

S1 Table | **Examples of microbial manipulation of innate immune receptor crosstalk**

Pathogens	Effector microbial molecule(s) and action	Crosstalking receptors		Cell type	Crosstalk outcome	Refs
		R1	R2			
Co-option of inhibitory receptors						
HIV-1, other viruses?	Activation of DCIR induces phosphorylation of its ITIM; ligands not identified	DCIR (CLECSF6)	TLR8, TLR9	Conventional and plasmacytoid DC	Inhibition of TLR8-induced TNF- α & IL-12 and of TLR9-induced IFN α	1-3
HCMV	Glycoprotein UL18 mimics class I MHC and binds ITIM-bearing ILT2 (LIR-1)	ILT2 (LIR-1)	Activating NK receptors (e.g., CD94/ NKG2C)	NK cells	Ligation of the inhibitory receptor ILT2 interferes with NK-mediated cytotoxicity	4,5
<i>M. catarrhalis</i> <i>M. meningitidis</i>	UspA1 and Opa bind and activate ITIM-bearing CEACAM1	CEACAM1	TLR2	pulmonary epithelial cells	Inhibition of TLR2-mediated PI3K-Akt-NF- κ B pathway	6
Group B <i>Streptococcus</i> (serotype Ia and III strains)	Cell wall-anchored β protein binds ITIM-bearing Siglec-5	Siglec-5	TLR?	neutrophils monocytes	Inhibition of phagocytosis, oxidative burst, IL-8, and extracellular trap formation, leading to bacterial survival	7
Group B <i>Streptococcus</i> serotype III	Sialylated capsular polysaccharide binds ITIM-bearing Siglec-9	Siglec-9	TLR?	neutrophils	Inhibition of oxidative burst, extracellular trap formation, and killing	8
<i>S. aureus</i>	Unknown ligand (of polyanionic nature) activates ITIM-bearing PIR-B	PIR-B	TLR2	macrophages	Inhibition of TLR2 inflammatory responses	9,10
<i>E. coli</i>	Non-opsonized <i>E. coli</i> binds Fc γ RIII and induces FcR γ -mediated ITAMi signals	Fc γ RIII (CD16)	MARCO	macrophages	Inhibition of MARCO-mediated phagocytosis by ITAMi-dependent inhibitory pathway	11
Synergistic induction of immunosuppressive mediators						
HIV-1 Measles virus Mycobacteria <i>C. albicans</i>	Mannose-containing ligands (e.g., mycobacterial ManLAM, fungal mannan, and gp120) bind DC-SIGN and activate RAF1-dependent signalling	DC-SIGN	TLR3 TLR4 TLR5	DC	Increased IL-10, IL-12, and IL-6; unbiased T _H 1 cell differentiation. Impaired or intermediate-stage DC maturation also reported.	12-15
<i>H. pylori</i>	Fucose-containing LPS Le antigens bind DC-SIGN and activate RAF1-independent signalling	DC-SIGN	TLR2 TLR4	DC	Upregulation of IL-10, downregulation of IL-6 and IL-12; inhibition of T _H 1 cell polarization	14,16
<i>B. burgdorferi</i>	Salp15 in tick saliva binds DC-SIGN and activates Raf-1 and MEK signalling. Salp15 is bound by <i>B. burgdorferi</i> OspC	DC-SIGN	TLR2	DC	Promotion of <i>Il6</i> and <i>Tnf</i> mRNA decay, impaired nucleosome remodeling at the <i>Il12a</i> promoter, enhanced IL-10 production, inhibition of TLR-dependent DC maturation and function	17
Mycobacteria	Ligand unknown	C-type lectin receptor (Clec5A)	TLR2 (MyD88 pathway)	neutrophils	Synergistic induction of IL-10, reduction of lung inflammation but persistence of high mycobacterial burden	18
<i>P. gingivalis</i>	HRgpA & RgpB convert C5 to C5a to activate C5aR, which co-associates with TLR2	C5aR	TLR2	monocytes macrophages	Synergistic elevation of cAMP and inhibition of killing <i>in vitro</i> and <i>in vivo</i>	19
<i>P. gingivalis</i>	Fimbriae bind and activate CXCR4, which co-associates with TLR2	CXCR4	TLR2	monocytes macrophages	Synergistic elevation of cAMP and inhibition of killing <i>in vitro</i> and <i>in vivo</i>	20
<i>S. aureus</i> <i>B. anthracis</i>	AdsA converts AMP to adenosine	Adenosine receptors	TLR?	neutrophils, whole blood cells	Adenosine receptor-mediated immunosuppressive signalling deactivates phagocytes and inhibits immune clearance	21

SUPPLEMENTARY INFORMATION

Exploitation of inside-out signalling for safe internalization by phagocytes						
<i>P. gingivalis</i>	Fimbriae induce CD14/TLR2 inside-out signalling	CD14/TLR2	CR3	monocytes macrophages	Activation of CR3-mediated entry, enhanced intracellular survival of pathogen (<i>in vitro</i>), suppression of pathogen clearance (<i>in vivo</i>)	22
<i>B. anthracis</i>	BclA induces CD14/TLR2 inside-out signalling	CD14/TLR2	CR3	monocytes macrophages	Activation of CR3-mediated internalization of spores leading to increased infection and host mortality	23
Mycobacteria	LAM induces CD14/TLR2 inside-out signalling	CD14/TLR2	CR3	monocytes macrophages	Activation of CR3-mediated internalization, coronin-1-dependent inhibition of lysosomal delivery	24,25
<i>B. pertussis</i>	FHA induces $\alpha\beta3$ /CD47 inside-out signalling	$\alpha\beta3$ /CD47	CR3	monocytes macrophages neutrophils	Activation of CR3-mediated internalization, suppression of pathogen clearance <i>in vivo</i>	26-28
<i>E. faecalis</i>	'Aggregation substance' glycoprotein induces $\alpha\beta3$ /CD47 inside-out signalling	$\alpha\beta3$ /CD47	CR3	macrophages neutrophils	Activation of CR3 entry, inhibition of oxidative burst and killing	29-31
Inhibition of IL-12 and T cell immunity via subversive receptor crosstalk						
Measles virus	Hemagglutinin binds CD46	CD46	TLR4	monocytes	Selective inhibition of IL-12 and T_H1 immunity	32,33
Measles virus	Hemagglutinin binds CD150 (SLAM)	CD150 (SLAM)	TLR4	DC	Selective inhibition of IL-12 and T_H1 immunity	34
Human herpesvirus 6	Glycoprotein H binds CD46	CD46	TLR4	macrophages	Selective inhibition of IL-12 and T_H1 immunity	35,36
Adenovirus (Groups B and D)	Fiber protein binds CD46	CD46	TLR4	peripheral blood mononuclear cells	Inhibition of IL-12 and other proinflammatory cytokines (IL-1, IL-6)	37,38
Hepatitis C virus	Core protein binds gC1qR	gC1qR	TLR4	macrophages DC	Selective inhibition of IL-12 and T_H1 differentiation	39,40
<i>P. gingivalis</i>	Microbial C5 convertase-like enzymes generate C5a	C5aR	TLR2	macrophages	Selective inhibition of IL-12 and upregulation of IL-1 β , IL-6, and TNF- α <i>in vivo</i> ; promotion of pathogen survival <i>in vivo</i>	41
<i>L. major</i>	C5a generation via complement activation	C5aR	TLR4	macrophages	Inhibition of IL-12 and T_H1 immunity leading to increased pathogen survival	42
<i>P. gingivalis</i>	Fimbriae bind CR3	CR3	TLR2	monocytes macrophages	Inhibition of IL-12/IFN γ -dependent clearance <i>in vivo</i>	43
<i>H. capsulatum</i>	Hsp60 binds CR3	CR3	TLR4	monocytes	Selective inhibition of IL-12	44,45
<i>B. pertussis</i>	FHA binds CR3	CR3	TLR4	macrophages	Selective inhibition of IL-12	46
Mycobacteria	ManLAM binds mannose receptor	Mannose receptor	TLR4	DC	Inhibition of IL-12 and other proinflammatory cytokines	47,48
<i>P. falciparum</i>	PfEMP-1 (on infected erythrocytes) binds CD36	CD36	TLR4	DC	Inhibition of IL-12 and suppression of DC maturation and T cell activation	49,50
Microbial exploitation of TLR-TLR interplay						
Hepatitis C virus	Core protein activates TLR2 in monocytes	TLR2	TLR9	plasmacytoid DC	Inhibition of TLR9-induced IFN α	51
<i>M. tuberculosis</i>	Lipoproteins and glycolipids act as inhibitory TLR2 agonists	TLR2	TLR9	myeloid DC	Inhibition of TLR9-induced IFN α / β and MHC-I cross processing	52
Mycobacteria <i>T. gondii</i>	Unknown ligand(s)	TLR2, other MyD88-dependent receptors	TLR4, other iNOS-inducing receptors	macrophages	MyD88-dependent Arg1 induction prevents NO production leading to increased <i>M. tuberculosis</i> load in infected mice, and wasting disease in <i>T. gondii</i> -infected mice.	53,54

Disruption of cooperative interactions between innate receptors						
<i>C. burnetii</i>	Disruption of $\alpha\beta3$ -CD47 interaction required for CR3 transactivation; possible involvement of smooth-type LPS	$\alpha\beta3$ /CD47	CR3	monocytes	Inhibition of $\alpha\beta3$ /CD47-CR3 crosstalk; pathogen taken up by $\alpha\beta3$ but not CR3 (lectin site), leading to intracellular survival	55,56
Group A <i>Streptococcus</i>	Mac, a CD11b-like protein, binds CD16 and blocks CD16-CR3 interactions for outside-in signalling	CD16	CR3	neutrophils	Inhibition of opsonophagocytosis, oxidative burst, and killing	57
Filarial nematodes	Secreted glycoprotein ES-62 forms complex with TLR4 leading to sequestration and degradation of PKC- α	TLR4	Fc ϵ RI	mast cells	Inhibition of Fc ϵ RI-mediated mast cell degranulation	58

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