN7;CLR19.4
	NLRP8		PYD	NALP8;PAN4;NOD16;CLR19.2
	NLRP9		PYD	NALP9;NOD6;PAN12;CLR19.1
		Nlrp9a	PYD	*Nalp9a;Nalp-theta*
		Nlrp9b	PYD	*Nalp9b;Nalp-delta*
		Nlrp9c	PYD	*Nalp9c;Nalp-zeta*
	NLRP10		PYD	NALP10;PAN5;NOD8;PYNOD;CLR11.1
		Nlrp10	PYD	Nalp10;Pynod
	NLRP11		PYD	NALP11;PYPAF6;NOD17;PAN10;CLR19.6
			PYD	
	NLRP12		PYD	NALP12;PYPAF7;Monarch1;RNOS;PAN6;CLR19.3
		Nlrp12	PYD	*Nalp12*
	NLRP13		PYD	NALP13;NOD14;PAN13;CLR19.7
			PYD	

Table 1. *Continued*

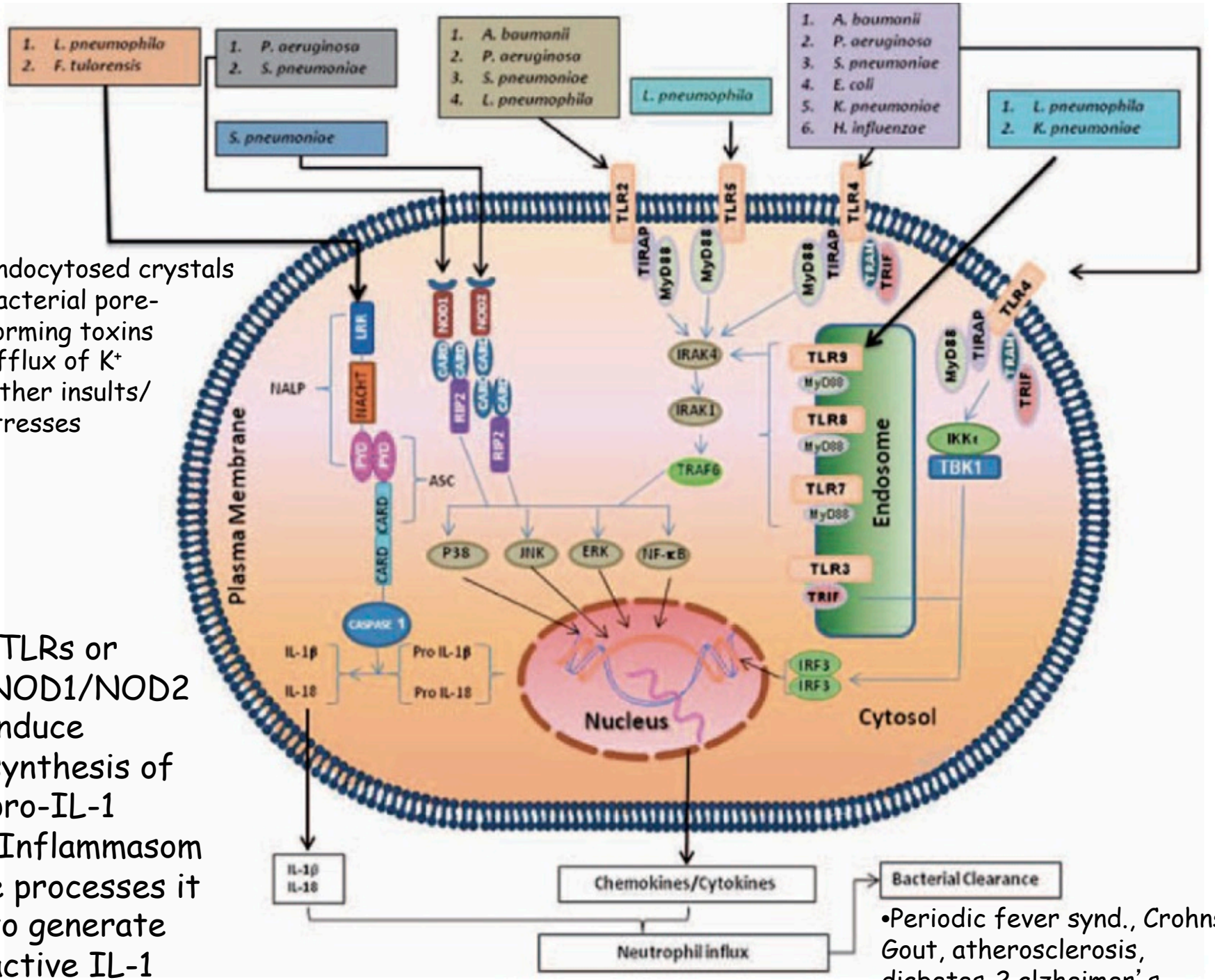
Subfamily	Human	Mouse	N Terminus	Other Names
	NLRP14		PYD	NALP14;NOD5;PAN8;CLR11.2
		Nlrp14	PYD	*Nalp14;Nalp-iota;GC-LRR*
NLRX1				
	NLRX1		CARD[a]	NOD9;CLR11.3
		Nlrx1	CARD[a]	

This table is adapted from Kanneganti et al. (2006) and Bryant and Fitzgerald (2009).
[a] Currently disputed as to whether it contains a CARD, PYD, or another N terminus binding domain.





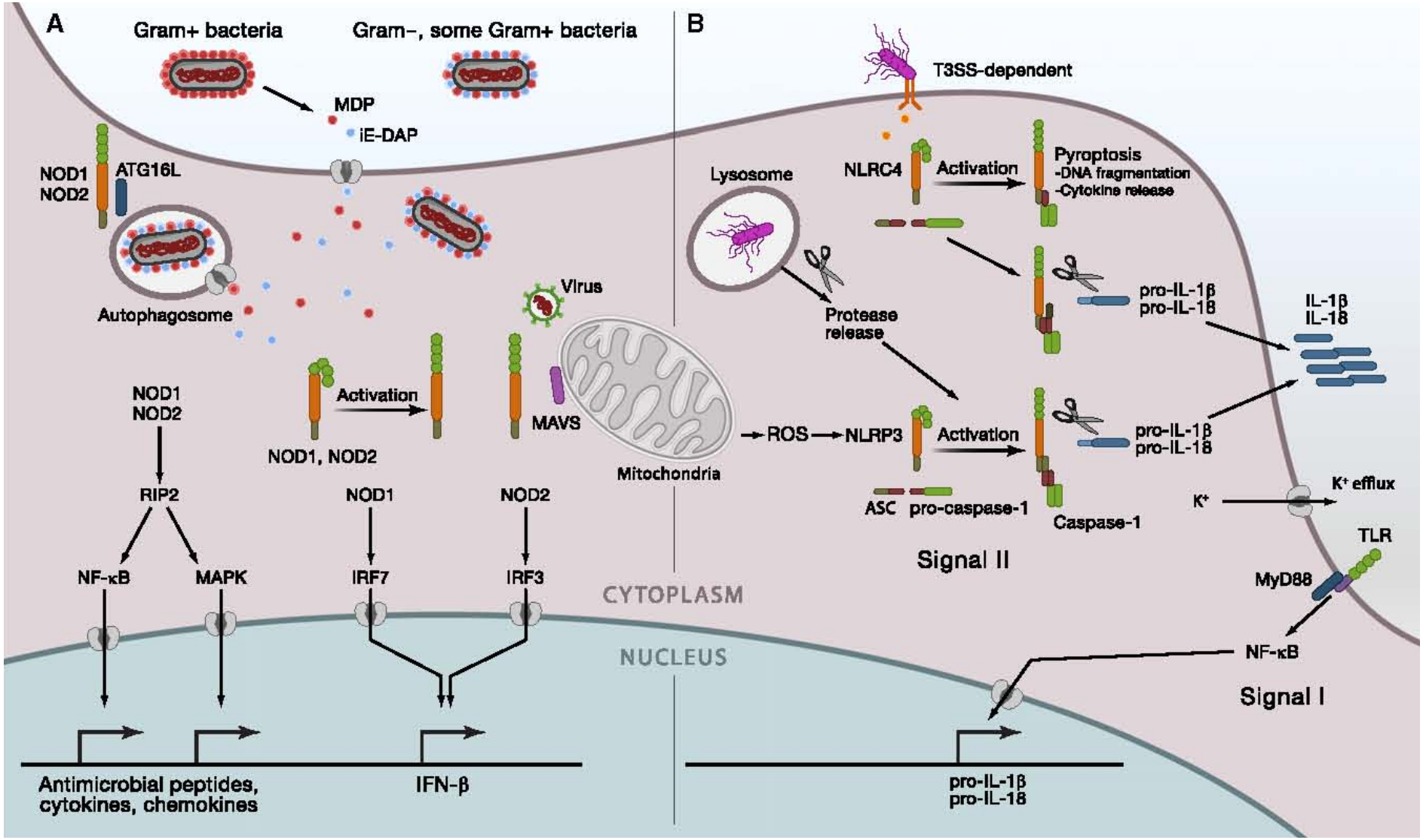
NOD1 and NOD2 are intracellular molecules and resemble some plant disease resistance proteins; best understood of the "NOD-like receptors" or NLRs



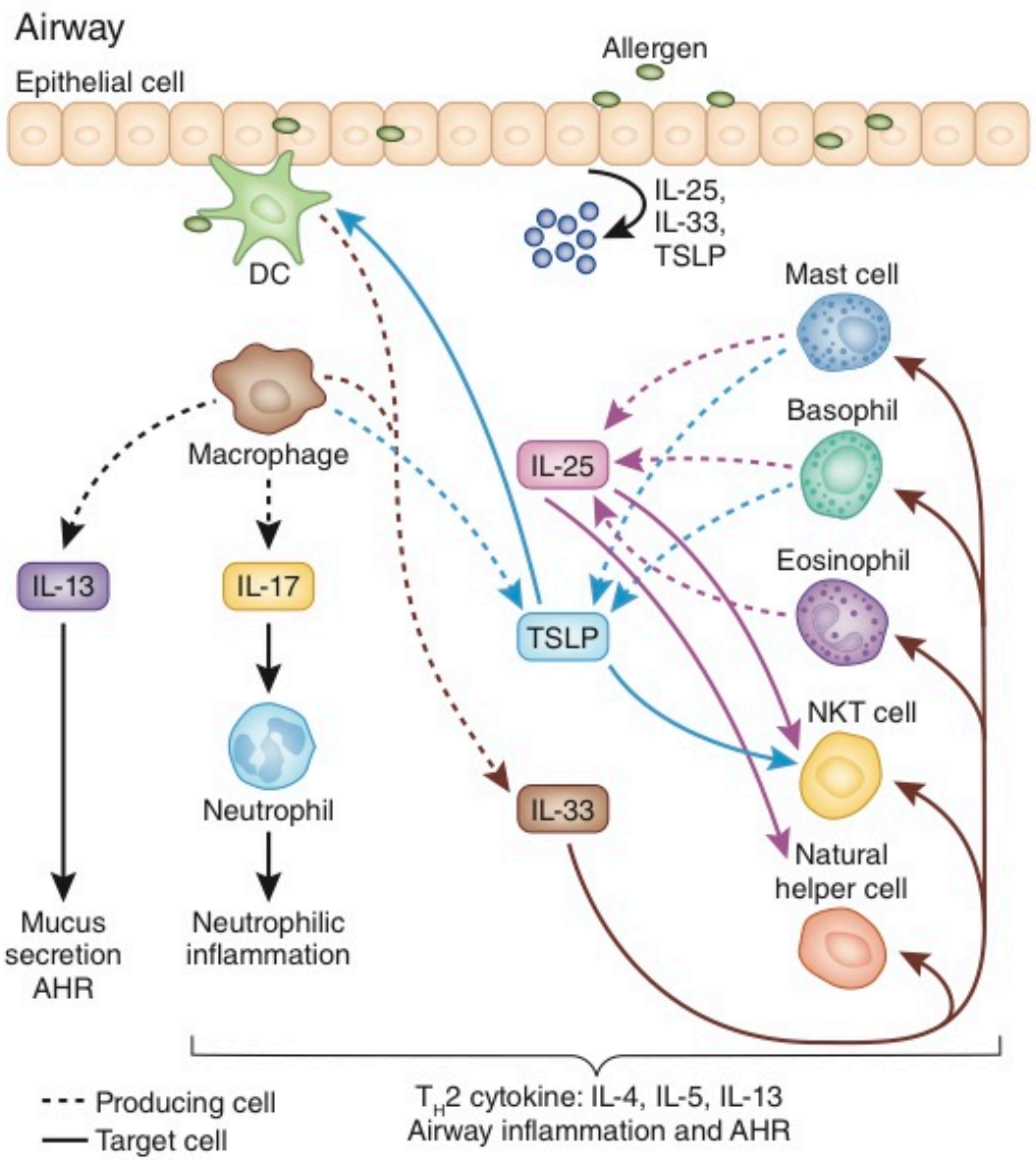
- TLRs or NOD1/NOD2 induce synthesis of pro-IL-1
- Inflammasome processes it to generate active IL-1

- Periodic fever synd., Crohns Gout, atherosclerosis, diabetes-2,alzheimer's

Crosstalk between TLR and NLR pathways



Newly Identified Cells and Cytokines f the Innate Immune System in Asthma



Kim et al. nature immunology 11: 7july 2010

NLRP3 inflammasome is required in murine asthma in the absence of aluminum adjuvant

A.-G. Besnard et al Allergy 66, Issue 8, pages 1047–1057, August 2011

- **Used an adjuvant-free model of allergic lung inflammation induced by ovalbumin (OVA) to investigate the role of NLRP3 inflammasome and related it to IL-1R1 signaling pathway.**
- **Employed mice deficient in NLRP3 inflammasome, and examined IL-1R1, IL-1β or IL-1α. Eosinophil recruitment, Th2 cytokine, and chemokine levels were determined in bronchoalveolar lavage fluid, lung homogenates, and mediastinal lymph node cells ex vivo.**
- **Allergic airway inflammation depends on NLRP3 inflammasome activation. Dendritic cell recruitment into lymph nodes, Th2 lymphocyte activation in the lung and secretion of Th2 cytokines and chemokines are reduced in the absence of NLRP3.**
- **Absence of NLRP3 and IL-1β is associated with reduced expression of other proinflammatory cytokines such as IL-5, IL-13, IL-33, and thymic stromal lymphopoietin. Furthermore, the critical role of IL-1R1 signaling in allergic inflammation is confirmed in IL-1R1-, IL-1β-, and IL-1α-deficient mice.**
- **NLRP3 inflammasome activation leading to IL-1 production is critical for the induction of a Th2 inflammatory allergic response.**

Mite allergen is a danger signal for the skin via activation of inflammasome in keratinocytes

- Investigated whether HDM allergens activate the inflammasome in epidermal keratinocytes.
- Keratinocytes were stimulated with Dermatophagoides pteronyssinus (Dp), and examinedthe activation of caspase-1 and secretion of IL-1β and IL-18 and analyzed the subcellular distributions of inflammasome proteins.
- Dp activated caspase-1 and induced caspase-1-dependent release of IL-1β and IL-18 from keratinocytes.
- Dp stimulated assembly of the inflammasome by recruiting apoptosis-associated specklike protein containing a caspase-recruitment domain (ASC), caspase-1, and nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin-domain containing 3 (NLRP3) to the perinuclear region.
- Infection with lentiviral particles carrying ASC, caspase-1, or NLRP3 shRNAs suppressed the release of IL-1β and IL-18 from the keratinocytes. Activation of the NLRP3 inflammasome by Dp was dependent on cysteine protease activity.
- Thus, house dust mite allergens are danger signals for the skin. In addition, HDM-induced activation of the NLRP3 inflammasome may play a pivotal role in the pathogenesis of atopic dermatitis.

Dai et al J Allergy Clin Immunol. 2011 Mar;127 (3):806-14.e1-4. Epub 2011