The regulation of inflammation by interferons and their STATs

Isabella Rauch,[1] Mathias Müller[2] and Thomas Decker[1,*]

[1]Max F. Perutz Laboratories; University of Vienna; Vienna, Austria; [2]Institute of Animal Breeding and Genetics and Biomodels Austria; University of Veterinary Medicine Vienna; Vienna, Austria

Interferons (IFN) are subdivided into type I IFN (IFN-I, here synonymous with IFN-α/β), type II (IFN-γ) and type III IFN (IFN-III/IFN-λ) that reprogram nuclear gene expression through STATs 1 and 2 by forming STAT1 dimers (mainly IFN-γ) or the ISGF3 complex, a STAT1-STAT2-IRF9 heterotrimer (IFN-I and IFN-III). Dominant IFN activities in the immune system are to protect cells from viral replication and to activate macrophages for enhanced effector function. However, the impact of IFN and their STATs on the immune system stretches far beyond these activities and includes the control of inflammation. The goal of this review is to give an overview of the different facets of the inflammatory process that show regulatory input by IFN/STAT.

Inflammation constitutes an essential part of the innate immune response to pathogens or the release of self molecules acting as endogenous danger signals. Exposure of peripheral tissue to pathogen- or danger-associated molecular patterns (PAMPs and DAMPs, respectively) stimulates the release of proinflammatory mediators by tissue-resident cells that activate the endothelium of blood vessels and initiate a chain of events that ends with the transmigration of blood leukocytes and their penetration of the infected or otherwise irritated tissue. The strength and persistence of the proinflammatory stimulus decides whether systemic responses such as the mobilization of bone marrow leukopoiesis or the liver acute phase response ensues. The potentially harmful consequences of the inflammatory response need to be tightly controlled. Otherwise inflamed tissue may be irreversibly damaged as a consequence of lytic enzyme release or through oxidative stress. Moreover, an overshooting systemic response may cause a generalized shock syndrome.[1,2] Consequently the outcome of the innate response to infection is determined by the balance between microbicidal effects and the damage inflicted to the host organism by the inflammation-induced loss of cell, tissue or organ function.

A large number of cytokines and chemokines that regulate the generation, trafficking and effector activity of leukocytes forming the inflammatory cell infiltrate control inflammation. In some cases the predominant effect of these cytokines is clearly proinflammatory, as in the case of TNF, or predominantly anti-inflammatory as in the case of TGF-β or IL-10. In other cases cytokines may act to support or suppress inflammation, depending on context. Interferons (IFN) are frequent contributors to the inflammatory cytokine stew. According to structural similarities, IFN and IL-10 families are grouped as class II cytokines.[3-5] Based on their evolution, structure and interaction with distinct receptor complexes IFN are subdivided into three distinct types. With together around 20 members the mammalian type I IFN (IFN-I) includes more than 10 IFN-α and usually a single IFN-β. Most likely all tissues and cell types produce IFN-I when exposed to appropriate pathogen or danger-associated molecular patterns. This contrasts the type II IFN, IFN-γ, which is produced predominantly by various T cell and NK cell populations. Type III IFN is comprised of three family members called IFN-λ1-3, or, synonymously, IL-29, IL-28A and IL-28B. The conditions and molecular mechanism controlling their synthesis are most likely similar, although not identical,[6,7] to those of IFN-I and both differ strongly from the regulation of IFN-γ synthesis by T and NK cells. Unlike IFN-I and IFN-γ, IFN-III receptors show highly restricted tissue distribution and appear to be expressed mainly on epithelia and, in humans but not in mice, on hepatocytes.

Receptors of all IFN types belong to the class II of cytokine receptors and share the attribute of employing JAK-STAT signal transduction for nuclear signaling.[4,8,9] In keeping with highly similar biological properties of IFN-I and IFN-III, their receptor complexes (IFNAR and IFNλR, respectively), although composed, respectively, of IFNAR1 and IFNAR2 chains and IL28R/IL-10R2 chains, associate with JAK1 and Tyk2 kinases to phosphorylate and activate STAT1 as well as STAT2. This causes the formation of a STAT1/STAT2 heterodimer that associates with a third subunit, IRF9, to form the transcriptional complex ISGF3. By contrast the IFN-γ receptor (IFNGR), composed of IFNGR1 and IFNGR2 chains, uses JAK1 and JAK2 kinases and strongly favors association with STAT1 over all other STATs. Consistently, transcriptional responses to IFN-γ are dominated by the activity of the STAT1 homodimer. Although STAT3, STAT4 and STAT5 are activated by IFN in some cell types, all available evidence suggests that STATs 1 and 2 are the main mediators of cellular and organismic IFN biology. Hence the terms "STAT" and particularly "IFN/STAT" are used in this review to indicate

STATs 1 and 2, unless there is explicit reference to a different member of the STAT family.

To study the impact of individual IFN types in animal models of inflammatory disease, mice deficient for the IFNAR1 chain or for either the Ifng or Ifngr1 gene are used. IL28R^{-/-} mice have been generated, yet publications describing their application in experimental models of inflammatory disease are scarce. STAT1^{-/-} mice are used to eliminate the impact of all IFN. Although not subject of this review, STAT1 is also activated by receptors for IL-27 and IL-35, which may influence the contribution of T cells, which would be particularly relevant for IL-35-mediated Treg differentiation. Inflammatory responses have not been widely studied in STAT2^{-/-} mice. In theory this should equal a composite deficiency for IFN-I and IFN-III responses. However, in some tissues the lack of STAT2 causes a significant drop of STAT1 levels, thus producing at least partial absence of IFN-γ responsiveness.[10] Thus, phenotypic properties of STAT2^{-/-} mice are more difficult to interpret.

IFN/STAT upregulate the immunocompetence of many cell populations, which is particularly evident in the case of macrophage activation. This function corresponds to a local or systemic increase in IFN production. Particularly, type I IFN fulfill an important role as inducers of tonic IFNAR signaling in the steady-state. Low levels of synthesis provide sufficient stimulus to maintain transcription of inflammation/immunity-relevant genes and to keep cells in a state of alertness.[11,12] Recent studies show that constitutive IFN-I synthesis can be stimulated by commensal bacteria and their manipulation of host cell chromatin.[13] In interpreting data from IFN/STAT-deficient mice this constitutive IFN activity must be taken into account.

Impact of IFN and STAT1 on the Generation, Differentiation and Death of Hematopoietic Cells

Persistent inflammation stimulates bone marrow hematopoiesis and thus produces an increase in blood leukocyte numbers. Mice deficient for IFN receptors have no major hematopoietic abnormalities, thus IFN are not major regulators of steady-state hematopoiesis. It appears clear, however, that they feed information from ongoing infection/inflammation to hematopoietic stem cells (HSC) of the bone marrow. Treatment of mice with the proinflammatory, IFN-inducing agent poly-IC causes the mobilization of dormant hematopoietic stem cells (HSC) and this response is abrogated in mice lacking either the IFN-I receptor or STAT1.[14] Exhaustion of the stem cell niche in this situation is prevented by the interferon regulatory factor-2 (IRF2), a negative regulator of IFN and IFN-induced genes. In HSC IRF2 abolishes IFN-α-mediated suppression of genes limiting excessive cycling and maintaining the self-renewing potential of HSC.[15] In a murine model of mycobacterial disease HSC mobilization required IFN-γ and STAT1. IFNAR deficiency had a minor effect in this situation despite the ability of Mycobacteria to stimulate IFN-I synthesis.[16] Together these studies suggest that STAT1 target genes push HSC from a dormant state into the cell cycle, shifting the balance toward enhanced hematopoietic differentiation. Contrasting mouse HSC, the growth of human CD34^{+} hematopoietic cells, which represent uncommitted progenitors, is inhibited by IFN-α. This response requires the p38MAPK pathway and may be independent of STAT signaling.[17] A recent study suggests the importance of the IFN-γ pathway in regulating the differentiation of inflammatory dendritic cells in situ. Intraperitoneal infection of mice with *Toxoplasma gondii* causes the replacement of resident peritoneal leukocytes with blood-borne monocytes that differentiate in situ in both macrophages and inflammatory DC. These events required NK cell-derived IFN-γ.[18] The study did not include STAT1^{-/-} mice.

During an infection cells may become sensitive to a death-enhancing effect of IFN-I. Studies from our lab demonstrate enhanced death of macrophages infected with intracellular *L. monocytogenes* due to the activity of a pathway requiring IFN-I, STAT1 and NO production.[19] Possibly linked to this, death mechanisms requiring Rip3 kinase or caspase 1/11 activation referred to as necroptosis or pyroptosis, respectively, are enhanced by IFN-I.[20,21] In the latter situation upregulation of the inflammasome subunit Aim2 by STAT-signaling provides an explanation for enhanced bacteria-induced macrophage death. In virally infected mice IFN-I-mediated neutrophil depletion may occur. This provides a potential explanation for the increased sensitivity to bacterial superinfection in the wake of viral disease.[22] It should be noted however that reduced neutrophil counts upon virus infection have also been explained by IFN-I-mediated alterations in chemokine production.[23,24] During infection with the intracellular bacterium *Listeria monocytogenes* massive death of splenic T cells occurs and this is almost completely reversed upon conditional deletion of either the IFNAR or STAT1.[25,26] Removal of apoptotic lymphocytes is thought to stimulate IL-10 synthesis and the suppression of a protective inflammatory response. Treatment of mice with TNF increased the fraction of apoptotic enterocytes and hepatocytes. The apoptotic response was reduced in mice deficient for the IFN-I receptor.[27] Together these reports support the view that IFN/STAT are important regulators of cell survival during innate, proinflammatory immune responses. However, favorable or adverse consequences of abrogating their regulatory input are observed, depending on the proinflammatory stimulus and environment.[28]

Regulation of Cell Trafficking: the Impact of IFN/STAT on Chemokine Expression

The recruitment of leukocytes to sites of infection or to sites exposed to non-infectious inflammatory agents, and the subsequent formation of inflammatory infiltrates, is controlled by the CCL and CXCL families of chemokines.[29] A large number of studies document the ability of IFN-I, IFN-γ or both, to regulate chemokine synthesis (**Table 1**). Among the chemokines consistently reported to show IFN regulation are the CCR2 ligand CCL2, CCL5, which binds to multiple receptors, and the CXCR3 ligands CXCL9, CXCL10 and CXCL11. Not all studies investigating the regulation of chemokines by IFN establish a clear link to STAT1 dimer or ISGF3 activity. The interpretation of gene targeting is complicated by the fact that STAT1-deficient mice reveal differences in chemokine production, but

do not allow to distinguish between direct action of STAT1 on chemokine promoters and more indirect effects. That said, several chemokine promoters such as those regulating CCL2/MCP1, CCL5/RANTES, CXCL9 or CXCL10 contain binding sites for STAT1 dimers and/or ISGF3, thus fulfilling this important criterion of direct target genes.[30-34] The CCL5/RANTES promoter associates with members of the interferon regulatory factor family through a proximal promoter element, its regulation by IFN-γ thus involves a STAT1-IRF1 pathway.[35] The vast majority of investigated chemokine promoters respond to signals from classical proinflammatory pathways, most prominently the NFκB pathway. Functional cooperation between IFN and NFκB- activating cytokines, or, more directly, between STATs, IRFs and NFκB is frequently observed.[32,34,36-40] Moreover, the tissue-specific transcription factor Pu.1 was found to allow for the IFN-γ-induced expression of CXCL9 in myeloid cells, but not other cell types.[41] During infection with *L. monocytogenes* CCL2/MCP1 was shown to be under control of the MyD88 pathway early after infection and predominantly under IFN-I control at a later stage.[42] This regulatory switch may indicate cooperativity of NFκB and STAT pathways by sequential deployment.

Regulation by IFN is an attribute of chemokines associated with the IFN-γ/LPS-induced M1 polarization of macrophages whereas M2 polarization is associated with the production of a distinct set of chemokines.[43,44] Therefore, besides activation of nonpolarized macrophages, the induction of macrophage polarization is one of several ways by which IFN/STAT can influence the chemokine spectrum synthesized during inflammation. In addition, IFN/STAT may change the abundance and composition of chemokine-producing cell populations.[26] Active suppression of chemokine synthesis by IFN-I or IFN-γ in activated macrophages, splenocytes or pDC has also been reported[45,46] and may contribute to the successful treatment of MS patients with IFN-β.[47,48] Chemokines not usually upregulated by IFN/STAT such as CXCL1 and CXCL2 can be suppressed, whereas others show situation-dependent upregulation or suppression (**Table 1**). The mechanisms underlying the inhibition of chemokine synthesis or the factors determining the balance between induced synthesis and inhibition are not known.

Both chemokines recruiting predominantly myeloid cells (neutrophils, inflammatory macrophages and DC; e.g., the CCR2 ligand CCL2, the CCR1/5 ligand CCL3, the CCR1/3/5 ligand CCL5, and the CCR1/2/3 ligand CCL7) and chemokines recruiting predominantly lymphoid cells (NK cells, effector T cells; the CXCR3 ligands CXCL9, CXCL10 and CXCL11) are controlled by IFN/STAT (**Table 1**). IFN/STAT-regulated chemokine synthesis thus exerts profound effects on the mobilization, tissue infiltration and activation of inflammatory cell populations. This in turn is thought to alter immune responses of IFNAR, IFNGR, or STAT1-deficient mice and explain in part why such animals survive better or worse when infected or treated with inflammatory agents. While many studies document changes of cell recruitment in absence of IFN/STAT responses (most animal studies listed in **Table 1**, e.g., refs. 26, 34, 42 and 49–52) this alone does not support the conclusion of a causal relationship to the outcome of an immune response.

For example, we noted significantly altered chemokine production in Listeria-infected mice lacking STAT1 in DC, but this had no impact on the survival of such animals.[26] Comparison of IFN/STAT deficiency with mice lacking the regulated chemokine allows an estimation of the contribution of that chemokine to the immune response under study,[42,51,52] but not of the contribution of its regulation by IFN/STAT. More convincingly the impact of chemokine regulation can be determined by rescuing the effects of IFN/STAT deficiency by chemokine injection.[53] This approach has not been widely used.

Studies linking regulation of chemokines by IFN/STAT with the establishment of immunity suggest this can benefit or weaken host immunity. For example, infections with MCMV or HSV-1 viruses, or the intracellular bacteria *L. monocytogenes* and *F. tularensis* are accompanied by IFN/STAT-mediated upregulation of CCR2 ligands, particularly CCL2. These mediate the recruitment of inflammatory monocytes and neutrophils to increase resistance to infection. In addition to inflammatory monocyte recruitment by CCR2 ligands, MCMV infection triggers a protective cascade of IFN-α-upregulated CCL3, NK cell recruitment, IFN-γ synthesis and IFN-γ-induction of CXCL9 production.[50] In accordance with the beneficial effect on MCMV infection, IFN-α/STAT1-induced chemokines increased resistance against corneal infection with HSV-1, an infection protocol resulting in viral spread to the brain stem.[34,54] Contrasting these examples, intracranial infection with LCMV was worsened by IFN-γ-mediated recruitment of inflammatory cells, shown by the protective effects of a dominant negative IFN-γR expressed in macrophage-lineage cells.[55] In addition to infection models with a single pathogen, chemokine synthesis was shown to underlie the reduced resistance of mice previously infected with influenza virus to secondary infection with *S. pneumoniae*. Shahangian and colleagues demonstrated that the inhibition of the CXCR2 ligands CXCL1 and CXCL2 by virus-induced IFN-I lead to a drop in neutrophil infiltrates and a corresponding inhibition of bacterial clearance.[23]

Aside from infection, chemokine regulation by IFN/STAT has been studied using non-infectious inducers of inflammation. For example, expressing an IFN-γ transgene in the thyroid gland caused increased expression of CCL4, CCL5, CXCL9, CXCL10 and CXCL11 and a mononuclear infiltrate in the thyroid gland.[56] In the brain of mice suffering from experimental autoimmune encephalitis (EAE), IFN-γ-mediated protection correlated with the expression of CXCL10/IP10 in astrocytes.[57] Induction of hepatitis with the lectin Concanavalin A (ConA) in IFN-γ or STAT1-deficient mice resulted in decreased inflammatory infiltrates that correlated with reduced production of CXCL family chemokines in hepatic cells (**Table 1**). In a mouse asthma model IFN-γ and STAT1 contributed to allergic inflammation through enhanced production of CXCL9 and CXCL10.[58] The synthetic TLR7 agonist Imiquimod is an effective treatment against human skin cancer. In a mouse melanoma model the drug was shown to stimulate mast cells for TLR7-dependent IFN-I synthesis. Subsequent IFNAR signaling caused CCL2 production and the recruitment of a tumoricidal plasmacytoid dendritic cell (pDC) infiltrate.[59]

Table 1. Regulation of chemokine synthesis by IFN and STATs 1/2

Cell/animal	Stimulus/disease	IFN type involved	STAT involved	Chemokine regulated	References
Mouse macrophages	IFN-γ or IFN-γ/TNF	IFN-γ	STAT1	CCL2/MCP1 ↑ CXCL9/MIG ↑ CXCL10/IP10 ↑ CCL12/MCP5 ↑	37, 45 and 128
	IFN-γ/PamCys	IFN-γ	nd	CCL2/MCP1 ↑	52
	LPS	nd	STAT1	CXCL10/IP10 ↑ CCL12/MCP5↑	45 and 129
	LPS/IFN-γ	IFN-γ	STAT1	CXCL1/KC/GROα ↓ CXCL2/MIP2/GROβ ↓ CCL2/MCP1 ↓ CCL4/MIP1β ↓	45
	TNF	IFN-β	STAT1	CCL5/RANTES ↑ CXCL9/MIG ↑ CXCL10/IP10 ↑	11
	Listeria monocytogenes	IFN-I	nd	CCL2/MCP1 ↑	42
Mouse splenocytes	IFN-α	IFN-α	STAT1	CCL2/MCP1 ↓ CCL5/RANTES ↓ CCL7/MCP3 ↓	46
Human monocytes	IFN-γ	IFN-γ	STAT1	Inhibition of migration in response to CCL2	130
	TNF	IFN-β	STAT1	CCL5/RANTES ↑ CXCL9/MIG ↑ CXCL10/IP10 ↑	11
	M1 polarization (IFN-γ/LPS)	IFN-γ	nd	CCL5/RANTES ↑ CCL15/MIP1δ ↑ CCL20/MIP3α ↑	44 and 131
Human monocyte-derived DC	Sendai virus *Salmonella* Typhimurium	IFN-I	ISGF3	CCL19/MIP3β ↑	40
Human PBMC	IFN-λ	IFN-λ	nd	CXCL9/MIG ↑ CXCL10/IP10 ↑ CXCL11/I-TAC ↑	132
Mouse primary cortical neurons	IFN-α	IFN-α	STAT1	CXCL10/IP10 ↑	133
Human astrocytes	IFN-γ/IL-1β	IFN-γ	nd	CXCL11/I-TAC ↑	36
	IFN-β/IL-1β	IFN-β	ISGF3 (?)	CCL5/RANTES ↑	32
Mouse microglia	IFN-γ	IFN-γ	STAT1	CXCL9/MIG ↑	41
Human plasmacytoid DC (MS patient)	IFN-β/TLR9 ligand	IFN-β	nd	CCL3/MIP1α ↓ CCL4/MIP1β ↓ CCL5/RANTES ↓	48
Human T cells (MS patient)	IFN-β	IFN-β	nd	CCL3/MIP1α ↓ CCL5/RANTES ↓ CCR5 ↓	47
Mouse	MCMV infection	IFN-I	nd	CCL2/MCP1 ↑ CCL3/MIP1α ↑ CCL7/MCP3 ↑ CCL12 ↑	49 50 51

nd, not determined.

Table 1. Regulation of chemokine synthesis by IFN and STATs 1/2 (continued)

Mouse liver	MCMV infection	IFN-γ	nd	CXCL9/MIG ↑	49
Mouse brain	LCMV infection	IFN-γ	nd	CCL2/MCP1 ↑ CCL3/MIP1α ↑ CCL5/RANTES ↑ CXCL10/IP10 ↑	55
Mouse cornea	HSV-1	IFN-α	nd	CCL2/MCP1 ↑	34
Mouse	Vaccinia virus	IFN-I, IFN-γ	nd	CXCL9/MIG ↑	134
	West Nile virus	IFN-I	nd	CCL2/MCP1 ↑ CCL5/RANTES ↑ CXCL10/IP10 ↑	135
	Influenza virus *Streptococcus pneumoniae*	IFN-I	nd	CXCL1/KC ↓ CXCL2/MIP2 ↓	23
Mouse peritoneal cavity	*Listeria monocytogenes*	IFN-I	nd	CCL2/MCP1 ↑	42
		nd	STAT1 (macrophages)	CCL3/MIP1α ↓	26
			STAT1 (DC)	CCL2/MCP1 ↑ CCL5/RANTES ↑	
			STAT1 (T cells)	CCL2/MCP1 ↑ CCL5/RANTES ↑	
Mouse	*Francisella tularensis*	IFN-γ	nd	CCL2/MCP1 ↑	52
	Polymicrobial peritonitis (CASP)	IFN-I	nd	CCL2 ↓	78
	Polymicrobial peritonitis (CLP)	IFN-I	nd	CXCL10 ↑	53
	Trypanosoma cruzi	IFN-γ	nd	CXCL9/MIG ↑ CXCL10/IP10 ↑	136
	Paracoccidioides brasiliensis	IFN-γ	nd	CCL5/RANTES ↑ CXCL1/KC/GROα ↓ CCL3/MIP1α ↓	137
	Candida albicans	IFN-I	nd	CCL2/MCP1 ↑ CXCL1/KC/GROα ↑	71
Mouse thyroid gland	IFN-γ transgene (thyroid gland)	IFN-γ	nd	CXCL9/MIG ↑ CXCL10/IP10 ↑ CCL4/MIP1β ↑ CCL5/RANTES ↑ CXCL11/I-TAC ↑	56
Mouse mast cells	Imiquimod	IFN-I	nd	CCL2/MCP1 ↑	59

nd, not determined.

While synthesis of chemokines is an important factor for the recruitment of inflammatory infiltrates, additional regulation can be provided through the expression of their receptors and by cellular adhesion molecules that mediate leukocyte transmigration. Alterations of chemokine receptor expression contribute to the distinct migratory properties of naïve and effector lymphocytes, DC before and after maturation, or of differently polarized macrophages. While the role of IFN/STAT in these processes has not been widely studied, preliminary evidence for their participation has been reported.[44,54,60] We expect future studies to confirm that all steps controlling leukocyte migration and tissue invasion are under surveillance of IFN/STAT.

Other Mediators of Inflammation Regulated by IFN/STAT

The inflammatory environment is shaped by the products of tissue resident cells as well as cells belonging to the inflammatory infiltrate. IFN-γ/STAT1 are well-established regulators of M1 polarization and classical activation of macrophages, thus

Table 1. Regulation of chemokine synthesis by IFN and STATs 1/2 (continued)

Mouse	TNF	IFN-I	nd	CXCL9/MIG ↑ CXCL10/IP10 ↑ CXCL11/I-TAC ↑	27
	Allergic asthma	IFN-γ	STAT1	CXCL9/MIG ↑ CXCL10/IP10 ↑	58
	ConA-induced hepatitis	IFN-γ	STAT1	CXCL5/ENA-78 ↑ CXCL9/MIG ↑ CXCL10/IP10 ↑ CXCL11/I-TAC ↑	138
Mouse (astrocytes)	EAE	IFN-γ	nd	CXCL10/IP10 ↑	57
Human (MS patient)	IFN-β	IFN-β	nd	CCL2/MCP1 ↑ CXCL10/IP10 ↑	139

nd, not determined.

controlling the synthesis of cytokines, nitric oxide (NO), reactive oxygen intermediates (ROI) and enzymes required for tissue remodelling.[5,43,61,62] Conditional STAT1 gene deletion in mice convincingly demonstrated the importance of macrophage activation in IFN-γ-dependent protective immunity and inflammation against *L. monocytogenes* infection.[26] Apart from macrophages the important role of inflammatory dendritic cells has been widely recognized, cells that may differentiate in situ from inflammatory monocytes.[63] One population of inflammatory DC are Tip-DC, characterized by production of large quantities of NO and TNF during *L. monocytogenes* infection.[64] NO is an important contributor to inflammation owing to its properties as a microbicidal agent as well as a signaling molecule and regulator of cell death.[19,65] NO synthesis is catalyzed by inducible nitric oxide synthase (Nos2 or iNOS). Whereas its regulation in Tip-DC has not been studied, reports performed in macrophages show that the Nos2 gene is synergistically activated by NFκB and STAT pathways.[66] Interaction of a STAT1 dimer activates the Nos2 promoter when IFN-γ and PAMPS are present. By contrast PAMPS like LPS, or pathogens such as *Listeria monocytogenes* stimulate Nos2 transcription through an IFN-I intermediate and ISGF3 activation. ISGF3 and NFκB cooperate in the assembly of a transcription initiation complex with ISGF3 holding responsible for the recruitment of RNA polymerase II and NFκB for promoter binding of the kinases phosphorylating the carboxy-terminal domain of RNA polymerase II.[67] It will be of interest to determine in how far this mode of cooperation between STAT and NFκB pathways is paradigmatic for the regulation of proinflammatory genes and whether it extends to cell types other than macrophages, such as Tip-DC.

A novel, but as yet fairly unexplored activity of IFN/STAT is their regulation of IL1-β production by inflammasomes. IFN-I via STAT1 exert suppressive activity on NLRP1 and NLRP3 inflammasomes that induce caspase 1 to process the IL1-β precursor in response to a large variety of intracellular PAMPs.[68] Two mechanisms have been proposed to explain the reduced IL1-β processing in IFN-I-stimulated cells. On the one hand STAT1 target gene products directly repress these inflammasomes. On the other hand the IFN-I/STAT1 pathway increases IL-10 synthesis,

IL-10-mediated STAT3 activation and the suppression of IL1-β precursor synthesis by activated STAT3.[69] A study addressing *M. tuberculosis* infection reported an intriguing connection between IFN/STAT and NO synthesis.[70] Upregulation of NO production by IFN-γ caused nitrosylation and inactivation of the NLRP3 inflammasome, reduced IL1-β synthesis and a concomitant decrease in inflammatory pathology. Since IFN-I, like IFN-γ, is an inducer of Nos2 synthesis and NO production, the same mechanism may underlie the suppression of inflammasome-mediated IL1-β production by IFN-I. IFN-I-dependent suppression of IL1-β synthesis correlated with increased susceptibility to *Candida albicans* infection.[69,71] It is also thought to contribute to the benefits of IFN-β for the anti-inflammatory treatment of MS, as monocytes from treated patients secrete significantly less IL1-β.[69]

IFN/STAT in Infection-Associated Systemic Inflammation and Sepsis

Treatment of mice with LPS causes a septic shock syndrome, and, ultimately, death. STAT1 enhances the systemic inflammation resulting from LPS administration through the recruitment and activation of macrophages and additional inflammatory leukocytes. Consistently, IFN-γ plays a well-documented role in the pathogenesis of the endotoxin shock.[72,73] STAT1-/- mice survive moderate LPS quantities better than wildtype mice, but succumb to relatively high doses of LPS, that are survived by mice lacking a functional IFN-β gene.[74,75] The reasons underlying this STAT1-independent contribution of IFN-β are not completely understood. One potential explanation is provided by the surprising finding that late-stage induction of IFN-induced genes after viral infection can occur in a STAT2-dependent, STAT1-independent manner.[76] Possibly this STAT1-independent phase of the IFN response accelerates the septic shock syndrome. IFNAR or IFN-β-deficient mice also show a remarkable degree of resistance when the septic shock syndrome is evoked by injection of TNF.[27] Huys and colleagues attribute resistance to a combination of protection from cell death, reduced synthesis of proinflammatory cytokines, and deregulated chemokine production. The

prominent contribution of IFN-I to systemic, pathogen-induced inflammation has sparked the idea of IFN-I neutralization as a means of anti-septic therapy.[77]

A more physiologic way of studying sepsis is to injure the intestine by surgical procedures. Two commonly used methods are cecal ligation and puncture (CLP) or colon ascendens stent peritonitis (CASP). Surprisingly the two procedures produced opposing effects of IFN-I on resistance to the resulting polymicrobial peritonitis. CASP resulted in increased survival of Ifnar1^{-/-} mice and a corresponding increase in CCL2 secretion, neutrophil infiltration and ROI production.[78] By contrast, survival of Ifnar1^{-/-} mice in comparison to wildtype controls was decreased following CLP. In this case IFNAR deficiency abolished IFN-I-mediated upregulation of CXCL10 and the concomitant increase of neutrophil phagocytotic activity.[53] Counterintuitive to the report by Kelly-Scumpia, STAT1^{-/-} mice showed increased resistance to CLP despite decreased production of IFN-α and CXCL10.[79] At present the factors determining the difference between STAT1^{-/-} and Ifnar1^{-/-} in the CLP model are elusive.

To explain the discrepant role of IFN-I in the CASP and CLP models the authors suggest that the intensity of the inflammatory response may decide between adverse or protective effects of IFN-I. If correct, this implies that IFN-I are neither "good" nor "bad" regulators of inflammation, but that their protective or adverse character varies with more or less pronounced inflammatory environments. In line with this notion our recent findings show that the impact of IFN-I on *L. monocytogenes* infection varies with the route of infection. Whereas IFN-I worsen the outcome of i.p. infection, they protect after infection through the gastrointestinal tract. This is correlated with different kinetics and intensity of the proinflammatory response (ref. 28 and our unpublished results). In correspondence with the detrimental effects of type I IFN after CASP or intraperitoneal infection with *L. monocytogenes*, adverse effects of IFN-I were reported for a mouse model of *C. albicans* sepsis. Here, the protective effect of Ifnar1 gene deletion was explained by the lack of IFN-I-mediated upregulation of chemokines recruiting and activating neutrophils and inflammatory monocytes for increased kidney destruction.[71]

IFN/STAT in Intestinal Inflammation

The incidence of intestinal inflammation in humans has strongly risen over past decades.[80] According to current knowledge it results from a disturbed interplay between the intestinal mucosa and gut microbiota.[80] The most prominent type of intestinal inflammation is inflammatory bowel disease (IBD), consisting of two major sub-pathologies named Crohn disease (CD) and ulcerative colitis (UC). The relevance of JAK-STAT signaling for IBD was recently confirmed by a report that the JAK inhibitor tofacitinib improved the condition of patients suffering from UC.[81] In detail the JAK-dependent pathway(s) targeted by the inhibitor remain to be clarified.

The first direct evidence for a role of STAT1 in inflammatory bowel disease came from a study on human patients developing pouchitis, which is a major inflammatory complication after proctocolectomy in UC and familial adenomatous polyposis. In this study, increased expression and activation of STAT1 was observed in biopsies from inflamed mucosa compared with normal mucosa.[82] The same increase was shown in samples of ulcerative colitis and CD patients. The cell types showing increased STAT1 (activation) were identified as infiltrating monocytes and neutrophils.[83] Determination of STAT1 levels in lamina propria mononuclear cells (LPMC) and T cells of CD and UC patients by flow cytometry demonstrated a trend toward increased total STAT1 in LPMC during CD, whereas in UC a similar trend was observed for phosphorylated STAT1.[84] Confirming this result, a microarray on biopsies showed STAT1 expression to be increased in CD, but not in UC and non-IBD infectious colitis.[85] Biopsies from non-inflamed ileal pouches from a cohort of UC patients demonstrated a significant increase of phosphorylated STAT1 over biopsies of familial adenomatous polyposis patients and controls.[86] A more recent study on patients with UC and CD showed STAT1 mRNA slightly but not significantly increased, while reporting significantly increased expression of STAT1-induced genes encoding IRF1, Socs1, IP10, IL-12/23 p40 and T-bet in active CD, and of IP10 and IL-12/23 p40 in active UC.[87]

Prominent animal models of intestinal inflammatory disease are dextran sodium sulfate (DSS)-induced colitis, trinitrobenzene sulfonic acid (TNBS)-induced colitis, or the transfer of CD45RB^{high} T cells into Rag-deficient mice. Surprisingly, data on STAT1-deficient mice in these models are scarce. DSS treatment of STAT1^{-/-} mice on a 129S6/SvEv background suggested decreased tissue damage and hyaluronan deposition compared with wild-type controls, suggesting a contribution of STAT1 to colitis.[88] In our own experiments STAT1 deficiency in a different genetic background slightly protected concerning crypt damage and amount of tissue involved in inflammation caused by DSS.[89] There are no data on STAT1 deficient mice in other models of colitis, however recent papers using the colitis model of CD45RB^{high} T cell transfer into Rag-deficient mice suggest that the balance of STAT1 and STAT3 in the intestine is crucial for the equilibrium of Treg/TH17/TH1 levels, and if disturbed, can lead to increased or decreased pathology.[90,91] A small-molecule compound that triggers the tyrosine phosphorylation of Src homology 2-containing protein tyrosine phosphatase 2 (SHP-2) ameliorated TNBS colitis. The mechanism of this amelioration was shown to be interaction of tyrosine phosphorylated SHP-2 with cytosolic STAT1, preventing the recruitment of STAT1 to the IFNGR.[92]

Reperfusion injury is a type of tissue damage caused when blood supply returns to tissue after a period of ischemia, which can occur in clinical settings. STAT1-deficient mice showed increased survival to ischemia/reperfusion of the small intestine. Their intestines were protected from gross histomorphological tissue destruction and neutrophil infiltration.[93] In a study on celiac disease (gluten-sensitive enteropathy), STAT1 was found to be activated to higher levels than in controls, and in explant cultures of biopsies, gliadin induced the activation of STAT1.[94]

An infectious cause of intestinal inflammation whose containment in the intestinal tract and subsequent clearance was shown to be entirely dependent on STAT1 signaling is Norwalk virus.[95] After oral infection, wild-type animals clear murine Norwalk

virus from the gastrointestinal tract within one day, while STAT1-deficient animals cannot contain it, develop pathology in several organs and die at a rate of over 70%.[95] Rotavirus, another diarrhea-causing virus especially dangerous for newborns, was shown to be shed 100-fold more from STAT1-deficient animals than wild-types; however, the knockout animals could still clear the virus via the adaptive immune system.[96] A later study demonstrated that the STAT1-dependent pathway for rotavirus containment was IFN-λ signaling in epithelial cells of the intestine.[97]

Taken together the data suggest that STAT1 upregulation and/or activation are hallmarks of colonic inflammation. However, the role of STAT1 as a colitogenic driver is modest and varies depending on etiology.

Compared with STAT1, a larger data set is available describing the role of cytokines signaling via STAT1 for the development of IBD/colitis. Already in 1996, it was shown that IFN-γ is increased in human CD.[98] In clinical trials with fontolizumab, an IFN-γ blocking antibody, the clinical response was weak, but reduced inflammation was noted based on decreases in C-reactive protein levels.[99,100] T cell transfer-induced colitis in mice was prevented by the administration of an anti-IFN-γ antibody for up to 12 weeks.[101] Systemic administration of an anti-IFN-γ antibody produced a rather mild, yet significant beneficial effect on the development of DSS-induced colitis.[102,103] Consistently, IFN-γ-deficient animals were protected as well.[104] The effect of IFN-γ deficiency was subsequently attributed to homeostatic functions of IFN-γ signaling in enterocyte proliferation and apoptosis through serine-threonine protein kinase AKT-β-catenin and Wingless-Int-β-catenin signaling pathways.[105] Contrasting the DSS or T cell transfer models, TNBS-induced colitis remained unaffected by antibody-mediated neutralization of IFN-γ activity.[106] Moreover, TNBS administration had equal effects on IFN-γ-receptor-deficient mice and wild type controls.[106,107] Surprisingly, knockout mice for the ligand, IFN-γ, were slightly protected from mortality upon high TNBS doses however at intermediate doses the disease rather changed from a TH1 type to a TH2 type pathology in the absence of IFN-γ.[108]

Mice deficient for IL-10 spontaneously develop colitis. Interestingly, colitis in these animals was exacerbated upon IFN-γ deficiency. This anti-inflammatory role of IFN-γ was explained through inhibition of proinflammatory IL-23 in colonic Cd11b⁺ cells.[109]

Data on IFN-I in colitis have recently been reviewed elsewhere.[110] In brief, IFN-I produced by intestinal dendritic cells upon TLR9 stimulation or given systemically are thought to protect against acute DSS colitis. Our own studies suggest that the benefit of IFN-I varies with the severity of colonic inflammation. Protective effects are seen only at high DSS concentrations and a correspondingly strong inflammation (our unpublished results). As with models of bacterial infection and sepsis, the impact of IFN on inflammation again varies with the intensity of the inflammatory process. Clinical data from IFN-I treated IBD patients appear to confirm this notion by showing highly variable responses.[110] Contrasting bacterial sepsis however, IFN-I protect better with increasing severity of DSS-induced colitis. This may

be explained by a dual role of IFN-I signaling in the protection of the gut epithelium on the one hand and the promotion of tissue-destructive inflammation on the other.

Two very recent papers utilizing the T cell transfer model of colitis showed that IFN-I signaling is important in this model, too. In the colitogenic CD45RB^high cells it leads to CD69 induction which decreases their efficacy.[111] If suppressive CD45RB^low T cells are transferred along with the CD45RB^high effector T cells, IFN-I signaling is important for the maintenance of Foxp3 expression and thereby their disease suppressing potential.[112] IFN-I signaling as a regulatory mechanism for suppressor T cell activity adds yet another component to the multitude of pro- and antiinflammatory mechanisms under IFN/STAT control that requires future attention.

IFN/STAT in the Regulation of Autoimmunity-Related Inflammation

This topic has been subject to many previous reviews[24,110,113] and will be covered very briefly. Autoimmune syndromes such as multiple sclerosis, rheumatoid arthritis or the systemic lupus erythematosus (SLE) are characterized by local or systemic inflammatory episodes. The participation of IFN in some of these autoinflammatory syndromes was recognized with the finding that patients suffering from SLE have elevated plasma IFN-I levels and that their blood leukocytes display gene signatures with a prominent fraction of IFN-induced genes.[114,115] Recognition of self nucleic acids from necrotic cells by endosomal toll-like receptors is widely accepted as a mechanism inducing IFN-I synthesis by plasmacytoid dendritic cells (pDC) present in inflamed organs. It is enhanced by the presence of autoantibodies to nucleic acids (reviewed in ref. 116). Consistently, IFN-I accelerate the SLE syndrome of lupus-prone mouse strains[117] and Ifnar1 gene deletion is protective in such animals.[118] Anti-IFN-I therapy is considered as a promising therapeutic strategy in humans.[119] STAT1 is activated in cells from lupus patients and although there is no genetic evidence for its requirement, the STAT1 target gene signature provides a strong indication of its contribution to SLE-associated inflammation. The role of IFN/STAT is further emphasized by the demonstration that IFN-I as well as STAT1 and IRF9 enhance plasma cell differentiation and autoantibody production,[120,121] suggesting activity of the ISGF3 complex in the differentiation and autoantibody production by SLE patient B cells. An IFN-I contribution sharing similarities with that in SLE patients was shown for human psoriasis. Skin lesions display gene signatures resulting from IFN-I production by infiltrating pDC. Association of the cationic antimicrobial peptide LL37 with self nucleic acids is thought to facilitate their transport and association with endosomal TLR.[122]

The proinflammatory activities of IFN-I in SLE, psoriasis and other autoinflammatory syndromes contrast with the anti-inflammatory properties of IFN-I in at least some neurodegenerative disorders. Most prominently, patients afflicted with multiple sclerosis (MS) benefit from IFN-β therapy. An animal model recapitulating some of the properties of MS is experimental autoimmune encephalitis (EAE). In experimental animals

inflammatory neurodegeneration is caused by immunization with myelin basic protein. The disease shows a strong involvement of TH1 cells, as mice deficient for the TH1 fate-determining transcription factor T-bet are highly resistant.[123] Conditional ablation of the IFNAR on myeloid cells strongly increased EAE pathology, demonstrating that the IFN-I response of myeloid cells exerts a protective effect.[124]

Both IFN-γ^{-/-} and STAT1^{-/-} mice are highly susceptible to EAE.[123,125] This suggests that IFN-γ, like IFN-I, protects against EAE and that STAT1 is involved in signaling an anti-inflammatory response to both IFN types. The lack of STAT1 did not alter suppressor T cell abundance or function, but TH1 cells were prominently produced.[123] In the study evaluating the effects of IFN-I, Prinz et al. (2008) did not find a change in the composition of helper T cell populations. In contrast, another study of EAE reported IFN-I-mediated suppression of proinflammatory TH17 cells.[126] The potential of STAT1 signaling to alter TH differentiation is further emphasized by a recent study of human STAT1 mutations. Unlike all other STAT1 mutations found in the human population, which cause loss-of-function-associated immune defects, the 12 patients described in this paper suffer from chronic mucocutaneous candidiasis (CMCD) resulting from a STAT1 gain-of-function.[127] The mutations are localized to the N-terminal coiled coil domain and lead to a stronger activation of STAT1 by IFN, but also by cytokines usually activating other STATs, such as IL-6. This causes a suppression of TH17 activity, thus depriving affected subjects from a major effector system against fungal pathogens such as *C. albicans*.

Collectively the studies addressing the role of IFN/STAT in autoimmune-related inflammation emphasize their profound regulatory input into complex inflammatory scenarios.

Concluding Remarks

We have summarized considerable but by no means all evidence documenting that IFN/STAT exert control over important aspects of inflammation reaching from leukocyte migration and tissue invasion to their activation and effector functions (**Fig. 1**). Beyond the innate response, inflammation promoted by TH
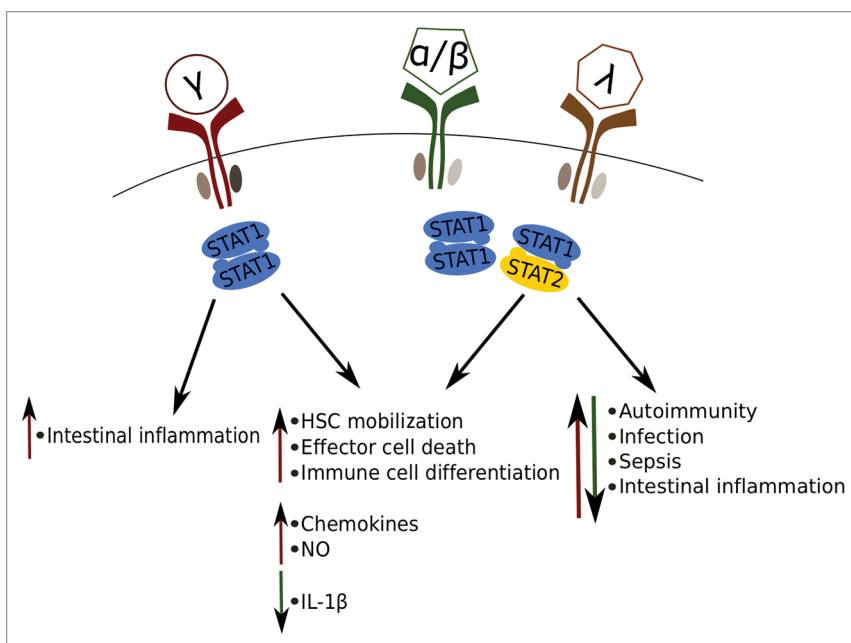

Figure 1. The control of Inflammation by interferons and their STATs. Arrows indicate whether a particular event is increased by IFN, decreased or whether either can occur in different inflammatory diseases. The IFN-γ receptor operates by activating a STAT1 dimer, whereas both the type I IFN (IFN-α/β) and IFN-λ receptors operate through the ISGF3 (STAT1/STAT2/IRF9) complex.

subsets or its suppression by Treg is under IFN/STAT control, although there is still little understanding of the importance of this for inflammatory disease or the positive impact of inflammation on the clearance of infection. Particularly the IFN-I/STAT system is linked to a number of autoinflammatory syndromes and can act both as a driver or suppressor of inflammation-related tissue damage. Exploring the factors determining this yin-yang character as well as fathoming the therapeutic potential of IFN-I inhibition at the potential cost of losing antiviral immunity appears of utmost importance.

References

1. Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454:428-35; PMID:18650913; http://dx.doi.org/10.1038/nature07201

2. Medzhitov R. Inflammation 2010: new adventures of an old flame. Cell 2010; 140:771-6; PMID:20303867; http://dx.doi.org/10.1016/j.cell.2010.03.006

3. Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines, and their receptors. Immunol Rev 2004; 202:8-32; PMID:15546383; http://dx.doi.org/10.1111/j.0105-2896.2004.00204.x

4. Donnelly RP, Kotenko SV. Interferon-lambda: a new addition to an old family. J Interferon Cytokine Res 2010; 30:555-64; PMID:20712453; http://dx.doi.org/10.1089/jir.2010.0078

5. Schroder K, Hertzog PJ, Ravasi T, Hume DA. Interferon-gamma: an overview of signals, mechanisms and functions. J Leukoc Biol 2004; 75:163-89; PMID:14525967; http://dx.doi.org/10.1189/jlb.0603252

6. Lauterbach H, Bathke B, Gilles S, Traidl-Hoffmann C, Luber CA, Fejer G, et al. Mouse CD8alpha+ DCs and human BDCA3+ DCs are major producers of IFN-lambda in response to poly IC. J Exp Med 2010; 207:2703-17; PMID:20975040; http://dx.doi.org/10.1084/jem.20092720

7. Osterlund PI, Pietilä TE, Veckman V, Kotenko SV, Julkunen I. IFN regulatory factor family members differentially regulate the expression of type III IFN (IFN-lambda) genes. J Immunol 2007; 179:3434-42; PMID:17785777.

8. Borden EC, Sen GC, Uze G, Silverman RH, Ransohoff RM, Foster GR, et al. Interferons at age 50: past, current and future impact on biomedicine. Nat Rev Drug Discov 2007; 6:975-90; PMID:18049472; http://dx.doi.org/10.1038/nrd2422

9. Levy DE, Darnell JEJ Jr. Stats: transcriptional control and biological impact. Nat Rev Mol Cell Biol 2002; 3:651-62; PMID:12209125; http://dx.doi.org/10.1038/nrm909

10. Park C, Li S, Cha E, Schindler C. Immune response in Stat2 knockout mice. Immunity 2000; 13:795-804; PMID:11163195; http://dx.doi.org/10.1016/S1074-7613(00)00077-7

11. Yarilina A, Park-Min KH, Antoniv T, Hu X, Ivashkiv LB. TNF activates an IRF1-dependent autocrine loop leading to sustained expression of chemokines and STAT1-dependent type I interferon-response genes. Nat Immunol 2008; 9:378-87; PMID:18345002; http://dx.doi.org/10.1038/ni1576

12. Gough DJ, Messina NL, Clarke CJP, Johnstone RW, Levy DE. Constitutive type I interferon modulates homeostatic balance through tonic signaling. Immunity 2012; 36:166-74; PMID:22365663; http://dx.doi.org/10.1016/j.immuni.2012.01.011

13. Ganal SC, Sanos SL, Kallfass C, Oberle K, Johner C, Kirschning C, et al. Priming of natural killer cells by nonmucosal mononuclear phagocytes requires instructive signals from commensal microbiota. Immunity 2012; 37:171-86; PMID:22749822; http://dx.doi.org/10.1016/j.immuni.2012.05.020

14. Essers MAG, Offner S, Blanco-Bose WE, Waibler Z, Kalinke U, Duchosal MA, et al. IFNalpha activates dormant haematopoietic stem cells in vivo. Nature 2009; 458:904-8; PMID:19212321; http://dx.doi.org/10.1038/nature07815

15. Sato T, Onai N, Yoshihara H, Arai F, Suda T, Ohteki T. Interferon regulatory factor-2 protects quiescent hematopoietic stem cells from type I interferon-dependent exhaustion. Nat Med 2009; 15:696-700; PMID:19483695; http://dx.doi.org/10.1038/nm.1973

16. Baldridge MT, King KY, Boles NC, Weksberg DC, Goodell MA. Quiescent haematopoietic stem cells are activated by IFN-gamma in response to chronic infection. Nature 2010; 465:793-7; PMID:20535209; http://dx.doi.org/10.1038/nature09135

17. Verma A, Deb DK, Sassano A, Uddin S, Varga J, Wickrema A, et al. Activation of the p38 mitogen-activated protein kinase mediates the suppressive effects of type I interferons and transforming growth factor-beta on normal hematopoiesis. J Biol Chem 2002; 277:7726-35; PMID:11773065; http://dx.doi.org/10.1074/jbc.M106640200

18. Goldszmid RS, Caspar P, Rivollier A, White S, Dzutsev A, Hieny S, et al. NK cell-derived interferon-γ orchestrates cellular dynamics and the differentiation of monocytes into dendritic cells at the site of infection. Immunity 2012; 36:1047-59; PMID:22749354; http://dx.doi.org/10.1016/j.immuni.2012.03.026

19. Stockinger S, Decker T. Novel functions of type I interferons revealed by infection studies with Listeria monocytogenes. Immunobiology 2008; 213:889-97; PMID:18926303; http://dx.doi.org/10.1016/j.imbio.2008.07.020

20. Broz P, Monack DM. Molecular mechanisms of inflammasome activation during microbial infections. Immunol Rev 2011; 243:174-90; PMID:21884176; http://dx.doi.org/10.1111/j.1600-065X.2011.01041.x

21. Robinson N, McComb S, Mulligan R, Dudani R, Krishnan L, Sad S. Type I interferon induces necroptosis in macrophages during infection with Salmonella enterica serovar Typhimurium. Nat Immunol 2012; 13:954-62; PMID:22922364; http://dx.doi.org/10.1038/ni.2397

22. Navarini AA, Recher M, Lang KS, Georgiev P, Meury S, Bergthaler A, et al. Increased susceptibility to bacterial superinfection as a consequence of innate antiviral responses. Proc Natl Acad Sci U S A 2006; 103:15535-9; PMID:17030789; http://dx.doi.org/10.1073/pnas.0607325103

23. Shahangian A, Chow EK, Tian X, Kang JR, Ghaffari A, Liu SY, et al. Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice. J Clin Invest 2009; 119:1910-20; PMID:19487810; http://dx.doi.org/10.1172/JCI35412

24. Trinchieri G. Type I interferon: friend or foe? J Exp Med 2010; 207:2053-63; PMID:20837696; http://dx.doi.org/10.1084/jem.20101664

25. Carrero JA, Unanue ER. Lymphocyte apoptosis as an immune subversion strategy of microbial pathogens. Trends Immunol 2006; 27:497-503; PMID:16997632; http://dx.doi.org/10.1016/j.it.2006.09.005

26. Kernbauer E, Maier V, Stoiber D, Strobl B, Schneckenleithner C, Sexl V, et al. Conditional Stat1 ablation reveals the importance of interferon signaling for immunity to Listeria monocytogenes infection. PLoS Pathog 2012; 8:e1002763; PMID:22719255; http://dx.doi.org/10.1371/journal.ppat.1002763

27. Huys L, Van Hauwermeiren F, Dejager L, Dejonckheere E, Lienenklaus S, Weiss S, et al. Type I interferon drives tumor necrosis factor-induced lethal shock. J Exp Med 2009; 206:1873-82; PMID:19687227; http://dx.doi.org/10.1084/jem.20090213

28. Decker T, Müller M, Stockinger S. The yin and yang of type I interferon activity in bacterial infection. Nat Rev Immunol 2005; 5:675-87; PMID:16110316; http://dx.doi.org/10.1038/nri1684

29. Charo IF, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med 2006; 354:610-21; PMID:16467548; http://dx.doi.org/10.1056/NEJMra052723

30. Zhou ZH, Chaturvedi P, Han YL, Aras S, Li YS, Kolattukudy PE, et al. IFN-gamma induction of the human monocyte chemoattractant protein (hMCP)-1 gene in astrocytoma cells: functional interaction between an IFN-gamma-activated site and a GC-rich element. J Immunol 1998; 160:3908-16; PMID:9558097.

31. Majumder S, Zhou LZ, Chaturvedi P, Babcock G, Aras S, Ransohoff RM. p48/STAT-1alpha-containing complexes play a predominant role in induction of IFN-gamma-inducible protein, 10 kDa (IP-10) by IFN-gamma alone or in synergy with TNF-alpha. J Immunol 1998; 161:4736-44; PMID:9794404.

32. Kim MO, Suh HS, Brosnan CF, Lee SC. Regulation of RANTES/CCL5 expression in human astrocytes by interleukin-1 and interferon-beta. J Neurochem 2004; 90:297-308; PMID:15228586; http://dx.doi.org/10.1111/j.1471-4159.2004.02487.x

33. Wong P, Severns CW, Guyer NB, Wright TM. A unique palindromic element mediates gamma interferon induction of mig gene expression. Mol Cell Biol 1994; 14:914-22; PMID:8289831.

34. Conrady CD, Zheng M, Mandal NA, van Rooijen N, Carr DJJ. IFN-α-driven CCL2 production recruits inflammatory monocytes to infection site in mice. Mucosal Immunol 2013; 6:45-55; PMID:22692455; http://dx.doi.org/10.1038/mi.2012.46

35. Liu J, Guan X, Ma X. Interferon regulatory factor 1 is an essential and direct transcriptional activator for interferon γ-induced RANTES/CCl5 expression in macrophages. J Biol Chem 2005; 280:24347-55; PMID:15860458; http://dx.doi.org/10.1074/jbc.M500973200

36. Cole KE, Strick CA, Paradis TJ, Ogborne KT, Loetscher M, Gladue RP, et al. Interferon-inducible T cell alpha chemoattractant (I-TAC): a novel non-ELR CXC chemokine with potent activity on activated T cells through selective high affinity binding to CXCR3. J Exp Med 1998; 187:2009-21; PMID:9625760; http://dx.doi.org/10.1084/jem.187.12.2009

37. Hiroi M, Ohmori Y. The transcriptional coactivator CREB-binding protein cooperates with STAT1 and NF-κB for synergistic transcriptional activation of the CXC ligand 9/monokine induced by interferon-γ gene. J Biol Chem 2003; 278:651-60; PMID:12403783; http://dx.doi.org/10.1074/jbc.M204544200

38. Ohmori Y, Hamilton TA. The interferon-stimulated response element and a kappa B site mediate synergistic induction of murine IP-10 gene transcription by IFN-gamma and TNF-alpha. J Immunol 1995; 154:5235-44; PMID:7730628.

39. Ohmori Y, Schreiber RD, Hamilton TA. Synergy between interferon-gamma and tumor necrosis factor-alpha in transcriptional activation is mediated by cooperation between signal transducer and activator of transcription 1 and nuclear factor kappaB. J Biol Chem 1997; 272:14899-907; PMID:9169460; http://dx.doi.org/10.1074/jbc.272.23.14899

40. Pietilä TE, Veckman V, Lehtonen A, Lin R, Hiscott J, Julkunen I. Multiple NF-kappaB and IFN regulatory factor family transcription factors regulate CCL19 gene expression in human monocyte-derived dendritic cells. J Immunol 2007; 178:253-61; PMID:17182562.

41. Ellis SL, Gysbers V, Manders PM, Li W, Hofer MJ, Müller M, et al. The cell-specific induction of CXC chemokine ligand 9 mediated by IFN-gamma in microglia of the central nervous system is determined by the myeloid transcription factor PU.1. J Immunol 2010; 185:1864-77; PMID:20585034; http://dx.doi.org/10.4049/jimmunol.1000900

42. Jia T, Leiner I, Dorothee G, Brandl K, Pamer EG. MyD88 and Type I interferon receptor-mediated chemokine induction and monocyte recruitment during Listeria monocytogenes infection. J Immunol 2009; 183:1271-8; PMID:19553532; http://dx.doi.org/10.4049/jimmunol.0900460

43. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol 2008; 8:958-69; PMID:19029990; http://dx.doi.org/10.1038/nri2448

44. Martinez FO, Gordon S, Locati M, Mantovani A. Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression. J Immunol 2006; 177:7303-11; PMID:17082649.

45. Kopydlowski KM, Salkowski CA, Cody MJ, van Rooijen N, Major J, Hamilton TA, et al. Regulation of macrophage chemokine expression by lipopolysaccharide in vitro and in vivo. J Immunol 1999; 163:1537-44; PMID:10415057.

46. Zimmerer JM, Lesinski GB, Radmacher MD, Ruppert A, Carson WE 3rd. STAT1-dependent and STAT1-independent gene expression in murine immune cells following stimulation with interferon-alpha. Cancer Immunol Immunother 2007; 56:1845-52; PMID:17503042; http://dx.doi.org/10.1007/s00262-007-0329-9

47. Zang YC, Halder JB, Samanta AK, Hong J, Rivera VM, Zhang JZ. Regulation of chemokine receptor CCR5 and production of RANTES and MIP-1alpha by interferon-beta. J Neuroimmunol 2001; 112:174-80; PMID:11108946; http://dx.doi.org/10.1016/S0165-5728(00)00397-0

48. Aung LL, Fitzgerald-Bocarsly P, Dhib-Jalbut S, Balashov K. Plasmacytoid dendritic cells in multiple sclerosis: chemokine and chemokine receptor modulation by interferon-beta. J Neuroimmunol 2010; 226:158-64; PMID:20621365; http://dx.doi.org/10.1016/j.jneuroim.2010.06.008

49. Salazar-Mather TP, Hamilton TA, Biron CA. A chemokine-to-cytokine-to-chemokine cascade critical in antiviral defense. J Clin Invest 2000; 105:985-93; PMID:10749577; http://dx.doi.org/10.1172/JCI9232

50. Salazar-Mather TP, Lewis CA, Biron CA. Type I interferons regulate inflammatory cell trafficking and macrophage inflammatory protein 1alpha delivery to the liver. J Clin Invest 2002; 110:321-30; PMID:12163451.

51. Crane MJ, Hokeness-Antonelli KL, Salazar-Mather TP. Regulation of inflammatory monocyte/macrophage recruitment from the bone marrow during murine cytomegalovirus infection: role for type I interferons in localized induction of CCR2 ligands. J Immunol 2009; 183:2810-7; PMID:19620305; http://dx.doi.org/10.4049/jimmunol.0900205

52. Pietras EM, Miller LS, Johnson CT, O'Connell RM, Dempsey PW, Cheng GA. A MyD88-dependent IFNγR-CCR2 signaling circuit is required for mobilization of monocytes and host defense against systemic bacterial challenge. Cell Res 2011; 21:1068-79; PMID:21467996; http://dx.doi.org/10.1038/cr.2011.59

53. Kelly-Scumpia KM, Scumpia PO, Delano MJ, Weinstein JS, Cuenca AG, Wynn JL, et al. Type I interferon signaling in hematopoietic cells is required for survival in mouse polymicrobial sepsis by regulating CXCL10. J Exp Med 2010; 207:319-26; PMID:20071504; http://dx.doi.org/10.1084/jem.20091959

54. Pasieka TJ, Cilloniz C, Carter VS, Rosato P, Katze MG, Leib DA. Functional genomics reveals an essential and specific role for Stat1 in protection of the central nervous system following herpes simplex virus corneal infection. J Virol 2011; 85:12972-81; PMID:21994441; http://dx.doi.org/10.1128/JVI.06032-11

55. Lin AA, Tripathi PK, Sholl A, Jordan MB, Hildeman DA. Gamma interferon signaling in macrophage lineage cells regulates central nervous system inflammation and chemokine production. J Virol 2009; 83:8604-15; PMID:19515766; http://dx.doi.org/10.1128/JVI.02477-08

56. Kimura H, Kimura M, Rose NR, Caturegli P. Early chemokine expression induced by interferon-gamma in a murine model of Hashimoto's thyroiditis. Exp Mol Pathol 2004; 77:161-7; PMID:15507231; http://dx.doi.org/10.1016/j.yexmp.2004.08.004

57. Glabinski AR, Krakowski M, Han Y, Owens T, Ransohoff RM. Chemokine expression in GKO mice (lacking interferon-gamma) with experimental autoimmune encephalomyelitis. J Neurovirol 1999; 5:95-101; PMID:10190695; http://dx.doi.org/10.3109/13550289909029750

58. Fulkerson PC, Zimmermann N, Hassman LM, Finkelman FD, Rothenberg ME. Pulmonary chemokine expression is coordinately regulated by STAT1, STAT6, and IFN-gamma. J Immunol 2004; 173:7565-74; PMID:15585884.

59. Drobits B, Holcmann M, Amberg N, Swiecki M, Grundtner R, Hammer M, et al. Imiquimod clears tumors in mice independent of adaptive immunity by converting pDCs into tumor-killing effector cells. J Clin Invest 2012; 122:575-85; PMID:22251703; http://dx.doi.org/10.1172/JCI61034

60. Tessitore A, Pastore L, Rispoli A, Cilenti L, Toniato E, Flati V, et al. Two gamma-interferon-activation sites (GAS) on the promoter of the human intercellular adhesion molecule (ICAM-1) gene are required for induction of transcription by IFN-gamma. Eur J Biochem 1998; 258:968-75; PMID:9990314; http://dx.doi.org/10.1046/j.1432-1327.1998.2580968.x

61. Gordon S. Alternative activation of macrophages. Nat Rev Immunol 2003; 3:23-35; PMID:12511873; http://dx.doi.org/10.1038/nri978

62. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. Nat Rev Immunol 2005; 5:953-64; PMID:16322748; http://dx.doi.org/10.1038/nri1733

63. Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K. Development of monocytes, macrophages, and dendritic cells. Science 2010; 327:656-61; PMID:20133564; http://dx.doi.org/10.1126/science.1178331

64. Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Pamer EG. TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. Immunity 2003; 19:59-70; PMID:12871639; http://dx.doi.org/10.1016/S1074-7613(03)00171-7

65. Bogdan C. Nitric oxide and the immune response. Nat Immunol 2001; 2:907-16; PMID:11577346; http://dx.doi.org/10.1038/ni1001-907

66. Kleinert H, Schwarz PM, Förstermann U. Regulation of the expression of inducible nitric oxide synthase. Biol Chem 2003; 384:1343-64; PMID:14669979; http://dx.doi.org/10.1515/BC.2003.152

67. Farlik M, Reutterer B, Schindler C, Greten F, Vogl C, Müller M, et al. Nonconventional initiation complex assembly by STAT and NF-kappaB transcription factors regulates nitric oxide synthase expression. Immunity 2010; 33:25-34; PMID:20637660; http://dx.doi.org/10.1016/j.immuni.2010.07.001.

68. Tschopp J, Schroder K. NLRP3 inflammasome activation: The convergence of multiple signalling pathways on ROS production? Nat Rev Immunol 2010; 10:210-5; PMID:20168318; http://dx.doi.org/10.1038/nri2725

69. Guarda G, Braun M, Staehli F, Tardivel A, Mattmann C, Förster I, et al. Type I interferon inhibits interleukin-1 production and inflammasome activation. Immunity 2011; 34:213-23; PMID:21349431; http://dx.doi.org/10.1016/j.immuni.2011.02.006

70. Mishra BB, Rathinam VAK, Martens GW, Martinot AJ, Kornfeld H, Fitzgerald KA, et al. Nitric oxide controls the immunopathology of tuberculosis by inhibiting NLRP3 inflammasome-dependent processing of IL-1β. Nat Immunol 2013; 14:52-60; PMID:23160153; http://dx.doi.org/10.1038/ni.2474

71. Majer O, Bourgeois C, Zwolanek F, Lassnig C, Kerjaschki D, Mack M, et al. Type I interferons promote fatal immunopathology by regulating inflammatory monocytes and neutrophils during Candida infections. PLoS Pathog 2012; 8:e1002811; PMID:22911155; http://dx.doi.org/10.1371/journal.ppat.1002811

72. Heremans H, Van Damme J, Dillen C, Dijkmans R, Billiau A. Interferon gamma, a mediator of lethal lipopolysaccharide-induced Shwartzman-like shock reactions in mice. J Exp Med 1990; 171:1853-69; PMID:2112583; http://dx.doi.org/10.1084/jem.171.6.1853

73. Heinzel FP. The role of IFN-gamma in the pathology of experimental endotoxemia. J Immunol 1990; 145:2920-4; PMID:2120341.

74. Karaghiosoff M, Steinborn R, Kovarik P, Kriegshäuser G, Baccarini M, Donabauer B, et al. Central role for type I interferons and Tyk2 in lipopolysaccharide-induced endotoxin shock. Nat Immunol 2003; 4:471-7; PMID:12679810; http://dx.doi.org/10.1038/ni910

75. Thomas KE, Galligan CL, Newman RD, Fish EN, Vogel SN. Contribution of interferon-beta to the murine macrophage response to the toll-like receptor 4 agonist, lipopolysaccharide. J Biol Chem 2006; 281:31119-30; PMID:16912041; http://dx.doi.org/10.1074/jbc.M604958200

76. Perry ST, Buck MD, Lada SM, Schindler C, Shresta S. STAT2 mediates innate immunity to Dengue virus in the absence of STAT1 via the type I interferon receptor. PLoS Pathog 2011; 7:e1001297; PMID:21379341; http://dx.doi.org/10.1371/journal.ppat.1001297

77. Mahieu T, Libert C. Should we inhibit type I interferons in sepsis? Infect Immun 2007; 75:22-9; PMID:17000722; http://dx.doi.org/10.1128/IAI.00829-06

78. Weighardt H, Kaiser-Moore S, Schlautkötter S, Rossmann-Bloeck T, Schleicher U, Bogdan C, et al. Type I IFN modulates host defense and late hyperinflammation in septic peritonitis. J Immunol 2006; 177:5623-30; PMID:17015750.

79. Herzig D, Fang G, Toliver-Kinsky TE, Guo Y, Bohannon J, Sherwood ER. STAT1-deficient mice are resistant to cecal ligation and puncture-induced septic shock. Shock 2012; 38:395-402; PMID:22777121; http://dx.doi.org/10.1097/SHK.0b013e318265a2ab

80. Maloy KJ, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. Nature 2011; 474:298-306; PMID:21677746; http://dx.doi.org/10.1038/nature10208

81. Sandborn WJ, Ghosh S, Panes J, Vranic I, Su C, Rousell S, et al; Study A3921063 Investigators. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med 2012; 367:616-24; PMID:22894574; http://dx.doi.org/10.1056/NEJMoa1112168

82. Kühbacher T, Gionchetti P, Hampe J, Helwig U, Rosenstiel P, Campieri M, et al. Activation of signal-transducer and activator of transcription 1 (STAT1) in pouchitis. Clin Exp Immunol 2001; 123:395-401; PMID:11298125; http://dx.doi.org/10.1046/j.1365-2249.2001.01455.x

83. Schreiber S, Rosenstiel P, Hampe J, Nikolaus S, Groessner B, Schottelius A, et al. Activation of signal transducer and activator of transcription (STAT) 1 in human chronic inflammatory bowel disease. Gut 2002; 51:379-85; PMID:12171960; http://dx.doi.org/10.1136/gut.51.3.379

84. Mudter J, Weigmann B, Bartsch B, Kiesslich R, Strand D, Galle PR, et al. Activation pattern of signal transducers and activators of transcription (STAT) factors in inflammatory bowel diseases. Am J Gastroenterol 2005; 100:64-72; PMID:15654782; http://dx.doi.org/10.1111/j.1572-0241.2005.40615.x

85. Wu F, Dassopoulos T, Cope L, Maitra A, Brant SR, Harris ML, et al. Genome-wide gene expression differences in Crohn's disease and ulcerative colitis from endoscopic pinch biopsies: insights into distinctive pathogenesis. Inflamm Bowel Dis 2007; 13:807-21; PMID:17262812; http://dx.doi.org/10.1002/ibd.20110

86. Leal RF, Ayrizono MLS, Milanski M, Coope A, Fagundes JJ, Velloso LA, et al. Activation of signal transducer and activator of transcription-1 (STAT-1) and differential expression of interferon-γ and anti-inflammatory proteins in pelvic ileal pouches for ulcerative colitis and familial adenomatous polyposis. Clin Exp Immunol 2010; 160:380-5; PMID:20345984; http://dx.doi.org/10.1111/j.1365-2249.2009.04088.x

87. Christophi GP, Rong R, Holtzapple PG, Massa PT, Landas SK. Immune markers and differential signaling networks in ulcerative colitis and Crohn's disease. Inflamm Bowel Dis 2012; 18:2342-56; PMID:22467146; http://dx.doi.org/10.1002/ibd.22957

88. Bandyopadhyay SK, de la Motte CA, Kessler SP, Hascall VC, Hill DR, Strong SA. Hyaluronan-mediated leukocyte adhesion and dextran sulfate sodium-induced colitis are attenuated in the absence of signal transducer and activator of transcription 1. Am J Pathol 2008; 173:1361-8; PMID:18818378; http://dx.doi.org/10.2353/ajpath.2008.080444

89. Berry D, Schwab C, Milinovich G, Reichert J, Ben Mahfoudh K, Decker T, et al. Phylotype-level 16S rRNA analysis reveals new bacterial indicators of health state in acute murine colitis. ISME J 2012; 6:2091-106; PMID:22572638; http://dx.doi.org/10.1038/ismej.2012.39

90. Kalim KW, Basler M, Kirk CJ, Groettrup M. Immunoproteasome subunit LMP7 deficiency and inhibition suppresses Th1 and Th17 but enhances regulatory T cell differentiation. J Immunol 2012; 189:4182-93; PMID:22984077; http://dx.doi.org/10.4049/jimmunol.1201183

91. Takahashi R, Nishimoto S, Muto G, Sekiya T, Tamiya T, Kimura A, et al. SOCS1 is essential for regulatory T cell functions by preventing loss of Foxp3 expression as well as IFN-gamma and IL-17A production. J Exp Med 2011; 208:2055-67; PMID:21893603; http://dx.doi.org/10.1084/jem.20110428

92. Wu X, Guo W, Wu L, Gu Y, Gu L, Xu S, et al. Selective sequestration of STAT1 in the cytoplasm via phosphorylated SHP-2 ameliorates murine experimental colitis. J Immunol 2012; 189:3497-507; PMID:22942432; http://dx.doi.org/10.4049/jimmunol.1201006

93. Costantino G, Egerbacher M, Kolbe T, Karaghiosoff M, Strobl B, Vogl C, et al. Tyk2 and signal transducer and activator of transcription 1 contribute to intestinal I/R injury. Shock 2008; 29:238-44; PMID:17693920.

94. Mazzarella G, MacDonald TT, Salvati VM, Mulligan P, Pasquale L, Stefanile R, et al. Constitutive activation of the signal transducer and activator of transcription pathway in celiac disease lesions. Am J Pathol 2003; 162:1845-55; PMID:12759242; http://dx.doi.org/10.1016/S0002-9440(10)64319-2

95. Karst SM, Wobus CE, Lay M, Davidson J, Virgin HW 4th. STAT1-dependent innate immunity to a Norwalk-like virus. Science 2003; 299:1575-8; PMID:12624267; http://dx.doi.org/10.1126/science.1077905

96. Vancott JL, McNeal MM, Choi AHC, Ward RL. The role of interferons in rotavirus infections and protection. J Interferon Cytokine Res 2003; 23:163-70; PMID:12716489; http://dx.doi.org/10.1089/107999003321532501

97. Pott J, Mahlaköiv T, Mordstein M, Duerr CU, Michiels T, Stockinger S, et al. IFN-λ determines the intestinal epithelial antiviral host defense. Proc Natl Acad Sci U S A 2011; 108:7944-9; PMID:21518880; http://dx.doi.org/10.1073/pnas.1100552108

98. Fuss IJ, Neurath M, Boirivant M, Klein JS, de la Motte C, Strong SA, et al. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. J Immunol 1996; 157:1261-70; PMID:8757634.

99. Reinisch W, Sandborn WJ, Hommes DW, D'Haens GR, Hanauer SB, Schreiber S, et al. 847t Adalimumab for Induction of Clinical Remission in Moderately to Severely Active Ulcerative Colitis. Gastroenterology 2010; 138:S114-5; http://dx.doi.org/10.1016/S0016-5085(10)60526-4

100. Hommes DW, Mikhajlova TL, Stoinov S, Stimac D, Vucelic B, Lonovics J, et al. Fontolizumab, a humanised anti-interferon gamma antibody, demonstrates safety and clinical activity in patients with moderate to severe Crohn's disease. Gut 2006; 55:1131-7; PMID:16507585; http://dx.doi.org/10.1136/gut.2005.079392

101. Powrie F, Leach MW, Mauze S, Menon S, Caddle LB, Coffman RL. Inhibition of Th1 responses prevents inflammatory bowel disease in scid mice reconstituted with CD45RBhi CD4+ T cells. Immunity 1994; 1:553-62; PMID:7600284; http://dx.doi.org/10.1016/1074-7613(94)90045-0

102. Obermeier F, Kojouharoff G, Hans W, Schölmerich J, Gross V, Falk W. Interferon-gamma (IFN-gamma)- and tumour necrosis factor (TNF)-induced nitric oxide as toxic effector molecule in chronic dextran sulphate sodium (DSS)-induced colitis in mice. Clin Exp Immunol 1999; 116:238-45; PMID:10337013; http://dx.doi.org/10.1046/j.1365-2249.1999.00878.x

103. Hans W, Schölmerich J, Gross V, Falk W. Interleukin-12 induced interferon-gamma increases inflammation in acute dextran sulfate sodium induced colitis in mice. Eur Cytokine Netw 2000; 11:67-74; PMID:10705301.

104. Ito R, Shin-Ya M, Kishida T, Urano A, Takada R, Sakagami J, et al. Interferon-gamma is causatively involved in experimental inflammatory bowel disease in mice. Clin Exp Immunol 2006; 146:330-8; PMID:17034586; http://dx.doi.org/10.1111/j.1365-2249.2006.03214.x

105. Nava P, Koch S, Laukoetter MG, Lee WY, Kolegraff K, Capaldo CT, et al. Interferon-gamma regulates intestinal epithelial homeostasis through converging beta-catenin signaling pathways. Immunity 2010; 32:392-402; PMID:20303298; http://dx.doi.org/10.1016/j.immuni.2010.03.001

106. Tozawa K, Hanai H, Sugimoto K, Baba S, Sugimura H, Aoshi T, et al. Evidence for the critical role of interleukin-12 but not interferon-gamma in the pathogenesis of experimental colitis in mice. J Gastroenterol Hepatol 2003; 18:578-87; PMID:12702051; http://dx.doi.org/10.1046/j.1440-1746.2003.03024.x

107. Camoglio L, te Velde AA, de Boer A, ten Kate FJ, Kopf M, van Deventer SJ. Hapten-induced colitis associated with maintained Th1 and inflammatory responses in IFN-gamma receptor-deficient mice. Eur J Immunol 2000; 30:1486-95; PMID:10820397; http://dx.doi.org/10.1002/(SICI)1521-4141(200005)30:5<1486::AID-IMMU1486>3.0.CO;2-8

108. Dohi T, Fujihashi K, Rennert PD, Iwatani K, Kiyono H, McGhee JR. Hapten-induced colitis is associated with colonic patch hypertrophy and T helper cell 2-type responses. J Exp Med 1999; 189:1169-80; PMID:10209035; http://dx.doi.org/10.1084/jem.189.8.1169

109. Sheikh SZ, Matsuoka K, Kobayashi T, Li F, Rubinas T, Plevy SE. Cutting edge: IFN-gamma is a negative regulator of IL-23 in murine macrophages and experimental colitis. J Immunol 2010; 184:4069-73; PMID:20228197; http://dx.doi.org/10.4049/jimmunol.0903600

110. González-Navajas JM, Lee J, David M, Raz E. Immunomodulatory functions of type I interferons. Nat Rev Immunol 2012; 12:125-35; PMID:22222875.

111. Radulovic K, Manta C, Rossini V, Holzmann K, Kestler HA, Wegenka UM, et al. CD69 regulates type I IFN-induced tolerogenic signals to mucosal CD4 T cells that attenuate their colitogenic potential. J Immunol 2012; 188:2001-13; PMID:22250092; http://dx.doi.org/10.4049/jimmunol.1100765

112. Lee SE, Li X, Kim JCK, Lee J, González-Navajas JM, Hong SH, et al. Type I interferons maintain Foxp3 expression and T-regulatory cell functions under inflammatory conditions in mice. Gastroenterology 2012; 143:145-54; PMID:22475534; http://dx.doi.org/10.1053/j.gastro.2012.03.042

113. Bancereau J, Pascual V. Type I interferon in systemic lupus erythematosus and other autoimmune diseases. Immunity 2006; 25:383-92; PMID:16979570; http://dx.doi.org/10.1016/j.immuni.2006.08.010

114. Baechler EC, Batliwalla FM, Karypis G, Gaffney PM, Ortmann WA, Espe KJ, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci U S A 2003; 100:2610-5; PMID:12604793; http://dx.doi.org/10.1073/pnas.0337679100

115. Bennett L, Palucka AK, Arce E, Cantrell V, Borvak J, Bancereau J, et al. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. J Exp Med 2003; 197:711-23; PMID:12642603; http://dx.doi.org/10.1084/jem.20021553

116. Rönnblom L, Alm GV, Eloranta ML. Type I interferon and lupus. Curr Opin Rheumatol 2009; 21:471-7; PMID:19525849; http://dx.doi.org/10.1097/BOR.0b013e32832e089e

117. Triantafyllopoulou A, Franzke CW, Seshan SV, Perino G, Kalliolias GD, Ramanujam M, et al. Proliferative lesions and metalloproteinase activity in murine lupus nephritis mediated by type I interferons and macrophages. Proc Natl Acad Sci U S A 2010; 107:3012-7; PMID:20133703; http://dx.doi.org/10.1073/pnas.0914902107

118. Agrawal H, Jacob N, Carreras E, Bajana S, Putterman C, Turner S, et al. Deficiency of type I IFN receptor in lupus-prone New Zealand mixed 2328 mice decreases dendritic cell numbers and activation and protects from disease. J Immunol 2009; 183:6021-9; PMID:19821195; http://dx.doi.org/10.4049/jimmunol.0803872

119. Yao Y, Richman L, Higgs BW, Morehouse CA, de los Reyes M, Brohawn P, et al. Neutralization of interferon-alpha/beta-inducible genes and downstream effect in a phase I trial of an anti-interferon-alpha monoclonal antibody in systemic lupus erythematosus. Arthritis Rheum 2009; 60:1785-96; PMID:19479852; http://dx.doi.org/10.1002/art.24557

120. Thibault DL, Chu AD, Graham KL, Balboni I, Lee LY, Kohlmoos C, et al. IRF9 and STAT1 are required for IgG autoantibody production and B cell expression of TLR7 in mice. J Clin Invest 2008; 118:1417-26; PMID:18340381; http://dx.doi.org/10.1172/JCI30065

121. Jego G, Palucka AK, Blanck JP, Chalouni C, Pascual V, Bancereau J. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. Immunity 2003; 19:225-34; PMID:12932356; http://dx.doi.org/10.1016/S1074-7613(03)00208-5

122. Ganguly D, Chamilos G, Lande R, Gregorio J, Meller S, Facchinetti V, et al. Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. J Exp Med 2009; 206:1983-94; PMID:19703986; http://dx.doi.org/10.1084/jem.20090480

123. Bettelli E, Sullivan B, Szabo SJ, Sobel RA, Glimcher LH, Kuchroo VK. Loss of T-bet, but not STAT1, prevents the development of experimental autoimmune encephalomyelitis. J Exp Med 2004; 200:79-87; PMID:15238607; http://dx.doi.org/10.1084/jem.20031819

124. Prinz M, Schmidt H, Mildner A, Knobeloch KP, Hanisch UK, Raasch J, et al. Distinct and nonredundant in vivo functions of IFNAR on myeloid cells limit autoimmunity in the central nervous system. Immunity 2008; 28:675-86; PMID:18424188; http://dx.doi.org/10.1016/j.immuni.2008.03.011

125. Willenborg DO, Fordham SA, Staykova MA, Ramshaw IA, Cowden WB. IFN-gamma is critical to the control of murine autoimmune encephalomyelitis and regulates both in the periphery and in the target tissue: a possible role for nitric oxide. J Immunol 1999; 163:5278-86; PMID:10553050.

126. Guo B, Chang EY, Cheng G. The type I IFN induction pathway constrains Th17-mediated autoimmune inflammation in mice. J Clin Invest 2008; 118:1680-90; PMID:18382764; http://dx.doi.org/10.1172/JCI33342

127. Liu L, Okada S, Kong XF, Kreins AY, Cypowyj S, Abhyankar A, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp Med 2011; 208:1635-48; PMID:21727188; http://dx.doi.org/10.1084/jem.20110958

128. Wong P, Severns CW, Guyer NB, Wright TM. A unique palindromic element mediates gamma interferon induction of mig gene expression. Mol Cell Biol 1994; 14:914-22; PMID:8289831.

129. Ohmori Y, Hamilton TA. Requirement for STAT1 in LPS-induced gene expression in macrophages. J Leukoc Biol 2001; 69:598-604; PMID:11310846.

130. Hu Y, Hu X, Boumsell L, Ivashkiv LB. IFN-gamma and STAT1 arrest monocyte migration and modulate RAC/CDC42 pathways. J Immunol 2008; 180:8057-65; PMID:18523269.

131. Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. Front Biosci 2008; 13:453-61; PMID:17981560; http://dx.doi.org/10.2741/2692

132. Pekarek V, Srinivas S, Eskdale J, Gallagher G. Interferon lambda-1 (IFN-lambda1/IL-29) induces ELR(-) CXC chemokine mRNA in human peripheral blood mononuclear cells, in an IFN-gamma-independent manner. Genes Immun 2007; 8:177-80; PMID:17252004; http://dx.doi.org/10.1038/sj.gene.6364372

133. Wang J, Campbell IL. Innate STAT1-dependent genomic response of neurons to the antiviral cytokine alpha interferon. J Virol 2005; 79:8295-302; PMID:15956575; http://dx.doi.org/10.1128/JVI.79.13.8295-8302.2005

134. Mahalingam S, Chaudhri G, Tan CL, John A, Foster PS, Karupiah G. Transcription of the interferon gamma (IFN-gamma)-inducible chemokine Mig in IFN-gamma-deficient mice. J Biol Chem 2001; 276:7568-74; PMID:11024052; http://dx.doi.org/10.1074/jbc.M005773200

135. Lazear HM, Lancaster A, Wilkins C, Suthar MS, Huang A, Vick SC, et al. IRF-3, IRF-5, and IRF-7 Coordinately Regulate the Type I IFN Response in Myeloid Dendritic Cells Downstream of MAVS Signaling. PLoS Pathog 2013; 9:e1003118; PMID:23300459; http://dx.doi.org/10.1371/journal.ppat.1003118

136. Aliberti JC, Souto JT, Marino AP, Lannes-Vieira J, Teixeira MM, Farber J, et al. Modulation of chemokine production and inflammatory responses in interferon-gamma- and tumor necrosis factor-R1-deficient mice during Trypanosoma cruzi infection. Am J Pathol 2001; 158:1433-40; PMID:11290561; http://dx.doi.org/10.1016/S0002-9440(10)64094-1

137. Souto JT, Aliberti JC, Campanelli AP, Livonesi MC, Maffei CM, Ferreira BR, et al. Chemokine production and leukocyte recruitment to the lungs of Paracoccidioides brasiliensis-infected mice is modulated by interferon-gamma. Am J Pathol 2003; 163:583-90; PMID:12875978; http://dx.doi.org/10.1016/S0002-9440(10)63686-3

138. Jaruga B, Hong F, Kim WH, Gao B. IFN-gamma/STAT1 acts as a proinflammatory signal in T cell-mediated hepatitis via induction of multiple chemokines and adhesion molecules: a critical role of IRF-1. Am J Physiol Gastrointest Liver Physiol 2004; 287:G1044-52; PMID:15246962; http://dx.doi.org/10.1152/ajpgi.00184.2004

139. Buttmann M, Merzyn C, Rieckmann P. Interferon-β induces transient systemic IP-10/CXCL10 chemokine release in patients with multiple sclerosis. J Neuroimmunol 2004; 156:195-203; PMID:15465611; http://dx.doi.org/10.1016/j.jneuroim.2004.07.016