Biochimica et Biophysica Acta 1813 (2011) 2165–2175

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Signal integration, crosstalk mechanisms and networks in the function of inflammatory cytokines☆

M. Lienhard Schmitz [a,*,1], Axel Weber [c,1], Thomas Roxlau [c], Matthias Gaestel [b], Michael Kracht [c,**]

[a] Institute of Biochemistry, Medical Faculty, Justus-Liebig-University Giessen, D-35392 Giessen, Germany
[b] Institute of Biochemistry, Hannover Medical School, D-30625 Hannover, Germany
[c] Rudolf-Buchheim-Institute of Pharmacology, Justus-Liebig-University Giessen, D-35392 Giessen, Germany

ARTICLE INFO

Article history:
Received 22 March 2011
Received in revised form 31 May 2011
Accepted 1 June 2011
Available online 20 July 2011

Keywords:
Cytokine signaling network
IL-1
TNF
Feed-forward loop
Feedback loop
Inflammation

ABSTRACT

Infection or cell damage triggers the release of pro-inflammatory cytokines such as interleukin(IL)-1α or β and tumor necrosis factor (TNF)α which are key mediators of the host immune response. Following their identification and the elucidation of central signaling pathways, recent results show a highly complex crosstalk between various cytokines and their signaling effectors. The molecular mechanisms controlling signaling thresholds, signal integration and the function of feed-forward and feedback loops are currently revealed by combining methods from biochemistry, genetics and *in silico* analysis. Increasing evidence is mounted that defects in information processing circuits or their components can be causative for chronic or overshooting inflammation. As progress in biosciences has always benefitted from the use of well-studied model systems, research on inflammatory cytokines may function as a paradigm to reveal general principles of signal integration, crosstalk mechanisms and signaling networks.

1. Cytokines and their function

Cytokines have been discovered almost half a century ago as small proteins or polypeptides that orchestrate cellular communication. They may act in an autocrine, juxtacrine, paracrine, endocrine or intracellular fashion and can be grouped by common biological characteristics, as summarized in Table 1. Pathogen-associated patterns (PAMPs) or damage- or danger-associated molecular patterns (DAMPs) are sensed by specific receptors. In turn, activation of these receptors leads to the induced synthesis and release of inflammatory cytokines (interleukins (e.g. IL-1, IL-6, IL-33), tumor necrosis factor (TNF)α, chemokines and macrophage migration inhibitory factor (MIF). These cytokines coordinate the host cell response in order to combat the infection [88], as schematically displayed in Fig. 1A. PAMPs are generated from products of pathogenic microorganisms [133], while DAMPs are triggers for sterile inflammation by endogenous mediators or exogenous stressors [22,87]. Cytokines are not produced and secreted from discrete glands but can be in principle produced by all nucleated cells to regulate the immune response. Pro-inflammatory cytokines represent a paradigm for illustrating how basic research feeds in successful translational research. A number of novel inflammatory cytokines have been discovered in recent years (IL-32, IL-33, IL-34, IL-35, IL-36, IL-37) whose functions are being explored at the moment [27,32,34,67,96,119,154]. On the other hand, the "oldest" pro-inflammatory cytokines IL-1α, IL-1β and TNFα have been studied in patients for quite some time [48] and antagonistic biologicals are in clinical use (see below).

2. The importance of cytokine regulatory loops

Once cytokines have been released in response to initial signals from PAMPs or DAMPs, they can bind to their own receptors and thus help to potently amplify the innate immune response. Rapid mounting of the immune response is absolutely essential to counteract rapidly growing invading pathogens. Cytokine-triggered signal amplification employs several feed-forward signaling loops. Once the infection has been cleared, the inflammatory process is antagonized by strong negative feedback loops that ensure the controlled shut-down of the immune response (Fig. 1A). Recent

☆ This work was supported by grants from the Deutsche Forschungsgemeinschaft Kr1143/4-3, Kr1143/6-1, Kr1143/7-1, SFB566 (Z02) and SFB566 (B12) to M.K. and SCHM1417/4-2, SCHM 1417/7-1, SCHM 1417/8-1, GRK1566/1, SFB/TRR81 to M.L. Schmitz and Deutscher akademischer Austauschdienst (A/08/98404) to M.L.S. Work from M.K. and M.L.S. was further supported by the Excellence Cluster Cardio-Pulmonary System (ECCPS), and the LOEWE/UGMLC program.

* Correspondence to: M.L. Schmitz, Institute of Biochemistry, Medical Faculty, Justus-Liebig-University, Friedrichstrasse 24, 35392 Giessen, Germany. Tel.: +49 641 9947570; fax: +49 641 9947589.
** Correspondence to: M. Kracht, Rudolf-Buchheim-Institute of Pharmacology, Justus-Liebig-University Giessen, Frankfurter Straße 107, D-35392 Gießen, Germany. Tel.: +49 641 99 47600; fax: +49 641 99 47619.
E-mail addresses: lienhard.schmitz@biochemie.med.uni-giessen.de (M.L. Schmitz), Michael.Kracht@pharma.med.uni-giessen.de (M. Kracht).
[1] Contributed equally.

0167-4889/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2011.06.019

Table 1
Functional classes of cytokines involved in inflammation (adapted from [32,35,97]. Blue colors indicate therapeutically used recombinant cytokines, purple colors indicate cytokines for which inhibitory drugs have been approved. Abbreviations: CD40L, CD40 ligand; CNS, central nervous system; Gro, growth-related; IFN, interferon; IL, interleukin, IL-1Ra, IL-1 receptor antagonist; MCP1, monocyte chemotactic protein-1; MIF, macrophage migration inhibitory factor; MIP1α, macrophage inflammatory protein-1α; RANKL, receptor activator of nuclear factor kappa-B ligand; Rantes, regulated upon activation, normal T-cell expressed; TGFβ, transforming growth factor beta; TNF, tumor necrosis factor.

functional class	major physiological or pathophysiological effects	examples
cytokines regulating adaptive immune functions		
lymphocyte growth and differentiation factors	clonal expansion of T-cells, ↑ Th1/TH2/TH17 responses, Th1/Th2/Th17 polarization, B-cell activation, 8-cell growth, auto-immune responses	IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, IL-15, IL-17, IL-18, IL-23, IL-25, IL-33, IL-35, IFNγ
cytokines positively regulating innate immune functions		
pro-inflammatory cytokines	↑ inflammatory mediators, ↑ innate immune responses, ↑ activation of most cell types, pro metastatic, ↑ bone-resorption, ↑ acute phase proteins	IL-1 α, IL-1 β, TNFα, IL-6, IL-12, IL-18, IL-23, IL-32, IL-33, IL-34, IL-36, MIF, CD40L, RANKL
chemokines	↑ cellular emigration, ↑ leucocyte infiltration, ↑ neovascularization, ↑ activation of many cell types, pro-metastatic	IL-8 (CXCL8), MCP1 (CCL2), MIP1α (CCL3), Rantes (CCL5), Groα/β/γ (CXCL1,2,3), MIF, others
interferons		
type II IFN	macrophage activation, ↑ MHC class II	IFNγ
type I IFN	anti-viral, ↑ MHC class I, anti-inflammatory, anti-angiogenic	IFNα, IFNβ
cytokines downregulating innate immune functions		
anti-inflammtory cytokines	↓ inflammatory mediators, ↓ cytokine-mediated lethality, ↓ autoimmune and autoinflammatory disease, ↑ fibrosis, anti-tumor effects	IL-10, IL-13, TGFβ, IL-22, IL-37 IL-1 Ra, IFNa/β

evidence in the IL-1 system suggests that dysregulation of either feed-forward or of feedback loops can be causative for diseases. A small number of patients with genetic defects in positive and negative feedback loops in extracellular control of IL-1 have been identified [3,4,36,106]. These patients develop systemic sterile inflammation of varying severity. Constitutive activity of the inflammasome complex which controls processing and release of IL-1 results in periodic fever syndromes (Fig. 1B), whereas life-threatening disease results from lack of negative control by the IL-1 receptor antagonist IL-1Ra (Fig. 1C/D). Even though this type of positive and negative feedback control appears to be relatively simple, it is of great pathophysiological relevance and underscores the importance of studies on regulatory circuits in inflammatory cytokine action.

3. Levels of complexity of intracellular inflammatory cytokine signaling

Research on signal transduction of inflammatory cytokines has proceeded through several phases. The field has moved from the discovery of ligands, receptors and co-receptors (Fig. 2A) toward identification of complex cytosolic and nuclear signaling mechanisms. For about a decade, the NF-κB, JNK (c-Jun N-terminal kinase), p38 MAPK (mitogen activated protein kinase), STAT (signal transducers and activators of transcription) and PI3K (phosphatidylinositol-3-kinase) pathways were viewed as separate "linear" cascades (Fig. 2B). However, an emerging theme is that separated linear pathways do not really exist. Rather, there is interconnected signaling at all levels of intracellular signal transduction resulting in the concept of complex signaling networks (Fig. 2C). This level of complexity by intracellular signaling networks can be typically exemplified by an IL-1 signaling map which covers the canonical components of IL-1 signaling that are used across various species [151]. It consists of 86 molecules involved in at least 186 reactions as shown in Fig. 3.

3.1. Modes of signal processing in inflammatory cytokine networks

Signal processing involves the study of pathways in which a cellular signaling response is accelerated or dampened in form of positive or negative feedback loops [122]. Multiple of these mechanisms are joined to form a network enabling signal integration at molecular, cellular and functional levels.

3.1.1. Signal integration at the molecular level

Positive and negative feedback mechanisms do not operate as separated entities. Rather, they are intimately linked at multiple levels by signal integration. This term refers to the phenomenon that two or more pathways downstream of a common receptor or effector converge on the same signaling node. This signaling node can be any molecular entity ranging from lipids or proteins to nucleic acids. Signal integration occurs at the molecular level by means of multiple combinatorial post-translational modifications such as phosphorylation, ubiquitination, sumoylation, acetylation or ADP-ribosylation [12,25]. A typical example for such a molecular signal integration point serving as a signaling hub is the MAP3K TAK1 (TGFβ-activated protein kinase 1), which receives inputs from a plethora of upstream receptors [113,114,121] as shown in Fig. 4A. TAK1 activation depends on TAB (TAK1-binding protein) adaptor proteins 1–3 which can bind to K63-linked polyubiquitin chains and thus allows the transient recruitment of ubiquitinated partner proteins that can activate TAK1. TAK1 further requires sequential phosphorylation in its catalytic domain, but also the attachment of K63-linked polyubiquitin chains by the E3 ligase TRAF6 for activation [31,63,90,95,113,121,132,138,147,149,160]. Once assembled this way, the TAK1–TAB complex determines the output signal and mediates activation of NF-κB or the MAP2Ks MKK4 and MKK3/6 [156]. TAK1-dependent NF-κB activation involves phosphorylation-dependent K48-linked ubiquitination and subsequent degradation of IκBα (Fig. 4A). Activation of NF-κB in response to pro-inflammatory cytokines or toll-like receptor (TLR) agonists also requires ubiquitination of NEMO (NF-κB essential modulator), a regulatory subunit of the IκB kinase

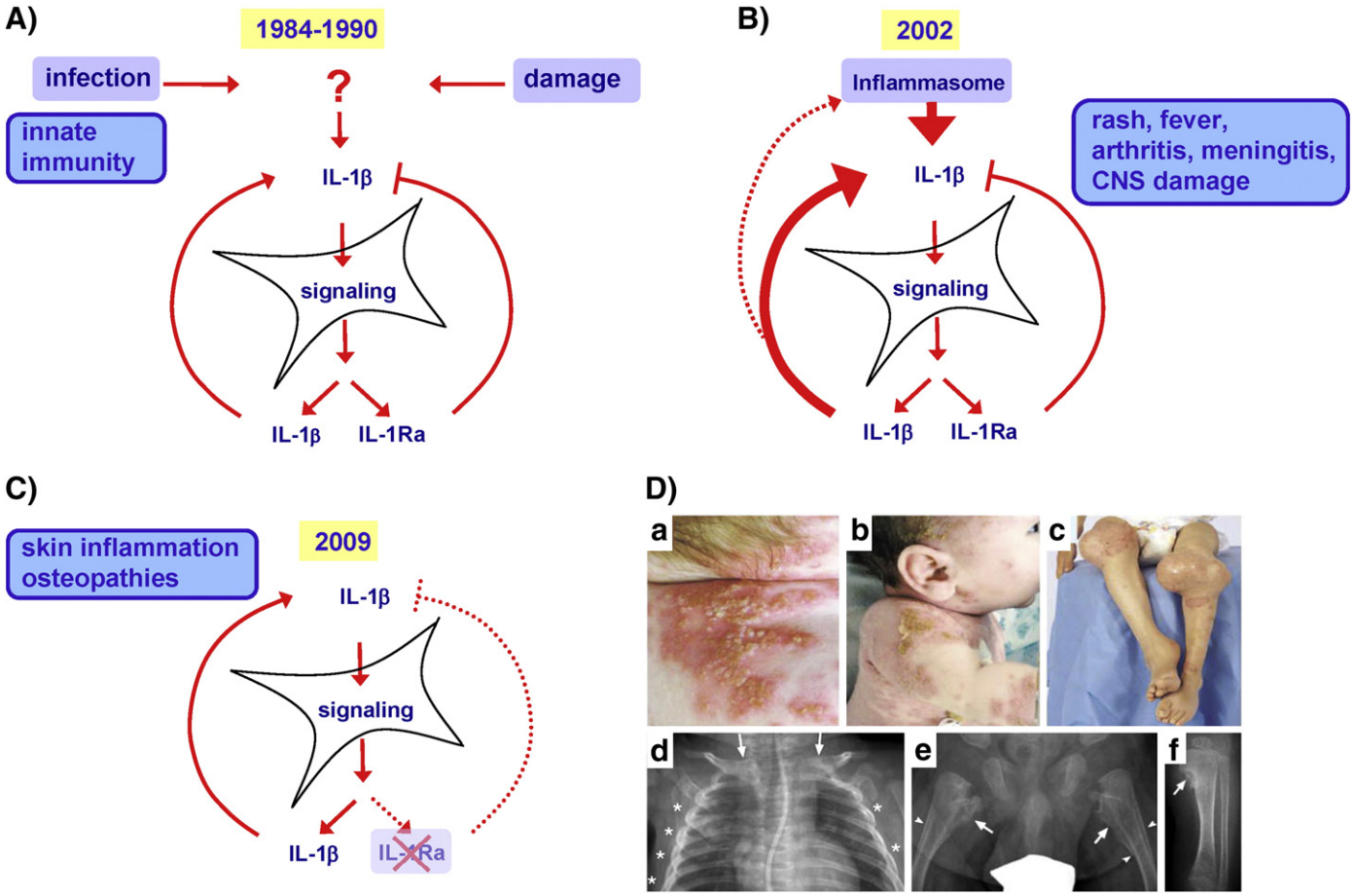


Fig. 1. Deregulation of cytokine loops as a major cause of inflammatory diseases. A) The discovery of IL-1β [9] revealed a major role of these cytokines in innate immune reactions in response to infection (PAMP signals) or damage (DAMP signals) [33,36]. It was also found that IL-1 induces its own expression as a positive feed-forward loop [40] as well as expression of its antagonist IL-1Ra in a negative feedback loop during inflammatory reactions [47]. A sophisticated balance between IL-1β release and counter-acting IL-1Ra levels suppresses spontaneous inflammation, but also ensures correct termination of IL-1-dependent inflammation [37,39]. B) Discovery of an IL-1-processing multi-protein complex (called inflammasome) and identification of patients with gain-of-functions mutations in inflammasome proteins revealed a number of auto-inflammatory diseases that are driven by excess IL-1β production as a result of dominant positive feed-forward loops. As symbolized by the thickness of the arrows and by additional arrows, the spontaneous release of preformed IL-1β overrides the balance of systemic IL-1β and IL-1Ra [85,86]. C) Recently, a few patients were identified that lack the IL-1Ra protein due to frame-shift mutations or gene deletions [4,37,106]. As shown, this lack of negative feedback control results in life-threatening systemic inflammation and osteopathy due to spontaneously released IL-1β (and IL-1α, not shown). D) The clinical features of patients with genetic deletion or mutation of the IL-1Ra comprise sterile pustulosis and skin inflammation (a, b), massive epiphyseal ballooning of long bones (c), radiographically visible enlargement of ribs and clavicles (d), ossification of the proximal femoral metaphysis and periosteal elevation of the diaphysis (e), and an osteolytic lesion with a sclerotic rim (f). Fig. 3D and the information described in the legend was reproduced with permission from [4] and the New England Journal of Medicine.

(IKK) complex ([75,118,127,128,139,152] and Fig. 4A. Disturbing the balance of signal integration at the level of the TAK1–TAB or IKK–NEMO complexes can result in skin inflammation, liver inflammation, fibrosis and cancer [11,58,118]. Downstream of TAK1–TAB and IKK–NEMO, the NF-κB subunit p65 is also a prominent example of signal integration at the molecular level. Nuclear activity of p65 is regulated by multiple phosphorylations, polyubiquitination and acetylation [23,45,98,108] and Fig. 4A. Many viral proteins hijack signal integrators in order to manipulate central cellular functions, thus supporting the idea that signal integrators are of major relevance for the coordination of signaling events. This also applies to the TAK1/TAB1 complex, which is for example activated by the T cell leukemia virus type 1 (HTLV-1) Tax protein [153], by Kaposi's sarcoma-associated herpes virus (KSHV) G protein-coupled receptor (vGPCR) protein [14], or by latent membrane protein 1 of Epstein–Barr virus [142,148]. Signal integration also occurs at functional levels. A very prominent example is the upregulation of mRNAs during pro-inflammatory cytokine responses. Triggers such as IL-1, TNFα or LPS induce mRNA expression of secondary inflammatory mediators (e.g. IL-6, IL-8, cyclooxygenase 2) by simultaneously activating transcriptional and post-transcriptional pathways. Within the nucleus, this is provided by co-ordinated recruitment of transcription factors and co-activators in concert with chromatin-relaxing mechanisms at the level of gene promoters (reviewed in [89]). Many of these mRNAs bind destabilizing proteins in the cytoplasm and are maintained at low steady-state levels by sequential deadenylation, decapping and RNA-degradation [18]. Other cytokine mRNAs are kept translational silent probably by directing these molecules to particles, where ribosome-mediated protein biosynthesis is blocked. Efficient gene responses during inflammation thus require stabilization of mRNAs and translational derepression by signal-mediated processes through the p38–MK2-pathway [44]. The importance of these pathways can be deduced from the phenotype of mice lacking destabilizing proteins such as tristetraproline (TTP). These mice display enhanced inflammatory cytokine expression and systemic inflammation [52,135]. However, the components of post-transcriptional cytokine pathways, their subcellular localization, regulation by post-translational modifications and role in translation as well as their interplay with transcriptional pathways are still not completely understood (reviewed in [7,8]).

3.1.2. Positive feed-forward loops

Feed-forward loops proceed through several signaling intermediates to provide sustained or elevated stimulation of a response. Such powerful feed-forward loops are needed to amplify the immune response in order to antagonize the logarithmic growth of pathogens.

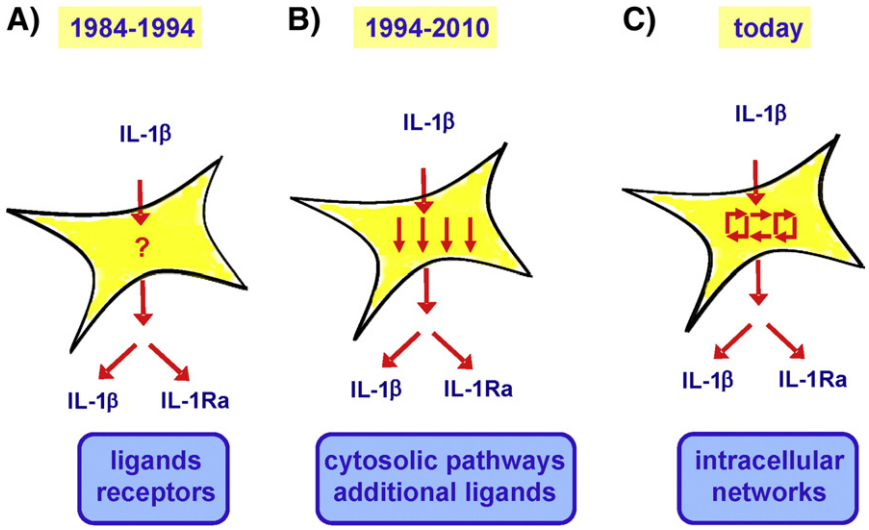


Fig. 2. Milestones of research on inflammatory cytokine signaling. (A) IL-1 family members and receptors were discovered more than 25 years ago [9,80,123]. (B) Research on signal transduction during the last decade has focussed on the concept of linear cascades primarily resulting in the activation of NF-κB, JNK, p38, ERK, STAT and PI3 kinase pathways (reviewed in [16,33,44,54,73,84]. (C) The current view describes a multitude of interactions and post-translational modifications interconnecting all known pathway components forming large signaling networks as shown in Fig. 3.

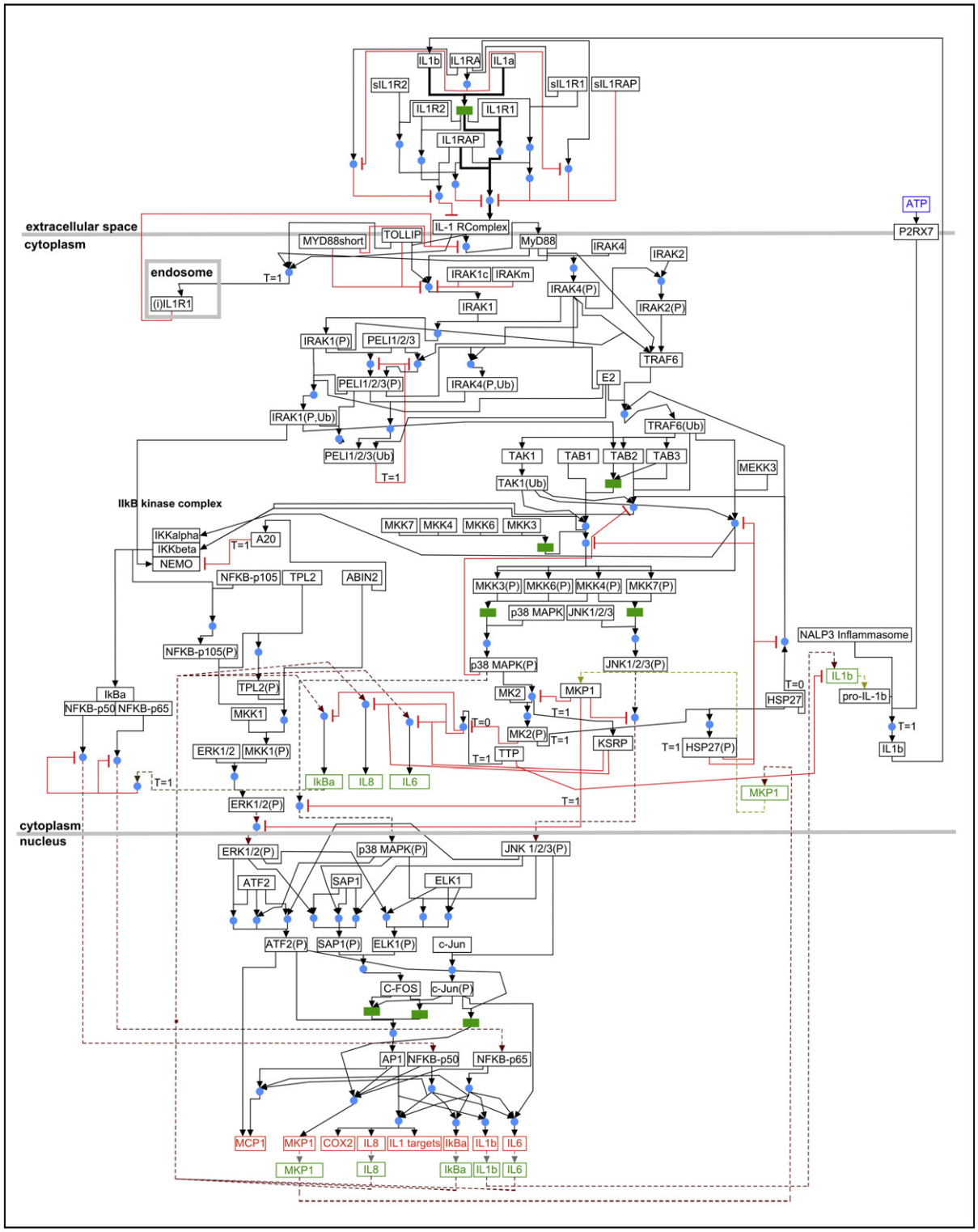
Multiple mechanisms ensure the efficient and rapid mounting of the inflammatory response including autocrine and paracrine feedforward and amplification loops. For example, many inflammatory cytokines such as IL-1β or TNFα promote the expression of their own genes (Fig. 4B), or LPS-induced secretion of TNFα, thus mediating autocrine NF-κB activation and amplification of pro-inflammatory signaling [29]. Other examples of this kind of signaling are the TNFα-induced induction of type I interferons [158] or the IL-1-induced secretion of IL-8 [83] which boost TNFα-or IL-1-responses, respectively (Fig. 4C). While IL-1, TNFα and LPS share many signaling components, the TNFα-induced IFN induction is also an example of crosstalk (see below), because IFNs signal through distinct JAK-STAT pathways [44]. This situation is similar for IL-8, which signals through G-protein-coupled CXCR1/2 chemokine receptors [150], as displayed in Fig. 4C).

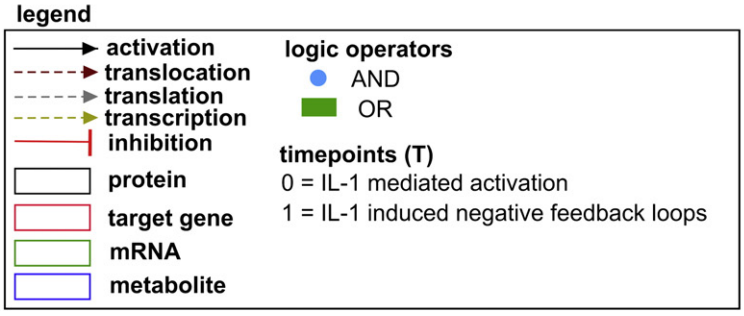
3.1.3. Negative feedback loops

Many signals of the induction phase already initiate a default termination program that allows a temporally and spatially well-controlled deactivation of the inflammatory response by negative feedback loops. Multiple cellular and molecular mechanisms ensure the resolution of inflammation, including the production of anti-inflammatory cytokines such as IL-1Ra, IL-10, TGF-β and IL-37, as schematically shown in Fig. 4D. The clearance of inflammation also involves further mechanisms such as the switch from prostaglandins/leukotriens to anti-inflammatory lipoxins and the elimination of neutrophils by apoptosis [92,93]. At the level of intracellular signaling, this default termination program is exemplified by the stereotypical pro-inflammatory transcription factor NF-κB, which is deactivated by multiple mechanisms including the NF-κB-induced synthesis of the inhibitory IκB proteins (Fig. 4D) [53,105,131,155]. While IκBα terminates the fast NF-κB response, the late NF-κB activity is antagonized by proteins such as A20 [120], Cyld [17,72,141] and COMMD1 [45] (Fig. 4D). The latter is an example of a novel mechanism in signal termination as it involves degradation of p65 on specific promoters [134]. Proteolytic mechanisms to destroy host cell signaling effectors have also been adopted by certain bacterial proteases such as the NleC Protein of pathogenic *Escherichia coli* which cleaves p65 [159] but also JNK [10].

Inappropriate termination of NF-κB activity can be causative for chronic inflammation and several ailments ranging from rheumatoid arthritis (RA) to inflammatory bowel disease (IBD). Defect termination might be due to gene mutations for the proteins mediating the negative feedback loops or to defect signaling circuits that serve to wind down NF-κB activity [144]. The RNA-destabilizing protein tristetraproline is not only an inducible negative regulator which reduces mRNA steady state levels [15,20,52,74,82] but which also interacts with and negatively regulates NF-κB [78,116]. Most of the negative regulators in the NF-κB system are inducibly expressed [107]. Likewise, activation of the MAPKs JNK and p38 which occurs in parallel to activation of the NF-κB pathway is switched off by inducible expression of MAPK-specific phosphatases such as MAPK phosphatase 1 (MKP-1) [1,2,24,25,62,64,79,161] and Fig. 4D. The importance of negative feedback loops and mechanisms that control the thresholds of signaling is mainly derived from mouse models but also from genetic polymorphisms observed in humans. A recent survey of loss-of-function phenotypes listed 81 genes whose mutations lead to spontaneous emergence of persistent inflammation in humans living in normal conditions or in standard laboratory mice without a known evident autoimmune or inflammatory insult [93]. Thus, it takes a highly co-ordinated response of 81 (or more) genes to suppress spontaneous inflammation. All observations cited above suggest that the true number of anti-inflammatory genes is not known yet and will likely be much higher. It can be concluded that spontaneous inflammation may arise whenever there is a loss of a non-redundant component or of a mechanism that regulates proliferation or signaling in lymphoid, myeloid, or epithelial cells responding to antigens, microbes, or injury [49,81,88,92,124]. The mediators and molecular mechanisms employing these important signal processing events are incompletely understood and the number of regulators and reactions involved raises the need to combine experimental data with *in silico* pathway building.

Fig. 3. Regulatory loops, feed-forward and feedback mechanisms in the canonical IL-1 signaling network. The software PathVisio [65,104,143] was used to draw a structured schematic visualization of the canonical IL-1 signaling network as published in ref. [151]. The evidence for each interaction between signaling components was taken from 469 references and can be accessed at (http://stke.sciencemag.org/cgi/cm/stkecm;CMP_21286). In the depicted map activating feed-forward and inactivating feedback loops, important post-translational modifications and cellular translocations of signaling components are specifically highlighted as indicated in the legend box. In addition, as shown by blue circles and green boxes decision points in intracellular signaling were connected by logical operators to visualize the information flow through the signaling system by using the program CellNetAnalyzer [68,69]. This network forms a basis for future network reconstruction by mathematical modeling (see text for details).


IL1b
IL1RA
IL1a
sIL1R2
sIL1R1
sIL1RAP
IL1R2
IL1R1
IL1RAP
ATP
P2RX7
extracellular space
cytoplasm
IL-1 RComplex
MYD88short
TOLLIP
MyD88
IRAK4
IRAK2
endosome
T=1
IRAK1c
IRAKm
IRAK4(P)
IRAK2(P)
(i)IL1R1
IRAK1
IRAK1(P)
PELI1/2/3
TRAF6
E2
PELI1/2/3(P)
IRAK4(P,Ub)
IRAK1(P,Ub)
TRAF6(Ub)
PELI1/2/3(Ub)
T=1
TAK1
TAB1
TAB2
TAB3
MEKK3
TAK1(Ub)
IkB kinase complex
MKK7
MKK4
MKK6
MKK3
IKKalpha
IKKbeta
NEMO
A20
T=1
NFKB-p105
TPL2
ABIN2
MKK3(P)
MKK6(P)
MKK4(P)
MKK7(P)
p38 MAPK
JNK1/2/3
NALP3 Inflammasome
NFKB-p105(P)
p38 MAPK(P)
JNK1/2/3(P)
IkBa
NFKB-p50
NFKB-p65
TPL2(P)
MKK1
MK2
MKP1
T=0
T=1
HSP27
IL1b
pro-IL-1b
MK2(P)
KSRP
T=1
HSP27(P)
ERK1/2
MKK1(P)
TTP
T=1
IkBa
IL8
IL6
T=1
MKP1
ERK1/2(P)
T=1
cytoplasm
nucleus
ERK1/2(P)
p38 MAPK(P)
JNK 1/2/3(P)
ATF2
SAP1
ELK1
ATF2(P)
SAP1(P)
ELK1(P)
c-Jun
C-FOS
c-Jun(P)
AP1
NFKB-p50
NFKB-p65
MCP1
MKP1
COX2
IL8
IL1 targets
IkBa
IL1b
IL6
MKP1
IL8
IkBa
IL1b
IL6


legend
activation
translocation
translation
transcription
inhibition
protein
target gene
mRNA
metabolite
logic operators
AND
OR
timepoints (T)
0 = IL-1 mediated activation
1 = IL-1 induced negative feedback loops

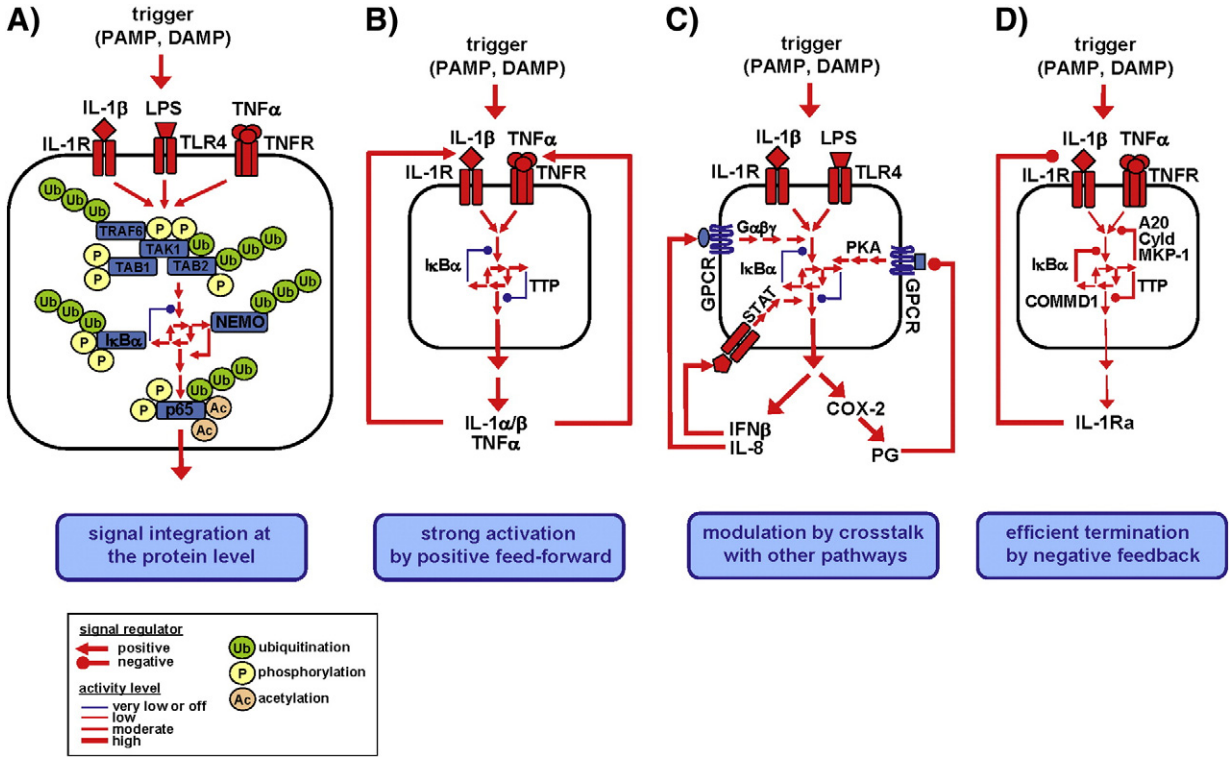


Fig. 4. Prototypical mechanisms of regulatory loops, crosstalk and signal integration in cytokine pathways. The concepts are schematically shown and the effects on signal strength or the on-off status are given in the legend. Abbreviations: COMMD1, copper metabolism (Murr1) domain containing 1; Cyld, cylindromatosis; COX-2, cyclooxygenase 2; Gαβγ, small G proteins; IL-1R, IL-1 receptor; PG, prostaglandin; TNFR, TNF receptor.

3.2. Crosstalk

Mutual influences of signals generated from different pathways are referred to as crosstalk. This crosstalk occurs at all levels: between different inflammatory cells, cytokines and also intracellular signaling pathways. At the molecular level, there is recent evidence for crosstalk of "canonical" NF-κB/MAPK signaling with "non-canonical" tyrosine kinase pathways [44]. Other examples are the modulation of inflammatory gene expression by circadian clock pathways [66] or by prostaglandin-cAMP-PKA (protein kinase A) pathways [13,46,56,70,140,146] and Fig. 4C). Further examples are the peroxisome proliferator-activated receptor beta/delta (PPARβ/δ)-mediated inhibition of IL-1 signaling [26], the induction of TH2 cytokines by IL-1 and STAT5 activation [51], or the epidermal growth factor (EGF)-mediated inhibition of TNFα-signaling [60]. The extent of crosstalk during inflammation is not known, but these few examples emphasize the need to imply and to study the influence of other pathways on basal and inducible activation states of inflammatory cytokine signaling pathways.

4. *In silico* reconstruction of inflammatory cytokine signaling networks

As evident from the arguments raised above, all mechanisms in inflammatory signaling act in an integrated fashion to form a biological signaling network. Signaling networks survey environmental conditions and make decisions to adapt cellular behavior. They convey information distinguishing them from metabolic networks, which convert extracellular material or recycle and dispose intracellular materials [57]. Signaling networks are built from components (proteins, nucleic acids, lipids) and their interactions. In a kind of retrograde approach a few inflammatory subnets have been delineated from transcriptome or proteome data sets [21,55,137,157]. However, a more sophisticated approach is to transfer current mechanistic knowledge into computer models, a process which is called signal network reconstruction. Reconstruction of signaling networks requires the generation of carefully curated databases for warehousing available information on components and their interactions. It also needs tools for mapping, organizing and visualizing data base information and appropriate algorithms for mathematical analyses and network reconstructions. Mathematical modeling then allows to describe and analyze network functionally, or, to predict gaps and missing components or interactions [102,111]. This can be achieved quantitatively by stoichiometric approaches [101,103]. Alternatively, Boolean approaches can be used which utilize sets of active or inactive components connected by logical operators [69]. The latter approach is better suited for large networks and does not require quantitative information on component concentrations, modifications and reaction parameters [57].

At present no comprehensive signaling network reconstruction of an eukaryotic cell has been achieved [57]. The largest network consists of 909 components and 752 interactions [77] and was adapted from a map of toll-receptor signaling [99]. This network does not involve RNA components, such as target mRNAs, micro-RNAs or other non-coding RNAs, which may also modulate signals at many steps. Next-generation sequencing [91] will facilitate the genome-scale assessment of coding and non-coding RNA constituents in available networks. Information on regulated mRNA transcripts and RNA components of ribonucleoprotein complexes is needed to expand the existing knowledge contained in available inflammatory cytokine pathways.

Another example for a reconstructed network is the recently published map of IL-1 signaling components that was generated by reviewing 25 years of research on IL-1 which resulted in a manually curated data base containing approximately 500 carefully selected publications. The largest version at present incorporates information on 237 molecules and 564 reactions (A. Weber, P. Wasiliew, M. Kracht, unpublished data). The canonical part of the IL-1 signaling network contains 86 molecules and 189 interactions representing the core pathways, which are activated by the cytokine in many different cell types of mice and men [151]. A graphic representation of this network highlighting post-translational modifications, changes in subcellular localization and regulatory loops is shown in Fig. 3. We have started to

transfer the information on the canonical IL-1-signaling network into a logical model by setting up Boolean equations (unpublished data) for all connecting edges and nodes of the map using CellNetAnalyzer [68,69]. The main nodes and operator settings have been superimposed on the map graphically as shown in Fig. 3. The underlying equations will facilitate computation of signaling network responses which can then be experimentally validated. In the long term, such reconstructed networks can be refined by a mutual process of virtual prediction and experimental verification to reflect as faithfully as possible the biological situation.

By the example described above, this overview displays the enormous complexity of signaling pathways that requires *in silico* analysis tools for the visualization of networks and the design of experiments to test experimental predictions.

There are only a few other networks of this type which, however, contain less information [5,19,59,61]. It can be concluded that reconstruction of inflammatory cytokine networks is still in its infancy and requires comprehensive analysis of protein and RNA components, expert-curated assessment of their interactions and network reconstruction by mathematical modeling.

5. Cytokines in the clinics

Frequently, attempts to apply recombinant inflammatory cytokines *in vivo* led to intolerable systemic side effects, as exemplified by IL-1 [94,125] or TNFα [30,117] which cause fever, nausea, and hypotension. However, TNFα has found a niche for localized treatment of soft tissue sarcoma and melanoma by isolated limb perfusion in combination with chemotherapy [50]. Only a limited number of other cytokine family members can be routinely used in the clinic (e.g. erythropoietin, G-CSF, GM-CSF, IFNβ, IFNγ). In contrast, protein-based drugs antagonizing individual cytokines or their receptors (antibodies, cytokine-traps) are much better tolerated than recombinant cytokines [35,41,42,100,112,115,130,136,145]. The largest group of these drugs targets pro-inflammatory cytokines. Since 1999, five agents directed against TNFα (Infliximab, Etanercept, Adalimumab, Golimunab, Certolizumab) and three agents neutralizing the effects of IL-1α and IL-1β (Anakinra, Canakinumab, Rilonacept) have been used to treat hundreds of thousands of patients suffering from diseases ranging from rare febrile syndromes (Muckle–Wells disease, neonatal-onset-multi-inflammatory disease) to common conditions such as rheumatoid arthritis, chronic IBD, psoriasis, gout [44,109,126] or even diabetes [76]. However, all antibodies and cytokine-traps currently in use do not cure chronic inflammatory diseases as symptoms re-occur immediately once therapy is ceased [38,71,93]. Moreover, one to two thirds of patients do not respond, loose response during therapy or develop non-tolerable side-effects [6,28,43,48,110]. Apart from this, protein-based drugs impose a heavy economic burden on society as they are very expensive [129]. Thus, there is an urgent need for identifying additional principles and targets to control cytokine action during disease [44,97]. Certainly, a better understanding of cytokine signaling networks is one of the prerequisites to achieve these goals.

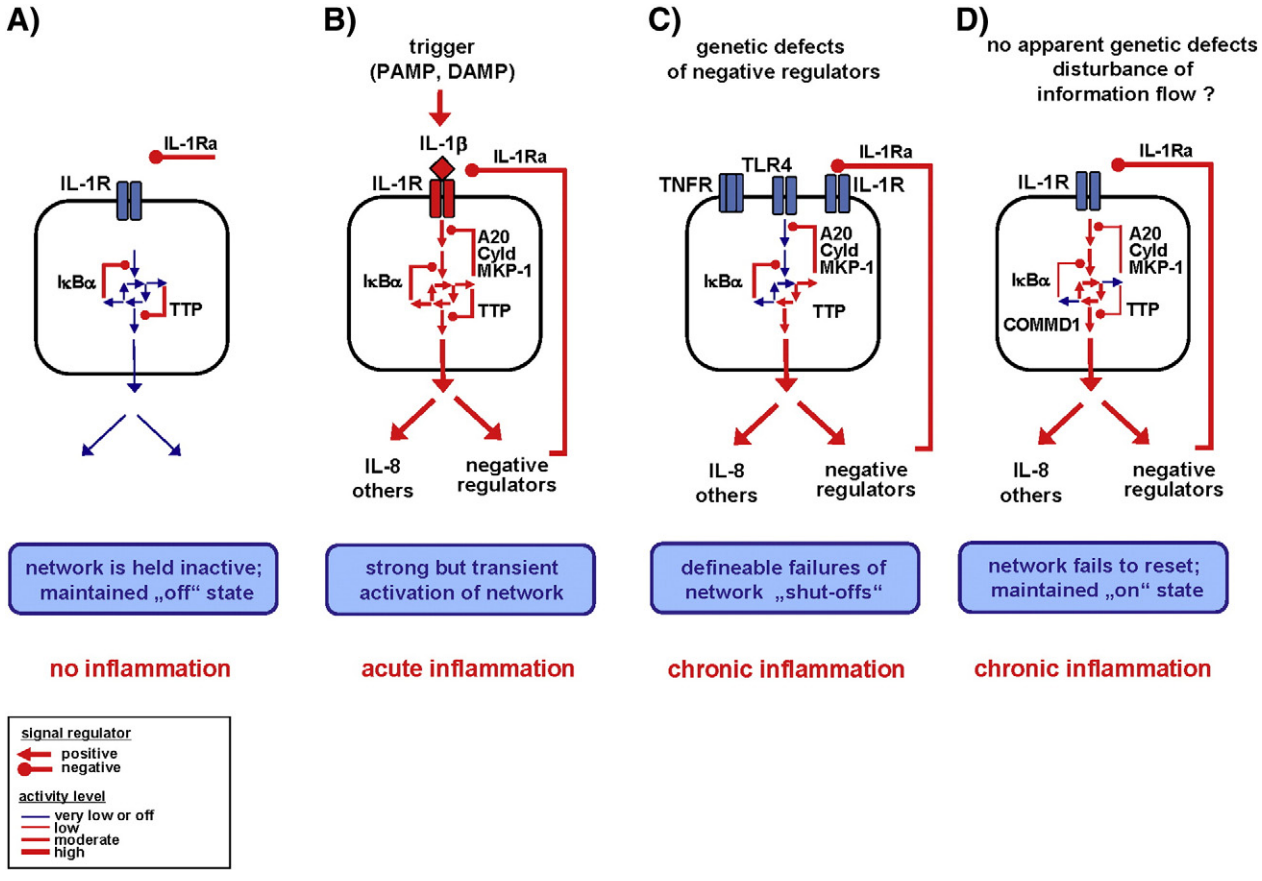


Fig. 5. Physiological and pathological malfunctions of intracellular cytokine networks—options for multiple disturbances which can all result in chronic inflammation. (A) In healthy conditions, inflammatory signaling is suppressed by dominance of constitutively expressed negative regulators which ensure an efficient "off" state of the system. (B) In "normal" inflammation a rapid, boost-like response is initiated by the co-operative action of positive feed-forward signals. The parallel increased expression of negative regulators ensures rapid subsequent termination of signaling and the systems eventually returns to the off-state. (C) As outlined in Ref. [93], at least 80 different genes have been identified whose products act as negative regulators at multiple levels of the signaling network. Mutation or deletion of any of them results in "stereotypic" chronic inflammation in the absence of exogenous triggers. In the depicted example TTP is missing. (D) Chronic inflammation may also arise in the absence of exogenous triggers under conditions where the signal flow is disturbed by fluctuations in activity of signaling molecules resulting in a maintained "on" state. In this scenario, no genetic alterations are observed, but signaling proteins display increased or reduced activity and the inflammatory phenotype is indistinguishable from the situation in (C).

6. Future directions

The inflammatory process is characterized by the co-ordinated release of many different cytokines that are used by cells to orchestrate immune and other complex responses. In the last decade it has become very clear that this enormous complexity is mirrored at the level of intracellular signal transduction. Apparently, evolution has generated signaling systems that are robust, because they are backed-up at multiple levels. At the same time the network architecture ensures rapid "switch-like" amplification of immune responses, but also their faithful terminations. The understanding of the underlying mechanisms of signal processing, signal integration and crosstalk is still in its infancy. Much insight has been derived by studying principles, mechanisms, regulation and overall consequences of signal transmission by cytokines in model systems that can be manipulated and analyzed in a quantitative manner. However, it will be equally important to study components, their post-translational modifications and their activity states in human individuals. Moreover, as we are dealing with networks, methods need to be developed to study and analyze as many signaling components as possible in individual patients. Antibody arrays or proteomics methods suiting this purpose have been developed; but unlike the analyses of nucleic acids, the comprehensive analyses of the regulatory proteome is far from being routine. However, at this point it can be speculated that sterile inflammation of any kind may be found in patients with no apparent abnormalities in the genes encoding negative or positive signal regulators. This scenario is schematically displayed in Fig. 5D, where such a situation is compared to other (patho) physiological situations of inflammatory gene expression (Fig. 5A–C). In this case, some kind of aberrant information flow may be maintained and might prevent resetting of signaling networks into their normal inactive state. Such events may happen stochastically, or as a result of slight, but cumulating fluctuations and disturbances of correct protein functions in space and time. In this case, there may be no "trackable" cause of sterile inflammation at the genetic level. Finally, we all know how easily computer programs break down, even though the hardware is perfectly fine. Searching for such "software" failures in inflammation remains one of the most interesting and challenging tasks for future research.

References

[1] S.M. Abraham, A.R. Clark, Dual-specificity phosphatase 1: a critical regulator of innate immune responses, Biochem. Soc. Trans. 34 (2006) 1018–1023.
[2] S.M. Abraham, T. Lawrence, A. Kleiman, P. Warden, M. Medghalchi, J. Tuckermann, J. Saklatvala, A.R. Clark, Antiinflammatory effects of dexamethasone are partly dependent on induction of dual specificity phosphatase 1, J. Exp. Med. 203 (2006) 1883–1889.
[3] L. Agostini, F. Martinon, K. Burns, M.F. McDermott, P.N. Hawkins, J. Tschopp, NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle–Wells autoinflammatory disorder, Immunity 20 (2004) 319–325.
[4] I. Aksentijevich, S.L. Masters, P.J. Ferguson, P. Dancey, J. Frenkel, A. Royen-Kerkhoff, R. Laxer, U. Tedgard, E.W. Cowen, T.H. Pham, M. Booty, J.D. Estes, N.G. Sandler, N. Plass, D.L. Stone, M.L. Turner, S. Hill, J.A. Butman, R. Schneider, P. Babyn, H.I. El Shanti, E. Pope, K. Barron, X. Bing, A. Laurence, C.C. Lee, D. Chapelle, G.I. Clarke, K. Ohson, M. Nicholson, M. Gadina, B. Yang, B.D. Korman, P.K. Gregersen, P.M. van Hagen, A.E. Hak, M. Huizing, P. Rahman, D.C. Douek, E.F. Remmers, D.L. Kastner, R. Goldbach-Mansky, An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist, N. Engl. J. Med. 360 (2009) 2426–2437.
[5] L.G. Alexopoulos, J. Saez-Rodriguez, B.D. Cosgrove, D.A. Lauffenburger, P.K. Sorger, Networks inferred from biochemical data reveal profound differences in toll-like receptor and inflammatory signaling between normal and transformed hepatocytes, Mol. Cell. Proteomics 9 (2010) 1849–1865.
[6] A. Alonso-Ruiz, J.I. Pijoan, E. Ansuategui, A. Urkaregi, M. Calabozo, A. Quintana, Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety, BMC Musculoskelet. Disord. 9 (2008) 52.
[7] P. Anderson, Post-transcriptional control of cytokine production, Nat. Immunol. 9 (2008) 353–359.
[8] P. Anderson, Intrinsic mRNA stability helps compose the inflammatory symphony, Nat. Immunol. 10 (2009) 233–234.
[9] P.E. Auron, A.C. Webb, L.J. Rosenwasser, S.F. Mucci, A. Rich, S.M. Wolff, C.A. Dinarello, Nucleotide sequence of human monocyte interleukin 1 precursor cDNA, Proc. Natl. Acad. Sci. U.S.A. 81 (1984) 7907–7911.
[10] K. Baruch, L. Gur-Arie, C. Nadler, S. Koby, G. Yerushalmi, Y. Ben-Neriah, O. Yogev, E. Shaulian, C. Guttman, R. Zarivach, I. Rosenshine, Metalloprotease type III effectors that specifically cleave JNK and NF-kappaB, EMBO J. 30 (2011) 221–231.
[11] K. Bettermann, M. Vucur, J. Haybaeck, C. Koppe, J. Janssen, F. Heymann, A. Weber, R. Weiskirchen, C. Liedtke, N. Gassler, M. Muller, V.R. de, M.J. Wolf, Y. Boege, G.M. Seleznik, N. Zeller, D. Erny, T. Fuchs, S. Zoller, S. Cairo, M.A. Buendia, M. Prinz, S. Akira, F. Tacke, M. Heikenwalder, C. Trautwein, T. Luedde, TAK1 suppresses a NEMO-dependent but NF-kappaB-independent pathway to liver cancer, Cancer Cell 17 (2010) 481–496.
[12] V.G. Bhoj, Z.J. Chen, Ubiquitylation in innate and adaptive immunity, Nature 458 (2009) 430–437.
[13] K. Boniface, K.S. Bak-Jensen, Y. Li, W.M. Blumenschein, M.J. McGeachy, T.K. McClanahan, B.S. McKenzie, R.A. Kastelein, D.J. Cua, M.R. de Waal, Prostaglandin E2 regulates Th17 cell differentiation and function through cyclic AMP and EP2/EP4 receptor signaling, J. Exp. Med. 206 (2009) 535–548.
[14] V. Bottero, N. Kerur, S. Sadagopan, K. Patel, N. Sharma-Walia, B. Chandran, Phosphorylation and polyubiquitination of transforming growth factor {beta}-activated kinase 1 are necessary for activation of NF-{kappa}B by the Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor, J. Virol. 85 (2011) 1980–1993.
[15] M. Brook, C.R. Tchen, T. Santalucia, J. McIlrath, J.S. Arthur, J. Saklatvala, A.R. Clark, Posttranslational regulation of tristetraprolin subcellular localization and protein stability by p38 mitogen-activated protein kinase and extracellular signal-regulated kinase pathways, Mol. Cell. Biol. 26 (2006) 2408–2418.
[16] J.W. Brooks, S.B. Mizel, Interleukin-1 signal transduction, Eur. Cytokine Netw. 5 (1994) 547–561.
[17] T.R. Brummelkamp, S.M. Nijman, A.M. Dirac, R. Bernards, Loss of the cylindromatosis tumour suppressor inhibits apoptosis by activating NF-kappaB, Nature 424 (2003) 797–801.
[18] J.R. Buchan, R. Parker, Eukaryotic stress granules: the ins and outs of translation, Mol. Cell 36 (2009) 932–941.
[19] S.E. Calvano, W. Xiao, D.R. Richards, R.M. Felciano, H.V. Baker, R.J. Cho, R.O. Chen, B.H. Brownstein, J.P. Cobb, S.K. Tschoeke, C. Miller-Graziano, L.L. Moldawer, M.N. Mindrinos, R.W. Davis, R.G. Tompkins, S.F. Lowry, A network-based analysis of systemic inflammation in humans, Nature 437 (2005) 1032–1037.
[20] E. Carballo, W.S. Lai, P.J. Blackshear, Feedback inhibition of macrophage tumor necrosis factor-alpha production by tristetraprolin, Science 281 (1998) 1001–1005.
[21] B.S. Chen, S.K. Yang, C.Y. Lan, Y.J. Chuang, A systems biology approach to construct the gene regulatory network of systemic inflammation via microarray and databases mining, BMC Med. Genomics 1 (2008) 46.
[22] G.Y. Chen, G. Nunez, Sterile inflammation: sensing and reacting to damage, Nat. Rev. Immunol. 10 (2010) 826–837.
[23] J. Chew, S. Biswas, S. Shreeram, M. Humaidi, E.T. Wong, M.K. Dhillion, H. Teo, A. Hazra, C.C. Fang, E. Lopez-Collazo, D.V. Bulavin, V. Tergaonkar, WIP1 phosphatase is a negative regulator of NF-kappaB signalling, Nat. Cell Biol. 11 (2009) 659–666.
[24] H. Chi, S.P. Barry, R.J. Roth, J.J. Wu, E.A. Jones, A.M. Bennett, R.A. Flavell, Dynamic regulation of pro- and anti-inflammatory cytokines by MAPK phosphatase 1 (MKP-1) in innate immune responses, Proc. Natl. Acad. Sci. U.S.A. 103 (2006) 2274–2279.
[25] H. Chi, R.A. Flavell, Acetylation of MKP-1 and the control of inflammation, Sci. Signal. 1 (2008) e44.
[26] H.C. Chong, M.J. Tan, V. Philippe, S.H. Tan, C.K. Tan, C.W. Ku, Y.Y. Goh, W. Wahli, L. Michalik, N.S. Tan, Regulation of epithelial–mesenchymal IL-1 signaling by PPARbeta/delta is essential for skin homeostasis and wound healing, J. Cell Biol. 184 (2009) 817–831.
[27] L.W. Collison, C.J. Workman, T.T. Kuo, K. Boyd, Y. Wang, K.M. Vignali, R. Cross, D. Sehy, R.S. Blumberg, D.A. Vignali, The inhibitory cytokine IL-35 contributes to regulatory T-cell function, Nature 450 (2007) 566–569.
[28] M.F. Costa, N.R. Said, B. Zimmermann, Drug-induced lupus due to anti-tumor necrosis factor alpha agents, Semin. Arthritis Rheum. 37 (2008) 381–387.
[29] M.W. Covert, T.H. Leung, J.E. Gaston, D. Baltimore, Achieving stability of lipopolysaccharide-induced NF-kappaB activation, Science 309 (2005) 1854–1857.
[30] P.J. Creaven, J.E. Plager, S. Dupere, R.P. Huben, H. Takita, A. Mittelman, A. Proefrock, Phase I clinical trial of recombinant human tumor necrosis factor, Cancer Chemother. Pharmacol. 20 (1987) 137–144.
[31] Y. Di, S. Li, L. Wang, Y. Zhang, M.E. Dorf, Homeostatic interactions between MEKK3 and TAK1 involved in NF-kappaB signaling, Cell. Signal. 20 (2008) 705–713.
[32] C. Dinarello, W. Arend, J. Sims, D. Smith, H. Blumberg, L. O'Neill, R. Goldbach-Mansky, T. Pizarro, H. Hoffman, P. Bufler, M. Nold, P. Ghezzi, A. Mantovani, C. Garlanda, D. Boraschi, A. Rubartelli, M. Netea, J. van der Meer, L. Joosten, T. Mandrup-Poulsen, M. Donath, E. Lewis, J. Pfeilschifter, M. Martin, M. Kracht, H. Muehl, D. Novick, M. Lukic, B. Conti, A. Solinger, K. Peyman, F. van de Veerdonk, C. Gabel, IL-1 family nomenclature, Nat. Immunol. 11 (2010) 973.
[33] C.A. Dinarello, Biologic basis for interleukin-1 in disease, Blood 87 (1996) 2095–2147.
[34] C.A. Dinarello, An IL-1 family member requires caspase-1 processing and signals through the ST2 receptor, Immunity 23 (2005) 461–462.
[35] C.A. Dinarello, Historical insights into cytokines, Eur. J. Immunol. 37 (Suppl 1) (2007) S34–S45.
[36] C.A. Dinarello, Immunological and inflammatory functions of the interleukin-1 family, Annu. Rev. Immunol. 27 (2009) 519–550.
[37] C.A. Dinarello, Interleukin-1beta and the autoinflammatory diseases, N. Engl. J. Med. 360 (2009) 2467–2470.

[38] C.A. Dinarello, Anti-inflammatory agents: present and future, Cell 140 (2010) 935–950.
[39] C.A. Dinarello, Interleukin-1 in the pathogenesis and treatment of inflammatory diseases, Blood (2011).
[40] C.A. Dinarello, T. Ikejima, S.J. Warner, S.F. Orencole, G. Lonnemann, J.G. Cannon, P. Libby, Interleukin 1 induces interleukin 1. I. Induction of circulating interleukin 1 in rabbits in vivo and in human mononuclear cells in vitro, J. Immunol. 139 (1987) 1902–1910.
[41] A.N. Economides, L.R. Carpenter, J.S. Rudge, V. Wong, E.M. Koehler-Stec, C. Hartnett, E.A. Pyles, X. Xu, T.J. Daly, M.R. Young, J.P. Fandl, F. Lee, S. Carver, J. McNay, K. Bailey, S. Ramakanth, R. Hutabarat, T.T. Huang, C. Radziejewski, G.D. Yancopoulos, N. Stahl, Cytokine traps: multi-component, high-affinity blockers of cytokine action, Nat. Med. 9 (2003) 47–52.
[42] S. Farasat, I. Aksentijevich, J.R. Toro, Autoinflammatory diseases: clinical and genetic advances, Arch. Dermatol. 144 (2008) 392–402.
[43] D.E. Furst, E.C. Keystone, B. Kirkham, A. Kavanaugh, R. Fleischmann, P. Mease, F.C. Breedveld, J.S. Smolen, J.R. Kalden, G.R. Burmester, J. Braun, P. Emery, K. Winthrop, B. Bresnihan, F. De Benedetti, T. Dorner, A. Gibofsky, M.H. Schiff, J. Sieper, N. Singer, P.L. Van Riel, M.E. Weinblatt, M.H. Weisman, Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008, Ann. Rheum. Dis. 67 (Suppl 3) (2008) iii2–iii25.
[44] M. Gaestel, A. Kotlyarov, M. Kracht, Targeting innate immunity protein kinase signalling in inflammation, Nat. Rev. Drug Discov. 8 (2009) 480–499.
[45] H. Geng, T. Wittwer, O. Dittrich-Breiholz, M. Kracht, M.L. Schmitz, Phosphorylation of NF-kappaB p65 at Ser468 controls its COMMD1-dependent ubiquitination and target gene-specific proteasomal elimination, EMBO Rep. 10 (2009) 381–386.
[46] M. Gosset, A. Pigenet, C. Salvat, F. Berenbaum, C. Jacques, Inhibition of matrix metalloproteinase-3 and -13 synthesis induced by IL-1{beta} in chondrocytes from mice lacking microsomal prostaglandin E synthase-1, J. Immunol. 185 (2010) 6244–6252.
[47] E.V. Granowitz, B.D. Clark, E. Vannier, M.V. Callahan, C.A. Dinarello, Effect of interleukin-1 (IL-1) blockade on cytokine synthesis: I. IL-1 receptor antagonist inhibits IL-1-induced cytokine synthesis and blocks the binding of IL-1 to its type II receptor on human monocytes, Blood 79 (1992) 2356–2363.
[48] N. Graudal, G. Jurgens, Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons, Arthritis Rheum. 62 (2010) 2852–2863.
[49] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell 140 (2010) 883–899.
[50] D.J. Grunhagen, J.H. de Wilt, T.L. ten Hagen, A.M. Eggermont, Technology insight: Utility of TNF-alpha-based isolated limb perfusion to avoid amputation of irresectable tumors of the extremities, Nat. Clin. Pract. Oncol. 3 (2006) 94–103.
[51] L. Guo, G. Wei, J. Zhu, W. Liao, W.J. Leonard, K. Zhao, W. Paul, IL-1 family members and STAT activators induce cytokine production by Th2, Th17, and Th1 cells, Proc. Natl. Acad. Sci. U.S.A. 106 (2009) 13463–13468.
[52] E. Hitti, T. Iakovleva, M. Brook, S. Deppenmeier, A.D. Gruber, D. Radzioch, A.R. Clark, P.J. Blackshear, A. Kotlyarov, M. Gaestel, Mitogen-activated protein kinase-activated protein kinase 2 regulates tumor necrosis factor mRNA stability and translation mainly by altering tristetraprolin expression, stability, and binding to adenine/uridine-rich element, Mol. Cell. Biol. 26 (2006) 2399–2407.
[53] A. Hoffmann, A. Levchenko, M.L. Scott, D. Baltimore, The IkappaB-NF-kappaB signaling module: temporal control and selective gene activation, Science 298 (2002) 1241–1245.
[54] E. Hoffmann, O. Dittrich-Breiholz, H. Holtmann, M. Kracht, Multiple control of interleukin-8 gene expression, J. Leukoc. Biol. 72 (2002) 847–855.
[55] T. Horn, T. Sandmann, B. Fischer, E. Axelsson, W. Huber, M. Boutros, Mapping of signaling networks through synthetic genetic interaction analysis by RNAi, Nat. Methods (2011).
[56] L.L. Hubbard, M.N. Ballinger, P.E. Thomas, C.A. Wilke, T.J. Standiford, K.S. Kobayashi, R.A. Flavell, B.B. Moore, A role for IL-1 receptor-associated kinase-M in prostaglandin E(2)-induced immunosuppression post-bone marrow transplantation, J. Immunol. 184 (2010) 6299–6308.
[57] D.R. Hyduke, B.O. Palsson, Towards genome-scale signalling-network reconstructions, Nat. Rev. Genet. 11 (2010) 297–307.
[58] S. Inokuchi, T. Aoyama, K. Miura, C.H. Osterreicher, Y. Kodama, K. Miyai, S. Akira, D.A. Brenner, E. Seki, Disruption of TAK1 in hepatocytes causes hepatic injury, inflammation, fibrosis, and carcinogenesis, Proc. Natl. Acad. Sci. U.S.A. 107 (2010) 844–849.
[59] K.A. Janes, J.G. Albeck, S. Gaudet, P.K. Sorger, D.A. Lauffenburger, M.B. Yaffe, A systems model of signaling identifies a molecular basis set for cytokine-induced apoptosis, Science 310 (2005) 1646–1653.
[60] K.A. Janes, S. Gaudet, J.G. Albeck, U.B. Nielsen, D.A. Lauffenburger, P.K. Sorger, The response of human epithelial cells to TNF involves an inducible autocrine cascade, Cell 124 (2006) 1225–1239.
[61] K.A. Janes, H.C. Reinhardt, M.B. Yaffe, Cytokine-induced signaling networks prioritize dynamic range over signal strength, Cell 135 (2008) 343–354.
[62] K.L. Jeffrey, M. Camps, C. Rommel, C.R. Mackay, Targeting dual-specificity phosphatases: manipulating MAP kinase signalling and immune responses, Nat. Rev. Drug Discov. 6 (2007) 391–403.
[63] T. Kajino, H. Ren, S. Iemura, T. Natsume, B. Stefansson, D.L. Brautigan, K. Matsumoto, J. Ninomiya-Tsuji, Protein phosphatase 6 down-regulates TAK1 kinase activation in the IL-1 signaling pathway, J. Biol. Chem. 281 (2006) 39891–39896.
[64] O. Kassel, A. Sancono, J. Kratzschmar, B. Kreft, M. Stassen, A.C. Cato, Glucocorticoids inhibit MAP kinase via increased expression and decreased degradation of MKP-1, EMBO J. 20 (2001) 7108–7116.
[65] T. Kelder, A.R. Pico, K. Hanspers, M.P. van Iersel, C. Evelo, B.R. Conklin, Mining biological pathways using WikiPathways web services, PLoS One 4 (2009) e6447.
[66] M. Keller, J. Mazuch, U. Abraham, G.D. Eom, E.D. Herzog, H.D. Volk, A. Kramer, B. Maier, A circadian clock in macrophages controls inflammatory immune responses, Proc. Natl. Acad. Sci. U.S.A. 106 (2009) 21407–21412.
[67] S.H. Kim, S.Y. Han, T. Azam, D.Y. Yoon, C.A. Dinarello, Interleukin-32: a cytokine and inducer of TNFalpha, Immunity 22 (2005) 131–142.
[68] S. Klamt, J. Saez-Rodriguez, E.D. Gilles, Structural and functional analysis of cellular networks with Cell NetAnalyzer, BMC Syst. Biol. 1 (2007) 2.
[69] S. Klamt, J. Saez-Rodriguez, J.A. Lindquist, L. Simeoni, E.D. Gilles, A methodology for the structural and functional analysis of signaling and regulatory networks, BMC Bioinformatics 7 (2006) 56.
[70] A.R. Klatt, G. Klinger, B. Paul-Klausch, J.H. Renno, J. Schmidt, G. Malchau, K. Wielckens, TAK1 mediates the collagen-II-dependent induction of the COX-2 gene and PGE2 release in primary human chondrocytes, Connect. Tissue Res. 51 (2010) 452–458.
[71] M. Kopf, M.F. Bachmann, B.J. Marsland, Averting inflammation by targeting the cytokine environment, Nat. Rev. Drug Discov. 9 (2010) 703–718.
[72] A. Kovalenko, C. Chable-Bessia, G. Cantarella, A. Israel, D. Wallach, G. Courtois, The tumour suppressor CYLD negatively regulates NF-kappaB signalling by deubiquitination, Nature 424 (2003) 801–805.
[73] M. Kracht, J. Saklatvala, Transcriptional and post-transcriptional control of gene expression in inflammation, Cytokine 20 (2002) 91–106.
[74] W.S. Lai, J.S. Parker, S.F. Grissom, D.J. Stumpo, P.J. Blackshear, Novel mRNA targets for tristetraprolin (TTP) identified by global analysis of stabilized transcripts in TTP-deficient fibroblasts, Mol. Cell. Biol. 26 (2006) 9196–9208.
[75] E. Laplantine, E. Fontan, J. Chiaravalli, T. Lopez, G. Lakisic, M. Veron, F. Agou, A. Israel, NEMO specifically recognizes K63-linked poly-ubiquitin chains through a new bipartite ubiquitin-binding domain, EMBO J. 28 (2009) 2885–2895.
[76] C.M. Larsen, M. Faulenbach, A. Vaag, A. Volund, J.A. Ehses, B. Seifert, T. Mandrup-Poulsen, M.Y. Donath, Interleukin-1-receptor antagonist in type 2 diabetes mellitus, N. Engl. J. Med. 356 (2007) 1517–1526.
[77] F. Li, I. Thiele, N. Jamshidi, B.O. Palsson, Identification of potential pathway mediation targets in Toll-like receptor signaling, PLoS Comput. Biol. 5 (2009) e1000292.
[78] J. Liang, T. Lei, Y. Song, N. Yanes, Y. Qi, M. Fu, RNA-destabilizing factor tristetraprolin negatively regulates NF-kappaB signaling, J. Biol. Chem. 284 (2009) 29383–29390.
[79] Y. Liu, E.G. Shepherd, L.D. Nelin, MAPK phosphatases—regulating the immune response, Nat. Rev. Immunol. 7 (2007) 202–212.
[80] P.T. Lomedico, U. Gubler, C.P. Hellmann, M. Dukovich, J.G. Giri, Y.C. Pan, K. Collier, R. Semionow, A.O. Chua, S.B. Mizel, Cloning and expression of murine interleukin-1 cDNA in *Escherichia coli*, Nature 312 (1984) 458–462.
[81] A.D. Luster, R. Alon, U.H. von Andrian, Immune cell migration in inflammation: present and future therapeutic targets, Nat. Immunol. 6 (2005) 1182–1190.
[82] K.R. Mahtani, M. Brook, J.L. Dean, G. Sully, J. Saklatvala, A.R. Clark, Mitogen-activated protein kinase p38 controls the expression and posttranslational modification of tristetraprolin, a regulator of tumor necrosis factor alpha mRNA stability, Mol. Cell. Biol. 21 (2001) 6461–6469.
[83] S.K. Manna, G.T. Ramesh, Interleukin-8 induces nuclear transcription factor-kappaB through a TRAF6-dependent pathway, J. Biol. Chem. 280 (2005) 7010–7021.
[84] M.U. Martin, W. Falk, The interleukin-1 receptor complex and interleukin-1 signal transduction, Eur. Cytokine Netw. 8 (1997) 5–17.
[85] F. Martinon, K. Burns, J. Tschopp, The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta, Mol. Cell 10 (2002) 417–426.
[86] F. Martinon, A. Mayor, J. Tschopp, The inflammasomes: guardians of the body, Annu. Rev. Immunol. 27 (2009) 229–265.
[87] B. McDonald, K. Pittman, G.B. Menezes, S.A. Hirota, I. Slaba, C.C. Waterhouse, P.L. Beck, D.A. Muruve, P. Kubes, Intravascular danger signals guide neutrophils to sites of sterile inflammation, Science 330 (2010) 362–366.
[88] R. Medzhitov, Inflammation 2010: new adventures of an old flame, Cell 140 (2010) 771–776.
[89] R. Medzhitov, T. Horng, Transcriptional control of the inflammatory response, Nat. Rev. Immunol. 9 (2009) 692–703.
[90] H. Mendoza, D.G. Campbell, K. Burness, J. Hastie, N. Ronkina, J.H. Shim, J.S. Arthur, R.J. Davis, M. Gaestel, G.L. Johnson, S. Ghosh, P. Cohen, Roles for TAB1 in regulating the IL-1-dependent phosphorylation of the TAB3 regulatory subunit and activity of the TAK1 complex, Biochem. J. 409 (2008) 711–722.
[91] M.L. Metzker, Sequencing technologies—the next generation, Nat. Rev. Genet. 11 (2010) 31–46.
[92] C. Nathan, Points of control in inflammation, Nature 420 (2002) 846–852.
[93] C. Nathan, A. Ding, Nonresolving inflammation, Cell 140 (2010) 871–882.
[94] J. Nemunaitis, F.R. Appelbaum, K. Lilleby, W.C. Buhles, C. Rosenfeld, Z.R. Zeigler, R.K. Shadduck, J.W. Singer, W. Meyer, C.D. Buckner, Phase I study of recombinant interleukin-1 beta in patients undergoing autologous bone marrow transplant for acute myelogenous leukemia, Blood 83 (1994) 3473–3479.
[95] J. Ninomiya-Tsuji, K. Kishimoto, A. Hiyama, J. Inoue, Z. Cao, K. Matsumoto, The kinase TAK1 can activate the NIK-I kappaB as well as the MAP kinase cascade in the IL-1 signalling pathway, Nature 398 (1999) 252–256.
[96] M.F. Nold, C.A. Nold-Petry, J.A. Zepp, B.E. Palmer, P. Bufler, C.A. Dinarello, IL-37 is a fundamental inhibitor of innate immunity, Nat. Immunol. 11 (2010) 1014–1022.

[97] L.A. O'Neill, Targeting signal transduction as a strategy to treat inflammatory diseases, Nat. Rev. Drug Discov. 5 (2006) 549–563.
[98] J.M. O'Shea, N.D. Perkins, Regulation of the RelA (p65) transactivation domain, Biochem. Soc. Trans. 36 (2008) 603–608.
[99] K. Oda, H. Kitano, A comprehensive map of the toll-like receptor signaling network, Mol. Syst. Biol. 2 (2006) 2006.
[100] R. Osborne, Fresh from the biologic pipeline, Nat. Biotechnol. 27 (2009) 222–225.
[101] J.A. Papin, T. Hunter, B.O. Palsson, S. Subramaniam, Reconstruction of cellular signalling networks and analysis of their properties, Nat. Rev. Mol. Cell Biol. 6 (2005) 99–111.
[102] J.A. Papin, B.O. Palsson, The JAK-STAT signaling network in the human B-cell: an extreme signaling pathway analysis, Biophys. J. 87 (2004) 37–46.
[103] J.A. Papin, B.O. Palsson, Topological analysis of mass-balanced signaling networks: a framework to obtain network properties including crosstalk, J. Theor. Biol. 227 (2004) 283–297.
[104] A.R. Pico, T. Kelder, M.P. van Iersel, K. Hanspers, B.R. Conklin, C. Evelo, WikiPathways: pathway editing for the people, PLoS Biol. 6 (2008) e184.
[105] P. Rao, M.S. Hayden, M. Long, M.L. Scott, A.P. West, D. Zhang, A. Oeckinghaus, C. Lynch, A. Hoffmann, D. Baltimore, S. Ghosh, IkappaBbeta acts to inhibit and activate gene expression during the inflammatory response, Nature 466 (2010) 1115–1119.
[106] S. Reddy, S. Jia, R. Geoffrey, R. Lorier, M. Suchi, U. Broeckel, M.J. Hessner, J. Verbsky, An autoinflammatory disease due to homozygous deletion of the IL1RN locus, N. Engl. J. Med. 360 (2009) 2438–2444.
[107] F. Renner, M.L. Schmitz, Autoregulatory feedback loops terminating the NF-kappaB response, Trends Biochem. Sci. 34 (2009) 128–135.
[108] K.M. Rothgiesser, M. Fey, M.O. Hottiger, Acetylation of p65 at lysine 314 is important for late NF-kappaB-dependent gene expression, BMC Genomics 11 (2010) 22.
[109] J.G. Ryan, R. Goldbach-Mansky, The spectrum of autoinflammatory diseases: recent bench to bedside observations, Curr. Opin. Rheumatol. 20 (2008) 66–75.
[110] K.G. Saag, G.G. Teng, N.M. Patkar, J. Anuntiyo, C. Finney, J.R. Curtis, H.E. Paulus, A. Mudano, M. Pisu, M. Elkins-Melton, R. Outman, J.J. Allison, A.M. Suarez, S.L. Bridges Jr., W.W. Chatham, M. Hochberg, C. MacLean, T. Mikuls, L.W. Moreland, J. O'Dell, A.M. Turkiewicz, D.E. Furst, American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis, Arthritis Rheum. 59 (2008) 762–784.
[111] J. Saez-Rodriguez, L. Simeoni, J.A. Lindquist, R. Hemenway, U. Bommhardt, B. Arndt, U.U. Haus, R. Weismantel, E.D. Gilles, S. Klamt, B. Schraven, A logical model provides insights into T cell receptor signaling, PLoS Comput. Biol. 3 (2007) e163.
[112] C. Salliot, M. Dougados, L. Gossec, Risk of serious infections during rituximab, abatacept and anakinra therapies for rheumatoid arthritis: meta-analyses of randomized placebo-controlled trials, Ann. Rheum. Dis. (2008).
[113] S. Sato, H. Sanjo, K. Takeda, J. Ninomiya-Tsuji, M. Yamamoto, T. Kawai, K. Matsumoto, O. Takeuchi, S. Akira, Essential function for the kinase TAK1 in innate and adaptive immune responses, Nat. Immunol. 6 (2005) 1087–1095.
[114] S. Sato, H. Sanjo, T. Tsujimura, J. Ninomiya-Tsuji, M. Yamamoto, T. Kawai, O. Takeuchi, S. Akira, TAK1 is indispensable for development of T cells and prevention of colitis by the generation of regulatory T cells, Int. Immunol. 18 (2006) 1405–1411.
[115] C. Scheinecker, J. Smolen, U. Yasothan, J. Stoll, P. Kirkpatrick, Tocilizumab, Nat. Rev. Drug Discov. 8 (2009) 273–274.
[116] Y.M. Schichl, U. Resch, R. Hofer-Warbinek, M.R. de, Tristetraprolin impairs NF-kappaB/p65 nuclear translocation, J. Biol. Chem. 284 (2009) 29571–29581.
[117] J.H. Schiller, B.E. Storer, P.L. Witt, D. Alberti, M.B. Tombes, R. Arzoomanian, R.A. Proctor, D. McCarthy, R.R. Brown, S.D. Voss, Biological and clinical effects of intravenous tumor necrosis factor-alpha administered three times weekly, Cancer Res. 51 (1991) 1651–1658.
[118] M. Schmidt-Supprian, W. Bloch, G. Courtois, K. Addicks, A. Israel, K. Rajewsky, M. Pasparakis, NEMO/IKK gamma-deficient mice model incontinentia pigmenti, Mol. Cell 5 (2000) 981–992.
[119] J. Schmitz, A. Owyang, E. Oldham, Y. Song, E. Murphy, T.K. McClanahan, G. Zurawski, M. Moshrefi, J. Qin, X. Li, D.M. Gorman, J.F. Bazan, R.A. Kastelein, IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines, Immunity 23 (2005) 479–490.
[120] N. Shembade, A. Ma, E.W. Harhaj, Inhibition of NF-kappaB signaling by A20 through disruption of ubiquitin enzyme complexes, Science 327 (2010) 1135–1139.
[121] J.H. Shim, C. Xiao, A.E. Paschal, S.T. Bailey, P. Rao, M.S. Hayden, K.Y. Lee, C. Bussey, M. Steckel, N. Tanaka, G. Yamada, S. Akira, K. Matsumoto, S. Ghosh, TAK1, but not TAB1 or TAB2, plays an essential role in multiple signaling pathways in vivo, Genes Dev. 19 (2005) 2668–2681.
[122] O. Shoval, U. Alon, SnapShot: network motifs, Cell 143 (2010) 326-3e1.
[123] J.E. Sims, C.J. March, D. Cosman, M.B. Widmer, H.R. MacDonald, C.J. McMahan, C.E. Grubin, J.M. Wignall, J.L. Jackson, S.M. Call, cDNA expression cloning of the IL-1 receptor, a member of the immunoglobulin superfamily, Science 241 (1988) 585–589.
[124] J.E. Sims, D.E. Smith, The IL-1 family: regulators of immunity, Nat. Rev. Immunol. 10 (2010) 89–102.
[125] J.W. Smith, W.J. Urba, B.D. Curti, L.J. Elwood, R.G. Steis, J.E. Janik, W.H. Sharfman, L.L. Miller, R.G. Fenton, K.C. Conlon, The toxic and hematologic effects of interleukin-1 alpha administered in a phase I trial to patients with advanced malignancies, J. Clin. Oncol. 10 (1992) 1141–1152.
[126] A. So, T. De Smedt, S. Revaz, J. Tschopp, A pilot study of IL-1 inhibition by anakinra in acute gout, Arthritis Res. Ther. 9 (2007) R28.
[127] L.A. Solt, L.A. Madge, M.J. May, NEMO-binding domains of both IKKalpha and IKKbeta regulate IkappaB kinase complex assembly and classical NF-kappaB activation, J. Biol. Chem. 284 (2009) 27596–27608.
[128] L.A. Solt, L.A. Madge, J.S. Orange, M.J. May, Interleukin-1-induced NF-kappaB activation is NEMO-dependent but does not require IKKbeta, J. Biol. Chem. 282 (2007) 8724–8733.
[129] J.G. Stoll, U. Yasothan, Rheumatoid arthritis market, Nat. Rev. Drug Discov. 8 (2009) 693–694.
[130] V. Strand, R. Kimberly, J.D. Isaacs, Biologic therapies in rheumatology: lessons learned, future directions, Nat. Rev. Drug Discov. 6 (2007) 75–92.
[131] S.C. Sun, P.A. Ganchi, D.W. Ballard, W.C. Greene, NF-kappa B controls expression of inhibitor I kappa B alpha: evidence for an inducible autoregulatory pathway, Science 259 (1993) 1912–1915.
[132] G. Takaesu, S. Kishida, A. Hiyama, K. Yamaguchi, H. Shibuya, K. Irie, J. Ninomiya-Tsuji, K. Matsumoto, TAB2, a novel adaptor protein, mediates activation of TAK1 MAPKKK by linking TAK1 to TRAF6 in the IL-1 signal transduction pathway, Mol. Cell 5 (2000) 649–658.
[133] O. Takeuchi, S. Akira, Pattern recognition receptors and inflammation, Cell 140 (2010) 805–820.
[134] T. Tanaka, M.J. Grusby, T. Kaisho, PDLIM2-mediated termination of transcription factor NF-kappaB activation by intranuclear sequestration and degradation of the p65 subunit, Nat. Immunol. 8 (2007) 584–591.
[135] G.A. Taylor, E. Carballo, D.M. Lee, W.S. Lai, M.J. Thompson, D.D. Patel, D.I. Schenkman, G.S. Gilkeson, H.E. Broxmeyer, B.F. Haynes, P.J. Blackshear, A pathogenetic role for TNF alpha in the syndrome of cachexia, arthritis, and autoimmunity resulting from tristetraprolin (TTP) deficiency, Immunity 4 (1996) 445–454.
[136] R. Terkeltaub, J.S. Sundy, H.R. Schumacher, F. Murphy, S. Bookbinder, S. Biedermann, R. Wu, S. Mellis, A. Radin, The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study, Ann. Rheum. Dis. 68 (2009) 1613–1617.
[137] A.E. Teschendorff, S. Gomez, A. Arenas, D. El-Ashry, M. Schmidt, M. Gehrmann, C. Caldas, Improved prognostic classification of breast cancer defined by antagonistic activation patterns of immune response pathway modules, BMC Cancer 10 (2010) 604.
[138] A. Thiefes, A. Wolf, A. Doerrie, G.A. Grassl, K. Matsumoto, I. Autenrieth, E. Bohn, H. Sakurai, R. Niedenthal, K. Resch, M. Kracht, The *Yersinia enterocolitica* effector YopP inhibits host cell signalling by inactivating the protein kinase TAK1 in the IL-1 signalling pathway, EMBO Rep. 7 (2006) 838–844.
[139] F. Tokunaga, S. Sakata, Y. Saeki, Y. Satomi, T. Kirisako, K. Kamei, T. Nakagawa, M. Kato, S. Murata, S. Yamaoka, M. Yamamoto, S. Akira, T. Takao, K. Tanaka, K. Iwai, Involvement of linear polyubiquitylation of NEMO in NF-kappaB activation, Nat. Cell Biol. 11 (2009) 123–132.
[140] L. Treffkorn, R. Scheibe, T. Maruyama, P. Dieter, PGE2 exerts its effect on the LPS-induced release of TNF-alpha, ET-1, IL-1alpha, IL-6 and IL-10 via the EP2 and EP4 receptor in rat liver macrophages, Prostaglandins Other Lipid Mediat. 74 (2004) 113–123.
[141] E. Trompouki, E. Hatzivassiliou, T. Tsichritzis, H. Farmer, A. Ashworth, G. Mosialos, CYLD is a deubiquitinating enzyme that negatively regulates NF-kappaB activation by TNFR family members, Nature 424 (2003) 793–796.
[142] N. Uemura, T. Kajino, H. Sanjo, S. Sato, S. Akira, K. Matsumoto, J. Ninomiya-Tsuji, TAK1 is a component of the Epstein–Barr virus LMP1 complex and is essential for activation of JNK but not of NF-kappaB, J. Biol. Chem. 281 (2006) 7863–7872.
[143] M.P. van Iersel, T. Kelder, A.R. Pico, K. Hanspers, S. Coort, B.R. Conklin, C. Evelo, Presenting and exploring biological pathways with PathVisio, BMC Bioinformatics 9 (2008) 399.
[144] L. Vereecke, R. Beyaert, G. van Loo, The ubiquitin-editing enzyme A20 (TNFAIP3) is a central regulator of immunopathology, Trends Immunol. 30 (2009) 383–391.
[145] J. Vilcek, M. Feldmann, Historical review: cytokines as therapeutics and targets of therapeutics, Trends Pharmacol. Sci. 25 (2004) 201–209.
[146] E.A. Wall, J.R. Zavzavadjian, M.S. Chang, B. Randhawa, X. Zhu, R.C. Hsueh, J. Liu, A. Driver, X.R. Bao, P.C. Sternweis, M.I. Simon, I.D. Fraser, Suppression of LPS-induced TNF-alpha production in macrophages by cAMP is mediated by PKA-AKAP95-p105, Sci. Signal. 2 (2009) ra28.
[147] M.C. Walsh, G.K. Kim, P.L. Maurizio, E.E. Molnar, Y. Choi, TRAF6 autoubiquitination-independent activation of the NFkappaB and MAPK pathways in response to IL-1 and RANKL, PLoS One 3 (2008) e4064.
[148] J. Wan, W. Zhang, L. Wu, T. Bai, M. Zhang, K.W. Lo, Y.L. Chui, Y. Cui, Q. Tao, M. Yamamoto, S. Akira, Z. Wu, BS69, a specific adaptor in the latent membrane protein 1-mediated c-Jun N-terminal kinase pathway, Mol. Cell. Biol. 26 (2006) 448–456.
[149] C. Wang, L. Deng, M. Hong, G.R. Akkaraju, J. Inoue, Z.J. Chen, TAK1 is a ubiquitin-dependent kinase of MKK and IKK, Nature 412 (2001) 346–351.
[150] D.J. Waugh, C. Wilson, The interleukin-8 pathway in cancer, Clin. Cancer Res. 14 (2008) 6735–6741.
[151] A. Weber, P. Wasiliew, M. Kracht, Interleukin-1 (IL-1) pathway, Sci. Signal. 3 (2010) cm1.
[152] M. Windheim, M. Stafford, M. Peggie, P. Cohen, Interleukin-1 (IL-1) induces the Lys63-linked polyubiquitination of IL-1 receptor-associated kinase 1 to facilitate NEMO binding and the activation of IkappaBalpha kinase, Mol. Cell. Biol. 28 (2008) 1783–1791.
[153] X. Wu, S.C. Sun, Retroviral oncoprotein Tax deregulates NF-kappaB by activating Tak1 and mediating the physical association of Tak1-IKK, EMBO Rep. 8 (2007) 510–515.
[154] D. Xu, H.R. Jiang, P. Kewin, Y. Li, R. Mu, A.R. Fraser, N. Pitman, M. Kurowska-Stolarska, A.N. McKenzie, I.B. McInnes, F.Y. Liew, IL-33 exacerbates antigen-induced arthritis by activating mast cells, Proc. Natl. Acad. Sci. U.S.A. 105 (2008) 10913–10918.

[155] S. Yamauchi, H. Ito, A. Miyajima, IkappaBeta, a nuclear IkappaB protein, positively regulates the NF-kappaB-mediated expression of proinflammatory cytokines, Proc. Natl. Acad. Sci. U.S.A. 107 (2010) 11924–11929.
[156] K. Yamazaki, J. Gohda, A. Kanayama, Y. Miyamoto, H. Sakurai, M. Yamamoto, S. Akira, H. Hayashi, B. Su, J. Inoue, Two mechanistically and temporally distinct NF-kappaB activation pathways in IL-1 signaling, Sci. Signal. 2 (2009) ra66.
[157] S.K. Yang, Y.C. Wang, C.C. Chao, Y.J. Chuang, C.Y. Lan, B.S. Chen, Dynamic cross-talk analysis among TNF-R, TLR-4 and IL-1R signalings in TNFalpha-induced inflammatory responses, BMC Med. Genomics 3 (2010) 19.
[158] A. Yarilina, K.H. Park-Min, T. Antoniv, X. Hu, L.B. Ivashkiv, TNF activates an IRF1-dependent autocrine loop leading to sustained expression of chemokines and STAT1-dependent type I interferon-response genes, Nat. Immunol. 9 (2008) 378–387.
[159] H. Yen, T. Ooka, A. Iguchi, T. Hayashi, N. Sugimoto, T. Tobe, NleC, a type III secretion protease, compromises NF-kappaB activation by targeting p65/RelA, PLoS Pathog. 6 (2010) e1001231.
[160] Y. Yu, N. Ge, M. Xie, W. Sun, S. Burlingame, A.K. Pass, J.G. Nuchtern, D. Zhang, S. Fu, M.D. Schneider, J. Fan, J. Yang, Phosphorylation of Thr-178 and Thr-184 in the TAK1 T-loop is required for interleukin (IL)-1-mediated optimal NFkappaB and AP-1 activation as well as IL-6 gene expression, J. Biol. Chem. 283 (2008) 24497–24505.
[161] Q. Zhao, X. Wang, L.D. Nelin, Y. Yao, R. Matta, M.E. Manson, R.S. Baliga, X. Meng, C.V. Smith, J.A. Bauer, C.H. Chang, Y. Liu, MAP kinase phosphatase 1 controls innate immune responses and suppresses endotoxic shock, J. Exp. Med. 203 (2006) 131–140.