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# Termination of Immune Activation: An Essential Component of Healthy Host Immune Responses

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**Key Words**
Endocytosis · Immunoreceptor tyrosine-based activation motifs · Immunoreceptor tyrosine-based inhibitory motifs · Intracellular signalling · Leucocyte immunoglobulin-like receptors · Ubiquitination

**Abstract**
The ideal immune response is rapid, proportionate and effective. Crucially, it must also be finite. An inflammatory response which is disproportionate or lasts too long risks injury to the host; chronic un-regulated inflammation in autoimmune diseases is one example of this. Thus, mechanisms to regulate and ultimately terminate immune responses are central to a healthy immune system. Despite extensive knowledge of what drives immune responses, our understanding of mechanisms of immune termination remains relatively sparse. It is clear that such processes are more complex than a one-dimensional homeostatic balance. Recent discoveries have revealed ever more nuanced mechanisms of signal termination, such as intrinsically self-limiting signals, multiple inhibitory mechanisms acting in tandem and activating proteins behaving differently in a variety of contexts. This review will summarise some important mechanisms, including termination by immunoreceptor tyrosine-based inhibitory motifs (ITIM), inhibition by soluble antagonists, receptor endocytosis or ubiquitination, and auto-inhibition by newly synthesised intracellular inhibitory molecules. Several recent discoveries showing immunoreceptor tyrosine-based activation motifs transducing inhibitory signals, ITIM mediating activating responses and the possible roles of immunoreceptor tyrosine-based switch motifs will also be explored.


## Introduction

The immune system constantly deals with foreign antigens appropriately with minimal host 'collateral damage' despite the complex immune response involved. A multitude of activating immune signals generate a potent inflammatory reaction, which is regulated in space and time by continued signalling within and between responding immune cells, eventually leading to its timely termination. Advances in the understanding of immune activation have been greatly instructive, though mechanisms of immune regulation and termination remain poorly defined. Poorly regulated immune responses risk host tissue damage and induction of autoimmunity, thus the regulation is tight, multiple and acts at different levels. These include the regulation at cellular level through sig-

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nals from receptors and co-receptors leading to the down-regulation of receptor/co-receptor expression, growth inhibition, induction of apoptosis and induction of anergy. At a sub-cellular level, activating signals delivered by receptors are terminated by recruitment of tyrosine phosphatases or through de novo production of counter-regulatory signalling molecules, for instance termination of Toll-like receptor (TLR)-4-mediated responses through synthesis of IκB. Additionally, negative regulation of the immune system could occur through production of suppressive cytokines, such as interleukin (IL)-10 and transforming growth factor (TGF)-β, via activation of cytolysis and/or through physiological signalling switch-off processes. Negative immune regulation may be mediated by pairs of activating and inhibitory receptors that share common or similar ligands, by specialised inhibitory receptors that block signalling initiated by separate activation receptors, by negative feedback loops from activating receptors and/or termination by intracellular signal switching molecules.

This review aims to outline major mechanisms of immune termination and their synergistic, overlapping and/or concurrent effects. Recent findings that challenge some existing paradigms, including the role of immunoreceptor tyrosine-based activation motifs (ITAM) transducing inhibitory signals (ITAMi) and immunoreceptor tyrosine-based inhibitory motifs (ITIM) leading to immune activation (ITIMa) will be discussed.

## Striking a Delicate Balance between Immune Activation and Inhibition with ITAMs and ITIMs

ITAMs were first identified by Reth [1] in the amino acid sequence encoding the cytoplasmic tails of the T cell receptor, B cell receptor (BCR) and FcεR1. These motifs have the consensus structure YxxI/Lx$_{(6-12)}$YxxI/L (x represents any amino acid) spanning 14–18 amino acids (table 1). Ligand binding to an ITAM-bearing receptor leads to receptor aggregation, followed by the phosphorylation of both tyrosine residues in ITAM by proximal Src family protein tyrosine kinases [2]. A dually phosphorylated ITAM then provides a binding site for the two SH2 domains of Syk family non-receptor protein tyrosine kinases, typically Zap70 in T cells and Syk in B cells and monocytes [3]. This leads to activation of a cascade of downstream signalling molecules [2] (fig. 1a).

ITIMs are a series of 6 amino acids (consensus sequence S/I/V/LxYxxI/V/L) found on the intracellular domain of transmembrane proteins which can transduce inhibitory signals (table 1). Ligand binding and receptor clustering lead to phosphorylation of the ITIM tyrosine residue by Src tyrosine kinases that recruit SH2-domain-containing tyrosine phosphatases, usually SHP-1 or SHP-2, or the inositol phosphatases SHIP-1 or SHIP-2. These phosphatases then dephosphorylate up- and downstream signalling molecules leading to the termination of cellular activation [4] (fig. 1b). ITIM-containing inhibitory receptors mediate this function with activating molecules via shared or different ligands [5].

There are numerous examples of ITAM-containing activating receptors [6] (table 2) and over 100 ITIM-containing inhibitory receptors potentially involved in immune regulation [7]. Of particular interest are several closely related ITAM-containing activating and ITIM-containing inhibitory receptors that upon co-clustering through similar or shared ligands regulate the threshold for and amplitude of cellular activation [5]. One family of such molecules is the leucocyte immunoglobulin (Ig)-like receptors (LILRs), also known as Ig-like transcripts or CD85a-m [8]. LILRs have two or four highly homologous Ig-like extracellular domains and are classified as inhibitory, activating or soluble receptors based on their transmembrane and cytoplasmic domains [8] (fig. 2c). Inhibitory LILRs (LILRBs) have long cytoplasmic tails containing ITIMs that transmit negative regulatory signals [9, 10]. Activating LILRs (LILRAs) have short cytoplasmic domains lacking signalling motifs; the charged arginine residue in their transmembrane domain links with ITAMs of the FcRγ chain to transduce activation [9–11]. LILRAs

**Table 1.** Consensus sequences for ITAMs, ITIMs and ITSMs

| | | |
|---|---|---|
| ITIM | S/I/V/LxYxxI/V/L | 6 amino acids |
| ITAM | YxxI/Lx$_{(6-12)}$YxxI/L | 14–20 amino acids |
| ITSM | TxYxxI/V | 6 amino acids |

**Table 2.** ITAM sequences in adaptor proteins involved in immune signalling

| | |
|---|---|
| FcRγ | DGV**Y**TG**L**STRNQET**Y**ET**L** |
| DAP-12 | E<u>SP**Y**QE**L**</u>QGQRSDV**Y**SD**L** |
| Igα | ENL**Y**EG**L**NLDDC<u>SM**Y**ED**I**</u> |
| CD3γ chain | DQL**Y**QP**L**KDREDDQ**Y**SH**L** |

Consensus ITIM sequences are underlined, whilst canonical ITAM residues are highlighted in bold. Adapted from [2].

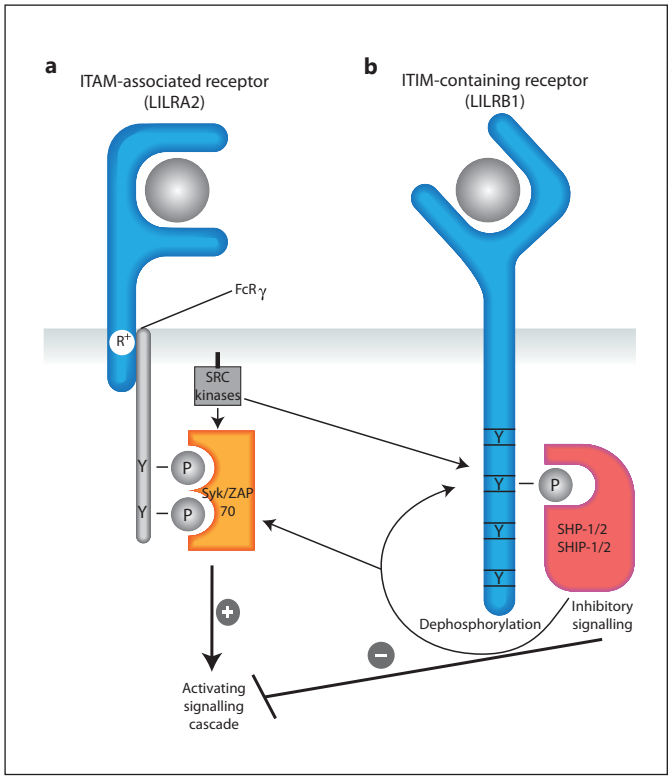


**Fig. 1.** Activating LILRA2 and inhibitory LILRB1 are examples of conventional ITAM- and ITIM-containing receptors, respectively. **a** Following ligand binding, LILRA2 complexes with the common γ chain of the Fc receptor, altering its conformation and permitting phosphorylation of both tyrosine residues in the ITAM by Src protein tyrosine kinases. Syk family kinases are then able to bind via their dual SH2 domains and phosphorylate downstream proteins that transduce cellular activation signals. **b** Ligand binding to inhibitory LILRB1 leads to conformational changes in its intracellular region, facilitating phosphorylation of single tyrosine residues in the ITIM motif. These phosphorylated tyrosine residues recruit tyrosine phosphatases SHP-1, SHP-2 and/or SHIP initiating a cascade of inhibitory signalling.

and LILRBs, which are widely co-expressed on the surface of leucocytes [9–12], have structural homology of >80% on their ligand binding extracellular domains [9] and may fine-tune signalling through co-engagement by shared ligands. Although ligands for most LILRs are unknown, recent evidence showing shared binding of activating LILRA1, LILRA2 and LILRA3, and inhibitory LILRB1 and LILRB2 to a number of MHC class I molecules supports this [8, 13]. LILRs represent a complex system in which pairing of closely related activating and inhibitory receptors may regulate responses in innate immune cells, lymphocytes and antigen-presenting cells.



This is supported by overwhelming in vitro evidence and strong associations of abnormal LILR expression in diseases characterised by excessive and/or perturbed chronic inflammation [14–18]. Other common examples of paired activating and inhibitory receptors that may regulate cellular activation include killer cell-activating and -inhibitory receptors [19], FcγRI and FcγRIIb IgG receptors, paired Ig-like receptors and triggering receptor expressed on myeloid cells (TREMs) [20, 21].

On the other hand, B cell signalling provides a well-established model of ITAMs and ITIMs as complementary mechanisms wherein co-engagement of unrelated activating and inhibitory receptors by their respective ligands determines the net outcome. BCR Ig-α and Ig-β subunits each contain an ITAM sequence (fig. 2a). Upon binding to foreign antigens, BCRs aggregate forming an ITAM-driven signalosome that generates potent activating signals [22, 23] (fig. 2a). This is in part counteracted by an ITIM-containing cell surface receptor (CD22) expressed on B and plasma cells [23] (fig. 2a). CD22, which is excluded from the activating signalosome, simultaneously binds sialic acid-bearing ligands leading to tyrosine phosphorylation of its ITIM residues and recruitment of SHP-1 and SHIP-1 to produce inhibitory signals that prevent B cell hyperstimulation [22]. Interestingly, engagement of BCR by a self-antigen leads to formation of a signalosome that includes CD22 and other inhibitory receptors providing a strong negative signal encouraging tolerance [22]. Similarly, cross-linking of BCR with antigen and ligation of the inhibitory FcγRIIb with Ig have been shown to fine-tune BCR-mediated downstream activating signalling [20] (fig. 2b).

## The Plot Thickens – Inhibitory ITAMs, Activating ITIMs and Immunoreceptor Tyrosine-Based Switch Motifs

Whilst the ITAM-mediated activation and ITIM-mediated counter-regulation is an attractive model for immune homeostasis, gathering evidence suggests that immune signalling can be much more complex. ITAMs and ITIMs may paradoxically be able to transduce negative (coined as ITAMi) and positive signalling (ITIMa), respectively. Recent studies by our group and others show that pre-stimulation of leucocytes through cross-linking of activating LILRA2 or LILRA4 profoundly suppressed pro-inflammatory mediator production in response to TLR ligation on monocytes [24] and dendritic cells [25], respectively. Importantly, the profound inhibitory effects

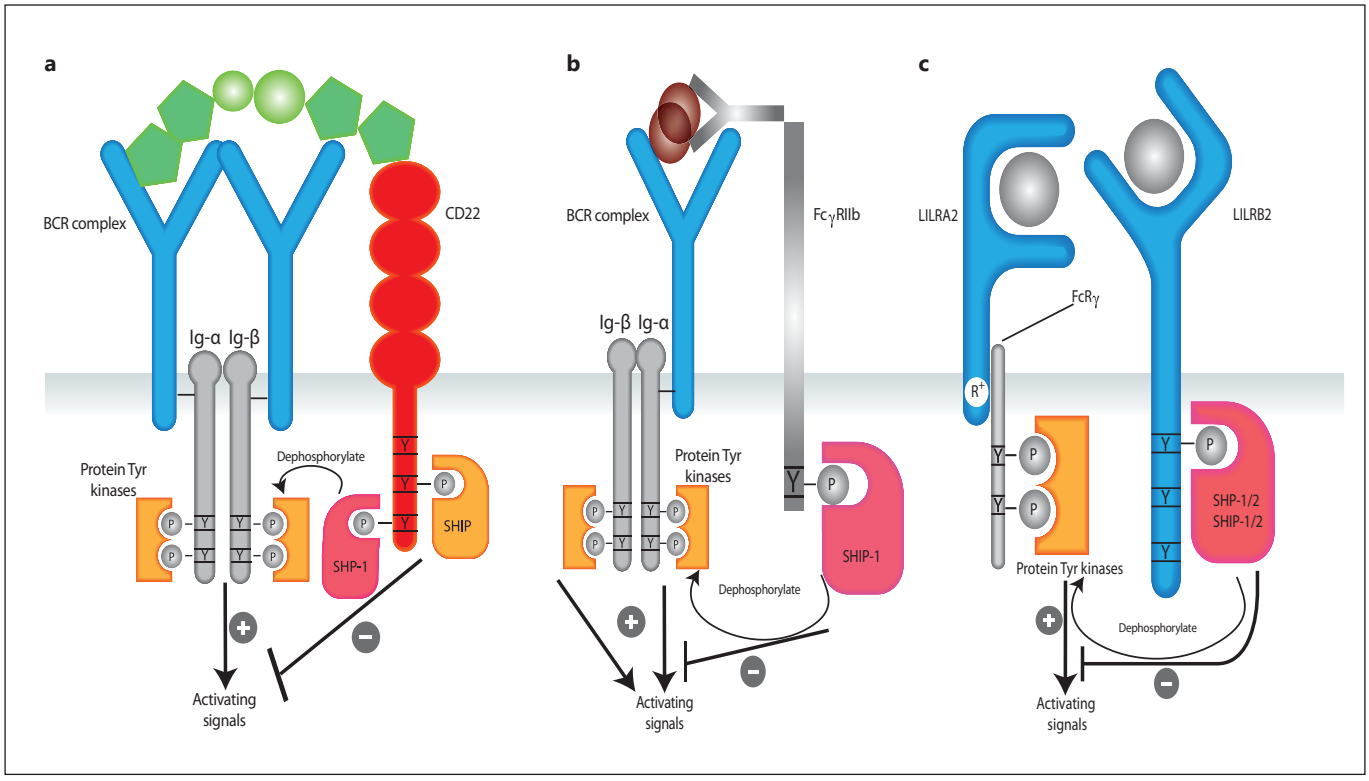


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**Fig. 2.** ITAM and ITIM crosstalk regulating cellular activation. **a** Engagement of ITAM-containing BCRs by foreign and/or self-antigens causes cellular activation. This is counter-regulated by ITIM-containing CD22 likely via shared ligands such as sialic acid motif-bearing glycans, widely expressed on native cells and foreign organisms. When the sialic acid motifs are 'self', CD22 exerts a net inhibitory signal by counteracting BCR-mediated activation. When the antigen is foreign, the inhibitory effects of CD22 are lower permitting a robust BCR-mediated response. **b** Alternatively, binding of BCR to immune complexes causes phosphorylation of the ITAM sequences on the intracellular Ig-α and Ig-β chains leading to cellular activation. This activation can be counter-regulated by shared binding of these immune complexes to the ITIM-containing FcγRIIb. **c** Activating LILRA2 and inhibitory LILRB2 are co-expressed on the surface of mono-myeloid cells and share 82% homology on their ligand-binding domains. They represent an ideal pair that may fine-tune cellular activation via co-engagement by similar or shared ligands.

of LILRA2 on monocytes appear to be highly selective to pro-inflammatory cytokines and not restricted to the regulation of soluble mediators [24]. For instance, LILRA2 cross-linking significantly suppresses lipopolysaccharide (LPS)-mediated tumour necrosis factor (TNF) production, Fc receptor-dependent phagocytosis [24] and GM-CSF-mediated dendritic cell maturation [25]. These results suggest that LILR-mediated immune regulation is much more complex than simple transduction of activating or inhibitory signals. We and others have proposed that the combined selective activating and inhibitory functions of activating LILRs are an important mechanism of LILR-mediated polarisation of the immune system [8, 18, 25]. This is supported by selective overexpression of LILRA2 observed in patients with Th-2-dominant lepromatous leprosy but not in Th-1-dominant tuberculoid leprosy in vivo [26], and the production of Th-2 cytokines upon LILRA2 cross-linking in monocytes [24] and macrophages infected with *Mycobacterium tuberculosis* [25].

Despite the overwhelming evidence showing activating LILRs transducing inhibitory signals, the underlying mechanisms are poorly understood. Some evidence from other similar ITAM-containing receptors indicate the nature of a ligand and its binding avidity/affinity may determine the net outcome. A typical example is ligation of FcαR1 by monomeric IgA eliciting anti-inflammatory effects, while IgA oligomers mediate strong pro-inflammatory effects [27]. Monomeric IgA induces partial 'weaker' phosphorylation of ITAMs that simultaneously recruit Syk and SHP-1 resulting in net inhibition [28]. By contrast, multimeric IgA induces greater phosphorylation

with enhanced recruitment of Syk family kinases but not SHP-1 leading to net cell activation [28]. Given that both FcαR1 and activating LILRs lack cytoplasmic domains but share the ITAM-bearing FcRγ chain adaptor protein, the opposing effects observed in activating LILRs may be mediated by similar processes.

The ability of ITAMs to generate inhibitory signalling has been described in a variety of other ITAM-containing receptors [29, 30]. O'Neill et al. [29] discovered that constitutive phosphorylation of SHIP-1 and its adaptor protein Dok-1 in anergic B cells is due to BCR ITAM monophosphorylation. By contrast, engagement with foreign antigens causes dual phosphorylation of BCR ITAMs leading to potent B cell activation [29]. This phenomenon has recently been postulated as a therapeutic mechanism following the administration of intravenous Ig for inflammatory disorders [31]. Another well-established example of an ITAM-containing adaptor protein with dual activating and inhibitory functions is DAP-12 [32]. DAP-12 transduces activating signals in a heterodimeric receptor complex with KIR, Ly49 and TREM receptors [32], but macrophages with genetic deletion of DAP-12 were shown to produce higher levels of pro-inflammatory cytokines suggesting DAP-12-mediated inhibitory signalling [33]. Moreover, association of DAP-12 with natural cytotoxicity receptor NKp44 [34] or sialic-acid Ig-binding lectin-H inhibited interferon (IFN)-α production in response to CpG oligonucleotides in IFN-producing effector cells [35]. Although not fully elucidated, one proposed molecular mechanism for DAP-12-mediated inhibition is a consensus ITIM 'SPYQEL' within its proximal ITAM [32] (table 2). Interestingly, sequestration of proximal activating signalling molecules such as Syk by ITAM containing EBV LMP2A has been shown as an effective immune evasion strategy leading to latent infection [36]. Whether such mechanisms contribute to ITAM-mediated inhibition by native receptors remains to be elucidated.

In parallel to the effect of ITAMi, there have been several, albeit fewer, reports suggesting that ITIMs have the capacity to generate activating signalling under certain circumstances (ITIMa). In the first such report, published in 2004, TREM-like transcript 1 was considered to have ITIMa properties [37]. This surface receptor expressed on platelets has two ITIM sequences on its intracellular domain [38]. Barrow et al. [37] found that one of the two ITIMs (Y281) of TREM-like transcript 1 enhanced FcεRI-mediated intracellular calcium flux through recruitment of SHP-2. Recently, our research group has used site-targeted mutagenesis to study the role of tyrosine residues in each of three ITIMs of LILRB4 and found that the position of phosphorylated tyrosine residues dictates whether the net effect is inhibitory or activating [unpubl. data]. Although the mechanisms involved are not well defined, several other ITIM-containing receptors have been shown to transduce activating signals. These include induction of nitric oxide production in macrophages upon ligation of signal-regulatory protein-α [39], activation of transfected COS-7 cells upon ligation of ITIM-containing chemokine receptor CCK2R [40–42] and dual activating and inhibitory roles of the paired Ig-like receptor B on murine eosinophils treated with eotaxin and leukotriene B4, respectively [43].

Immunoreceptor tyrosine-based switch motifs (ITSMs) further confound the one-dimensional ITAM- versus ITIM-mediated immune-homeostasis model. The ITSM contains 6 amino acid residues with the consensus sequence TxYxxI/V [44] (table 1). The roles of these motifs are less well understood than those of ITAMs and ITIMs. It becomes immediately obvious, however, that there are similarities between the consensus sequence for ITSMs and those of ITAMs and ITIMs (tables 1, 2) [2, 44]. Indeed, an ITSM could share its tyrosine residue with the first tyrosine residue in an ITAM or ITIM. ITSMs have been identified on a number of molecules involved in mediating immune responses, including inhibitory KIRs [45], CD150 [44], sialic acid-binding Ig-like lectins [46] and programmed cell death protein 1 [47]. As yet, there are few papers providing insight into the function of ITSMs, but it is likely that they moderate ITAM/ITIM effects due to their sequence similarities and often close proximity [47]. This is supported by a recent study showing phosphorylation of both ITIMs and ITSMs found in close proximity in the orexin receptor OX1R was necessary to provide the two SH2 domains needed for functional SHP-2 binding [48].

## Regulation of Immune Responses by Antagonist/Agonist Molecules

Production of soluble molecules that competitively antagonise their membrane-bound counterparts is one of the most common and effective mechanisms of regulating cellular responses. Some soluble receptors represent splice variants of their membrane-bound counterparts [49], some are cleaved products of surface receptors [50, 51] and some are molecules encoded by separate genes [52]. They act as decoy proteins by binding to the membrane-bound receptor or competitively binding ligand(s).

Many such examples exist within the immune system and other biological processes. One such example is IL-1 and its receptors. In brief, interaction of IL-1α and IL-1β with the IL-1 receptor (IL-1R1) initiates a cascade of activation signalling via the upstream Toll/IL-1R (TIR) domain and the downstream MAP kinase-nuclear factor (NF)κB pathway [53]. This pathway is counter-regulated through several key mechanisms. First, through production of soluble IL-1R antagonist that terminates response by competitively binding IL-1R1 [54]. Crucially, IL-1R antagonist production is up-regulated by a broad range of inflammatory stimuli, including LPS, immune complexes and pro-inflammatory cytokines such as IL-1 itself [52] providing a negative feedback loop. Secondly, via up-regulation of a true decoy receptor, IL-1R2, which possesses an IL-1-binding extracellular domain but lacks an intracellular signalling domain [55] and, finally, inhibition through single Ig IL-1R-related molecule that is shown to down-regulate IL-1α or IL-1β signalling via competitive interaction with MyD (myeloid differentiation primary-response protein) 88 [56]. Other typical examples include a promiscuous chemokine decoy receptor D6, which is shown to bind at least 12 distinct chemokines causing their internalisation and proteasomal degradation [57], regulation of apoptosis signalling via Fas-Fas ligand and decoy receptor 3 [58], regulation of bone remodelling by myeloid lineage cells via RANK (receptor activator of NFκB), RANK ligand and osteoprotegerin [59], and control of angiogenesis involving vascular endothelial growth factor with the dummy receptor VEGFR-1 [60].

### Immune Termination by Receptor De-/Ubiquitination

Ubiquitin is a highly conserved 8.5-kDa peptide that may mediate termination of immune responses by degradation of key regulatory proteins through its binding to lysine residues [61]. The ubiquitination reaction is catalysed by the sequential and cooperative actions of three enzymes: the ubiquitin-activating enzyme (E1), the ubiquitin-conjugating enzyme (E2) and the ubiquitin ligase (E3) [62]. Ubiquitin possesses seven lysine residues that can result in poly-ubiquitinated chains. Poly-ubiquitination formed via Lys48 marks target proteins for enzymatic degradation while poly-ubiquitination via Lys63 generally influences cell signalling by altering protein-protein interactions or by influencing cellular localisation [61]. Generally, a chain of at least four ubiquitin residues is required for proteasomal degradation [63]. Ubiquitination plays a vital role in many steps in innate immunity and is extensively reviewed by Bhoj and Chen [64].

A typical example regulated by several ubiquitination-related pathways is NFκB-mediated activation [64, 65] (fig. 3). In brief, constitutive binding of NFκB to IκB prevents its nuclear translocation, effectively keeping it in its inactive form in the cytoplasm. Activated IκB kinase (IKK) degrades IκB, allowing NFκB nuclear translocation and the induction of transcripts for pro-inflammatory mediators [65]. Ligation of TLRs [66], NOD (nucleotide-binding oligomerisation domain-containing protein)-like receptors [67, 68] or RIG-1-like receptors [69] leads to the NFκB-mediated activation and concomitant induction of the E3 ubiquitin ligases that mediate poly-ubiquitination of key intracellular regulatory molecules such as TNF receptor-associated factor (TRAF)2, TRAF3, TRAF6 or TRIM25 that act as both adaptors and E3 ubiquitin ligases catalysing Lys63-linked self-ubiquitination and the ubiquitination of other downstream signalling molecules [62]. In TLR4 responses, TRAF6 causes poly-ubiquitination of the IKK-regulatory subunit NEMO at Lys63 [63–65] (fig. 3). The IKK complex phosphorylates IκB, triggering its Lys48-linked ubiquitination, proteosomal degradation and its dissociation from p50 and p65 components of NFκB thus allowing nuclear translocation and DNA binding of NFκB thereby up-regulating the transcription of pro-inflammatory genes [63–65] (fig. 3). This is counter-regulated by concomitant up-regulation of the de-ubiquitinating enzymes A20 and CYLD and rapid de novo synthesis of IκB [63–65]. A20 forms a ubiquitin-editing complex that prevents Lys63 poly-ubiquitin chain formation by TRAF6 and IKK, leading to inhibition of NFκB signalling [63–65] (fig. 3). Newly synthesised and Lys48-deubiquitinated IκB provide another negative regulation of NFκB signalling [62].

### Auto-Inhibition of Immune Responses by Intrinsic Inhibitory Molecules

Auto-inhibition is another example whereby a stimulus initiates not only an appropriate positive response, but also begins the process of curtailing further responses to the same stimulus. In the innate immune system, the regulation of TLR signalling through the synthesis of new intracellular inhibitory molecules is one of the major pathways that fine-tune cellular responses. TLR-induced signalling follows two major pathways, MyD88-dependent and MyD88-independent pathways [70] (fig. 3). In brief, TLR (primarily TLR4) ligation recruits

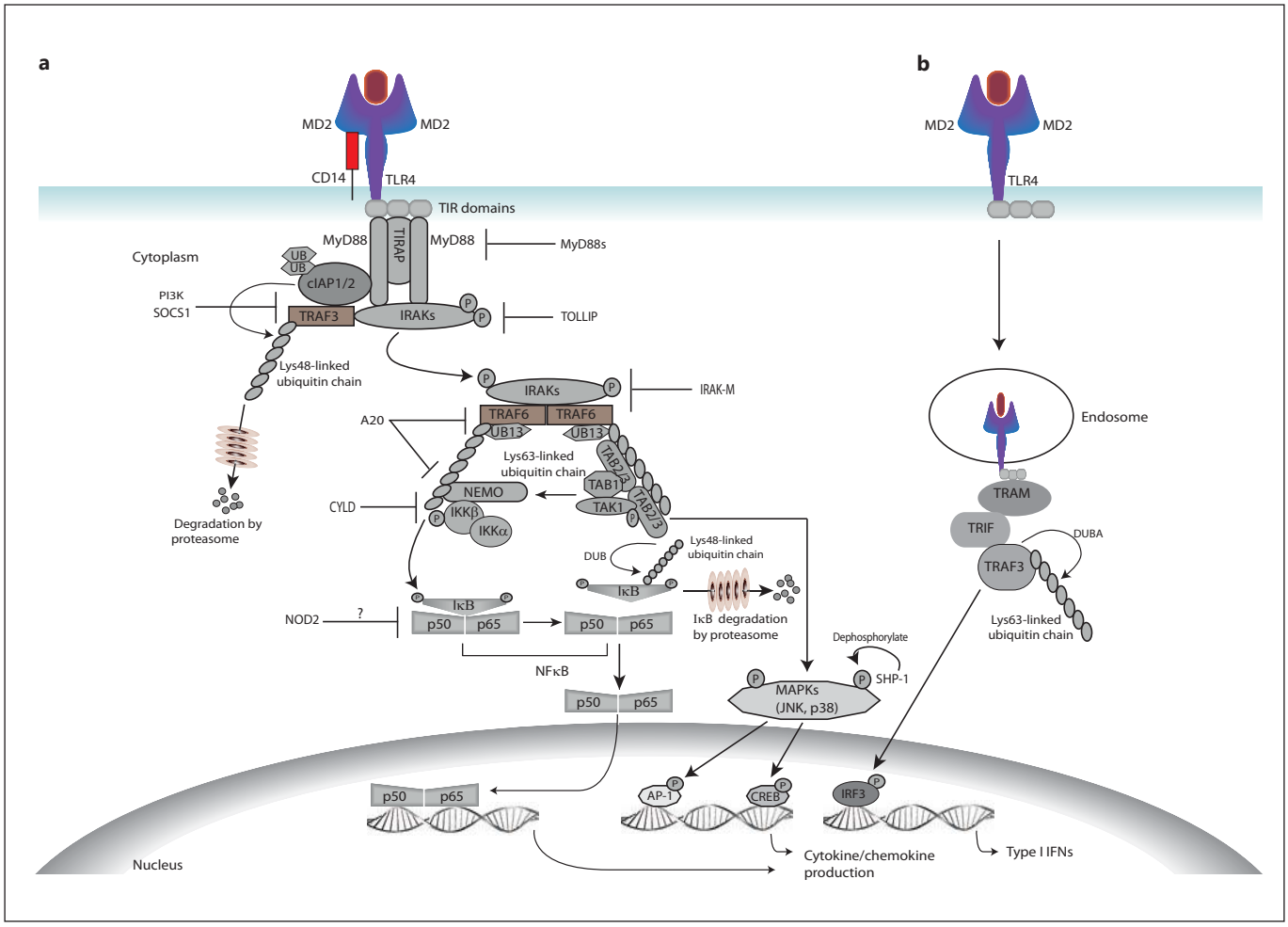


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**Fig. 3.** Termination of innate immune signalling by intracellular regulators. **a** In MyD88-dependent TLR signalling, Lys63 ubiquitination of TRAF6 causes its oligomerisation and triggers its E3 ligase activity. TRAF6 then synthesises poly-ubiquitin chains that bind the NEMO subunit of the IKK complex and the TGF-activating kinase (TAK)-binding protein (TAB2 and TAB3) subunits of the TAK1 complex with subsequent activation of kinases. Phosphorylated IκB (inhibitor of NFκB) is Lys48-linked poly-ubiquitinated and undergoes proteosomal degradation, releasing the NFκB dimer p50/p65 into the nucleus to switch on target genes including IKK inhibitor A20. Phosphorylated TAK1 may also induce target genes via downstream MAPK pathways. NFκB signalling is selectively terminated by A20- and probably CYLD-mediated Lys63 de-ubiquitination of TRAF6 and IKK leading to inhibition of IKK. Moreover, IκB is rapidly de novo synthesised and its Lys48 de-ubiquitination prevents its proteosomal degradation. **b** In MyD88-independent TLR signalling, de-ubiquitination of TRAF3 by DUBA is a specific and critical negative regulator of type 1 IFN production. Moreover, TLR signalling is auto-inhibited by several molecules that are induced by activation of TLRs. These include MyD88s, which competitively blocks association of IRAK4 with MyD88, IL-1R-associated kinase M (IRAK-M), which inhibits dissociation of IRAK1-IRAK4 complexes from the receptor, and other inhibitory proteins such as TOLLIP, SOCS1, PI3K, NOD2 and SHP-1. TIRAP = TIR domain-containing adaptor protein; cIAP = cellular inhibitor of apoptosis; TRIF = TIR-domain-containing adapter-inducing IFN-β; TRAM = TRIF-related adaptor molecule; IRF3 = IFN-regulatory factor 3; AP-1 = activator protein-1; CREB = cyclic AMP-responsive element-binding protein.

MyD88 and activates IL-1R-associated kinases (IRAKs) and allows propagation of downstream MAP kinase and/or NFκB activation pathways [71] (fig. 3). To counteract this, monocytes and macrophages may rapidly up-regulate intracellular negative regulators (fig. 3). These include MyD88s (a short form of MyD88), IRAK-M, SOCS1 (suppressor of cytokine signalling 1), NOD2, PI3K (phosphatidylinositol 3-kinase), TOLLIP (Toll-interacting protein), A20 and CYLD [72] and SHP-1 [73] (fig. 3).

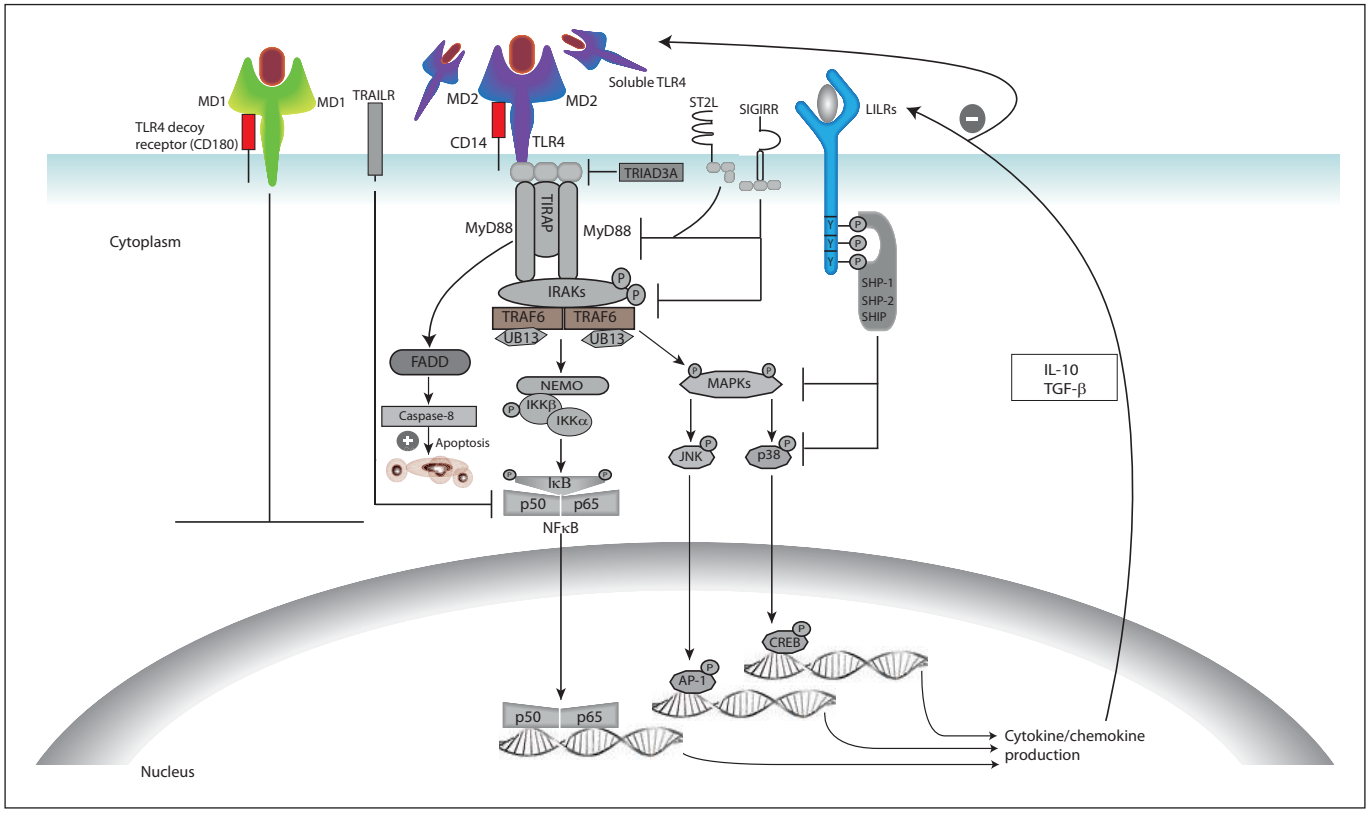


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**Fig. 4.** Negative regulation of innate immune responses by down-regulation of membrane receptors, induction of soluble receptors, up-regulation of decoy receptors, activation of transmembrane inhibitory molecules and/or by induction of apoptotic signals. TLR signalling can be controlled by reducing surface receptor expression through E3 ubiquitin ligase (TRIAD3A)-mediated ubiquitination and degradation or inhibition of expression by anti-inflammatory cytokines. Soluble TLRs could compete with their membrane-bound counterparts for microbial ligands or interact with MD2 and/or CD14 co-receptors preventing the formation of functional MD2-TLR complexes. Up-regulation of TLR4 decoy receptor (CD180) and its co-receptor MD1 by pro-inflammatory mediators can induce negative regulation via competitive ligand binding. Another mechanism by which TLR signalling can be abrogated is by transmembrane inhibitory receptors such as TIR domain containing receptors [single Ig IL-1R-related molecule (SIGIRR) and ST2] and ITIM-containing receptors [LILRs and TNF-related apoptosis-inducing ligand receptor (TRAILR)]. Under certain circumstances, TLR ligation may cause recruitment of FAS-associated death domain (FADD) to MyD88 and trigger caspase-dependent apoptosis of hyper-activated cells.

MyD88s is a truncated alternatively spliced protein of the most important adaptor in TLR signalling. It is up-regulated in response to LPS and pro-inflammatory cytokines, thus competitively preventing IRAK-mediated activation [74]. Interestingly, induction of MyD88s can inhibit NFκB signalling but permits continued JNK and activator protein-1 activation [75], indicating selective regulation that ensures proportionate response. IRAK-M is an inactive IRAK family member without kinase activity that competitively abrogates the IRAK-mediated activation cascade [76]. In MyD88-independent TLR signalling, the intracellular counter-regulatory pathways are less well understood [77, 78] although there is evidence that de-ubiquitination plays an important role [79, 80] (fig. 3).

Other mechanisms that regulate TLR responses include down-modulation of expression/function of TLRs and their accessory molecules [81] by TRIAD3A-mediated ubiquitination [72] or by anti-inflammatory mediators such as IL-10 [82] and TGF-β [83]; through expression of a soluble TLR4/CD14; via up-regulation of a true TLR4 decoy receptor, RP105 or CD180, and its accessory molecule MD-1 [84] (fig. 4); through transmembrane protein regulators such as LILRs [24], SIRGIRR, TNF-related apoptosis-inducing ligand receptor and ST2L, and through induction of apoptosis [72] (fig. 4). Interest-

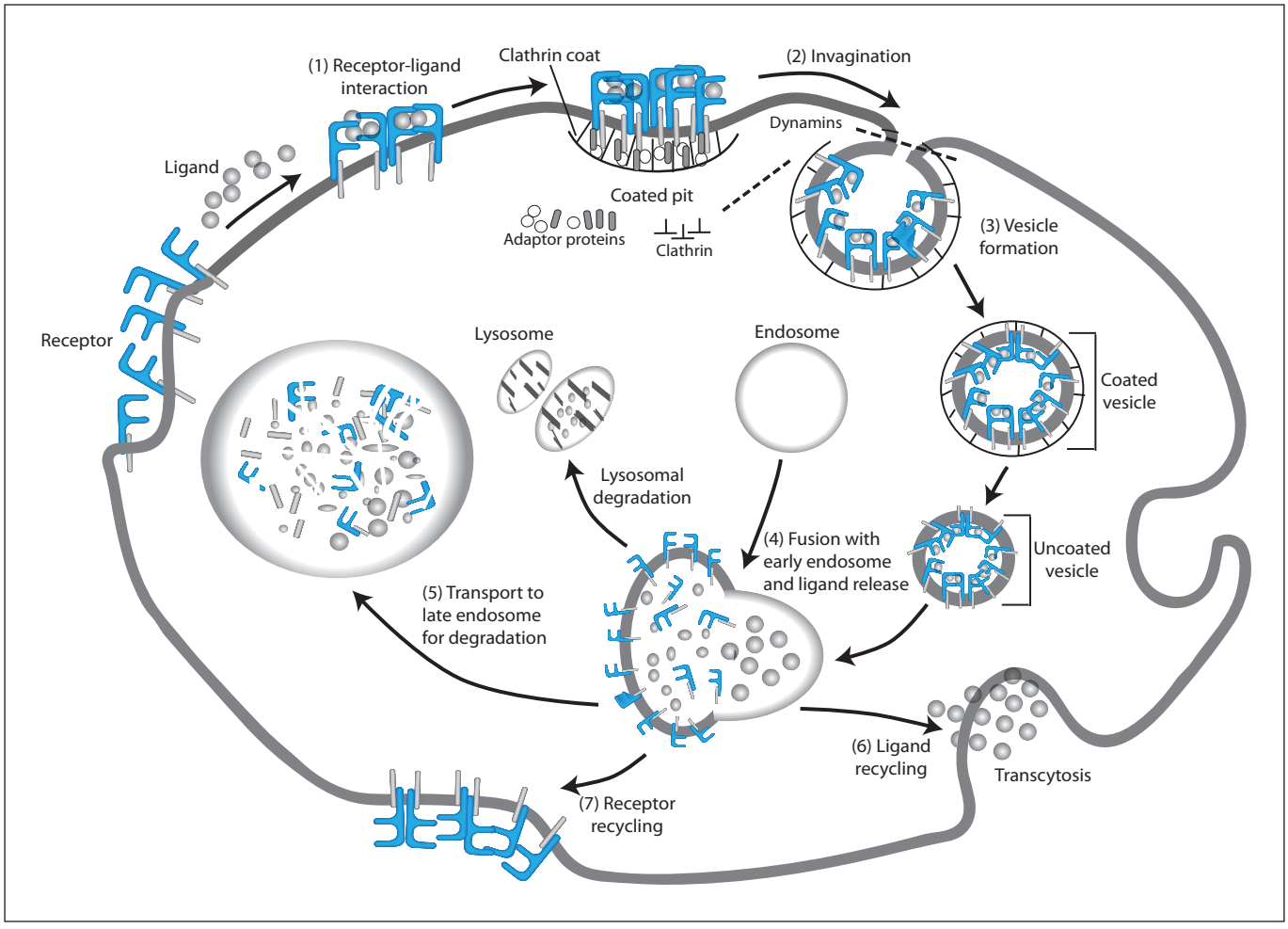


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**Fig. 5.** Termination of signal transduction by receptor endocytosis. Ligand binding to surface receptors transduces activating signals (1) and simultaneously initiates signals that cause lateral diffusion of receptor-ligand complexes to clathrin-coated pits, membrane invagination (2) and generation of coated vesicles (3). The vesicles then undergo a process of uncoating (a precondition for vesicles to join to other membranes), fuse with early endosomes and release ligands (4). The ligand is transported either to late endosome and/or lysosome for proteosomal and/or lysosomal degradation (5) or is recycled and secreted by transcytosis (6). Similarly, receptors may undergo proteosomal degradation or recycle to the cell surface (7). Adaptor proteins including α and β adaptins, μ chain and σ chain form complexes that mediate formation of clathrin pits through interaction with membrane-bound receptors. Dynamin is a large GTPase implicated in budding and cleavage of vesicles (clathrin coated) from the parent membrane.

ingly, treatment of cells with LPS temporarily down-regulates TLR4 while promoting the decoy receptor RP105 [85], further enhancing the counter-regulation [85].

### Termination of Immune Responses by Receptor Endocytosis

Physically removing a receptor from the cell surface is another effective way of regulating/terminating activation signals. A classic example of this is ligand binding-dependent internalisation of G-protein-coupled receptors, a broad family of receptors that play a key role in various biological processes [86]. In brief, binding of a ligand to these complex receptors induces phosphorylation and conformational changes of the different subunits of the receptor leading to transduction of activation signals [87]. This is followed by internalisation of ligand-receptor complexes and their transport into the endosomes [88] (fig. 5). In the endosomes, the ligand is removed and undergoes rapid degradation, while the receptor is either degraded or is recycled back to the cell

surface [89]. Ligands for G-protein-coupled receptors relevant in inflammation include chemokines, prostaglandins, bradykinins and platelet-activating factors [86]. Other receptors that can undergo similar processes of endocytosis and degradation include epidermal and vascular endothelial growth factor receptors [90] and platelet-derived growth factor receptors [91].

## Mediators Involved in the Resolution of Inflammation

In recent years, a number of mediators that may bridge the immune termination events and subsequent resolution and/or repair of inflammation have been identified [92–99]. These include a new class of pro-resolution lipid mediators, such as arachidonic acid-derived lipoxins, ω–3 polyunsaturated fatty acid-derived resolvins, protectins, and maresins [93, 94]. Pro-resolution lipids typically produced in the later stages of inflammation promote resolution through regulation of inflammatory cell recruitment, polarisation and death [94]. Pro-resolutions lipids may exhibit both pro-inflammatory and pro-resolution properties [95] allowing effective but well-regulated inflammatory responses and measured tissue repair that limits extensive fibrosis. Although the list is far from comprehensive, other pro-resolution or dual-effect mediators that regulate pro-resolving molecular and cellular circuits are several micro-RNAs [96], annexins [97], nitric oxide [98] and members of the S100 proteins [99].

## Host Response to Foreign Antigens – A High Stakes Game

We have outlined some important mechanisms by which immune responses are regulated. As an organism, we must respond aggressively to foreign antigens, but an over-exuberant reaction is damaging and potentially fatal. Immune termination is too important to fail, thus, it is multilayered, complex and tight. We have seen how immune signalling can be self-limiting through several intracellular and extracellular mechanisms that ensure effective termination. Moreover, multiple independent processes might collaboratively act to tightly regulate excessive inflammatory responses. These processes may occur simultaneously and/or sequentially and are highly dynamic. Identification and functional characterisation of key molecules involved in immune regulation/termination and understanding the underlying mechanisms would have significant clinical implications, though, much remains to be explained with regard to the relative contribution of each process.


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