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REVIEW

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Exposing the Two Contrasting Faces of STAT2 in Inflammation

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Inflammation is a natural immune defense mechanism of the body's response to injury, infection, and other damaging triggers. Uncontrolled inflammation may become chronic and contribute to a range of chronic inflammatory diseases. Signal transducer and activator of transcription 2 (STAT2) is an essential transcription factor exclusive to type I and type III interferon (IFN) signaling pathways. Both pathways are involved in multiple biological processes, including powering the immune system as a means of controlling infection that must be tightly regulated to offset the development of persistent inflammation. While studies depict STAT2 as protective in promoting host defense, new evidence is accumulating that exposes the deleterious side of STAT2 when inappropriately regulated, thus prompting its reevaluation as a signaling molecule with detrimental effects in human disease. This review aims to provide a comprehensive summary of the findings based on literature regarding the inflammatory behavior of STAT2 in microbial infections, cancer, autoimmune, and inflammatory diseases. In conveying the extent of our knowledge of STAT2 as a proinflammatory mediator, the aim of this review is to stimulate further investigations into the role of STAT2 in diseases characterized by deregulated inflammation and the mechanisms responsible for triggering severe responses.

Keywords: STAT2, interferon, viral, bacterial, inflammation, cancer, asthma

Introduction

STAT2 was discovered as a key transcriptional activator of type I interferon (IFN) signaling (Leung and others 1995; Qureshi and others 1996). IFNs are a family of pleiotropic cytokines first characterized by their role in eliciting antiviral responses through the induction of interferon-stimulated genes (ISGs), which include genes with proinflammatory and anti-inflammatory activities (Steen and Gamero 2013). The elucidated classical signal transduction pathway activated by type I IFNs involve members of the family of signal transducers and activators of transcription (STAT). These proteins were identified in the early 1990s as factors that reside in the cytoplasm. Treatment with IFN-α caused their phosphorylation on specific tyrosine (Y) residues (Y701 for STAT1 and Y690 for STAT2), and subsequent translocation to the nucleus. (Fu and others 1990, 1992; Schindler and others 1992; Leung and others 1995). Primarily, STAT2, in conjunction with STAT1 mediates the transcriptional responses to type I IFN, of which gene products are antiviral, immunomodulatory, antiproliferative, proinflammatory and anti-inflammatory.

IFNs are classified into 3 classes: Type I, Type II (IFN-γ), and Type III (IFN-λ1-4 also referred to as IL-28A, IL-28B, and IL-29). The largest group is type I IFN, which is composed of 13 IFN-α subtypes, a single IFN-β, and poorly characterized IFN-τ, IFN-κ, IFN-ω, IFN-σ, and IFN-ζ (Pestka and others 2004). Of note, IFN-α and IFN-β are the 2 forms of type I IFN used often for the study of type I IFN signaling. Activation of the pathway begins with type I IFN binding to its cognate receptor, which consists of 2 transmembrane subunits, IFNAR1 and IFNAR2, preassociated with Janus kinases TYK2 and JAK1, respectively. TYK2 and JAK1 are activated by transphosphorylation and then phosphorylate the intracellular chains of IFNAR1 and IFNAR2. In the case of type III IFN signaling, a different

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heterodimer receptor complex consisting of IFNLR1 and IL10R2 is engaged, which leads to STAT1 and STAT2 phosphorylation by JAK kinases in a similar manner as type I IFN.

As STAT1/STAT2 heterodimers assemble, they associate with interferon regulatory factor 9 (IRF9), resulting in the formation of a transcriptional complex termed interferon-stimulated gene factor-3 (ISGF3). The ISGF3 complex translocates to the nucleus and binds to the IFN-stimulated response element (ISRE) located in the promoters of IFN-stimulated genes (ISGs). While the major transcriptional complex is ISGF3, both type I IFN and type III IFNs can also induce the formation of STAT1 and STAT3 homodimers that bind to the IFN-γ-activated sequence (GAS) motif within target gene promoters.

The classical view of ISGF3 as a mediator within most of the transcriptional responses to type I IFN, however, is shifting. It has been known for some time that, in the absence of type I IFN, STAT2 and IRF9 can form a complex independently of STAT1 (Martinez-Moczygemba and others 1997), which shuttles between the cytoplasm and the nucleus (Banninger and Reich 2004). Additionally, unphosphorylated STAT2 is found bound to a subset ISG promoters before type I IFN stimulation takes place (Testoni and others 2011).

Without STAT1, type I IFN can activate an alternative signaling pathway mediated by the STAT2/IRF9 complex consisting of STAT2 homodimers bound to IRF9. This complex induces a delayed yet prolonged transcriptional response and antiviral effects in a manner analogous to ISGF3 (Blaszczyk and others 2015, 2016). These studies also indicated that increased expression of STAT2 and/or IRF9 was required to activate robust expression of shared ISGs. Increased levels of unphosphorylated ISGF3 following type I IFN stimulation has been proposed as a secondary response to prolonged transcription of ISGs (Wang and others 2017a). This information is illustrated in Fig. 1.

Under homeostatic conditions, constitutive low levels of type I IFN maintain cells with adequate levels of ISGF3 components (STAT1/STAT2/IRF9). In the absence of type I IFN, however, unphosphorylated STAT2 in complex with IRF9 (STAT2/IRF9) can drive ISG transcription independently of STAT1 (Platanitis and others 2019). Once type I IFN becomes available, ISGF3 replaces STAT2:IRF9 and powers a robust primary transcriptional response. This observation highlights the role of STAT2 as a signaling factor that can function without STAT1 and does not require tyrosine phosphorylation to maintain basal gene transcription levels. The latter finding emphasizes its potential relevance in other biological actions, which may not be entirely dependent on the classical type I IFN signaling pathway.

Our current understanding of the far-reaching effects of STAT2 in mediating the biological effects of type I and type III IFNs appear to be expanding. STAT2 may have a wider sphere of influence than previously assumed, and in fact, have a dual function in disease. As examples, pathological inflammation triggered by persistent activation of type I/III IFN signaling, lack of negative regulation provided by STAT2 deficiency, or excessive production of type I/III IFNs can be seen in inflammatory diseases. Collectively, studies of STAT2 in infectious, autoinflammatory, and autoimmune diseases such as psoriasis, asthma, hemophagocytic lymphohistiocytosis (HLH), and type I interferonopathies, shed new light on these additional functions of STAT2. The following summary describes those findings of current literature with respect to the inflammatory behavior of STAT2 and its role in the pathogenesis of various diseases marked by chronic inflammation.

STAT2 in Viral Infection

STAT2 is an integral downstream effector of type I and type III IFN signaling in restricting the replication of pathogenic viruses. Nonetheless, viruses are naturally equipped with their own armamentarium of genes to subvert the initial protective innate host response initiated by type I IFN. Similar responses are observed with type III IFN-induced activation of ISGF3 (Kotenko and Durbin 2017). Specific viruses inhibit the induction of type I IFN antiviral responses by targeting STAT2 for degradation or preventing its activation by impeding tyrosine phosphorylation. It is important to highlight that some of the IFN target genes or ISGs exert antiviral activity while others contribute to inflammation. The orchestrated activity of all these genes is necessary to eradicate viruses.

Seminal studies in mice lacking Stat2 have shown the importance of STAT2 in mediating the antiviral effects of type I IFN by restricting the replication of vesicular stomatitis virus (VSV) (Park and others 2000). In the context of influenza infection, *Stat2*-deficient mice are prone to hyperinflammation. Loss of Stat2 increases the levels of proinflammatory cytokines (IL1-α, IL1-β, IL-6, IL-12, IL17-A, and IFN-γ) (Gopal and others 2018). This inflammatory response intended to eradicate viruses was shown to be exacerbated resulting in severe lung injury (Tavares and others 2017).

An interesting phenotypic feature of Stat2 deficiency, first described in murine macrophages lacking STAT2, is the acquired ability to upregulate expression of major histocompatibility complex class II after type I IFN stimulation (Zhao and others 2007; Gothe and others 2022), a response unique to IFN-γ. A change in transcriptional response to type I IFN that mimics IFN-γ could initially be protective but then become potentially deleterious in the setting of persistent viral infection by favoring the activation of proinflammatory genes driven mainly by STAT1. In support of a regulatory role, STAT2 has been reported to inhibit STAT1 in response to several proinflammatory cytokines, including IL-6, IL-27, and IFN-γ (Ho and others 2016). Interestingly, effective control of mouse cytomegalovirus infection requires activation of STAT2 by all 3 types of IFNs (Zimmermann and others 2005; Le-Trilling and others 2018), suggesting that the presence of STAT2 is beneficial in antiviral IFN-γ responses. In the case of dengue virus, STAT2 and STAT1, independently, are protective in restricting infection (Perry and others 2011).

Following dengue infection, *Stat2*-deficient mice showed similar increase in serum levels of proinflammatory cytokine TNF-α as *Stat1*-deficient mice when compared with wild-type mice. In the absence of Stat1, Stat2 was able to activate a type I IFN antiviral response to clear infection. The same observation was noted in mice lacking Stat2. However, codeletion of *Stat1* and *Stat2* resulted in a heightened increase of circulating TNF-α levels associated with poor survival and high viral load, indicating a coregulatory effect of STAT1/STAT2 signaling. What surfaced

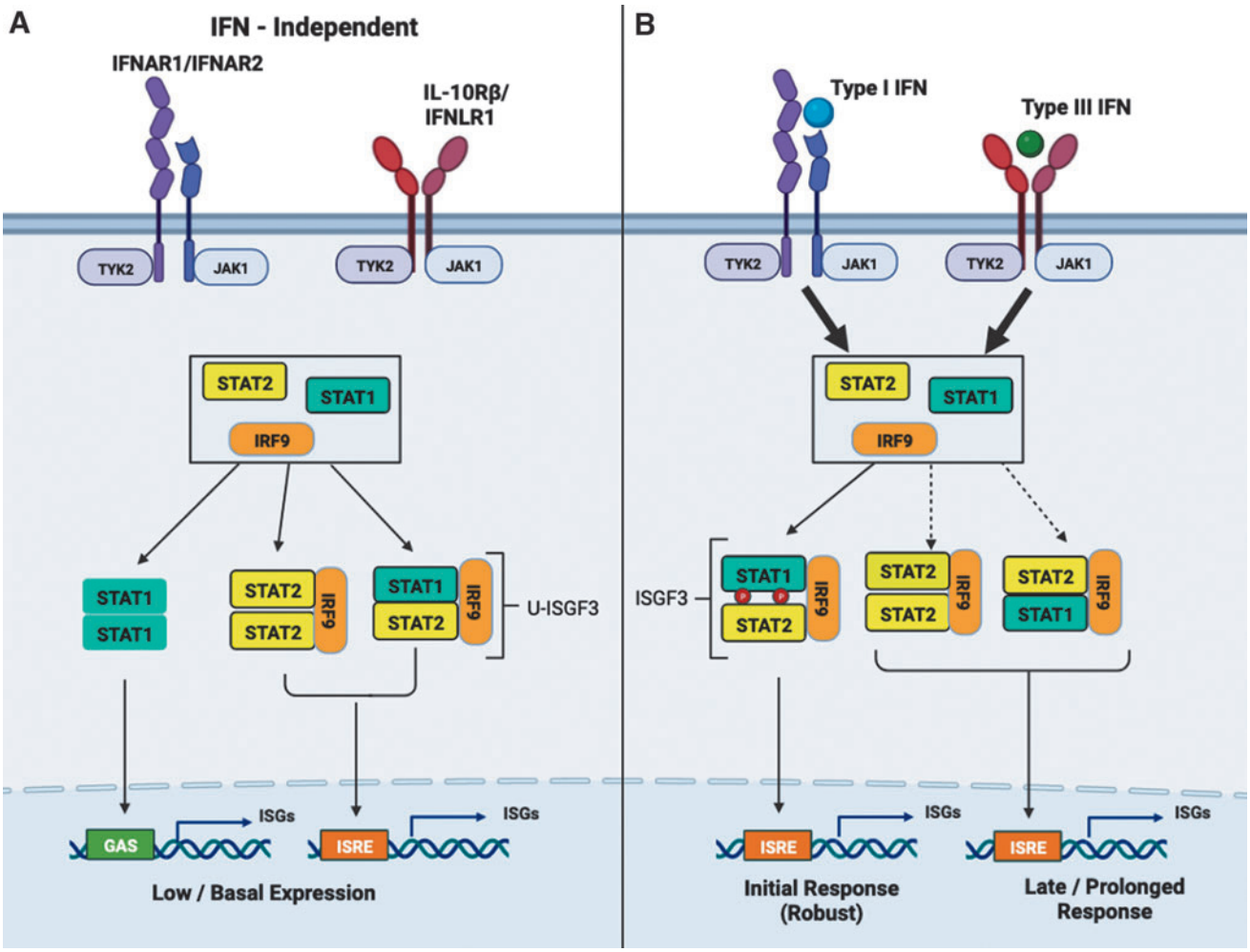

FIG. 1. STAT2 is key transcription factor in type I and type III IFN signaling. **(A)** In the absence of IFN receptor stimulation, STAT2 in its unphosphorylated form, can form complexes with IRF9 or STAT1/IRF9 and translocate to the nucleus. They bind the ISRE motif in promoters of ISGs to drive low-level ISG transcription. In contrast, STAT1 homodimers occupy the GAS motif in gene promoters. **(B)** Following IFN binding to the receptor, STAT1/STAT2 are tyrosine phosphorylated by JAK kinases and bind IRF9 to form the ISGF3 complex. In the nucleus, ISGF3 activates an initial and robust IFN transcriptional response. Subsequently, ISG transcription is maintained by a late IFN response driven by newly synthesized unphosphorylated ISGF3 and STAT2/IRF9 complexes. STAT, signal transducer and activator of transcription; ISG, interferon-stimulated gene; ISRE, IFN-stimulated response element.

from this study is that STAT2 can restrict infection *in vivo* and control TNF-α production independently from STAT1. It is worth noting that type III IFNs are also induced by dengue infection (Palma-Ocampo and others 2015; Hsu and others 2016). High levels of IFN-λ are detected in dengue fever patients. Pretreatment of epithelial cells with IFN-λ increased IFN-β production during infection indicating a potential crosstalk between both IFN signaling pathways that share STAT2 to mount a robust antiviral response (Palma-Ocampo and others 2015).

Type I IFNs are pivotal in restricting the replication and spread of lymphocytic choriomeningitis virus (LCMV) during acute infection (Ou and others 2001). In contrast, chronic LCMV infection is controlled by impeding type I IFN signaling (Teijaro and others 2013). *Ifnar1*-deficient mice lacking either *Stat2* or *Irf9* survived LCMV infection (Hofer and others 2012). Subsequent studies revealed that *Stat1*-deficient mice experienced a lethal host response to the infection (Li and others 2014a). These mice presented with elevated serum cytokine and chemokine levels (CCL2, CCL5, IL-5, IL-6), including type I IFN and IFN-γ during LCMV infection. Deletion of *Stat2*, *Irf9*, or *Ifnar1* in *Stat1*-deficient mice conferred survival to LCMV infection.

Type III IFN also shows antiviral activity against LCMV before the establishment of long-term infection; however, LCMV-infected cells had reduced expression of *Ifnlr1* (Lukacikova and others 2015). These findings point to the proinflammatory and lethal effects of noncanonical activation of type I and type III IFN signaling most likely driven by possible negative regulatory effects of STAT2/IRF9 as opposed to ISGF3, which enables persistent LCMV replication.

In recent years, we have learned that type I IFN-induced activation of STAT2 by phosphorylation on tyrosine (Y)-690 (Y689 in mice) is not the only occurring post-translational modification event. Type I IFN signaling is also impacted by STAT2 being further phosphorylated on serine (S287, S734) (Steen and others 2013, 2016) and threonine (T387 and T404/T403 in mice) (Wang and others

2017b, 2021), both of which impact type I IFN signaling. It is unclear as to whether type III IFNs also induce STAT2 phosphorylation on these same sites. Phosphorylation on S287, S734, and T387 negatively regulates whereas phosphorylation on T404 positively activates type I IFN antiviral responses. In the latter, phosphorylation on T404 was reported to cause disruption of the unphosphorylated STAT1/STAT2 heterodimer in its antiparallel ''inactive'' conformation to switch to the parallel conformation and facilitate STATs 1 and 2 phosphorylation following type I IFN stimulation.

In vivo studies show that mice carrying *Stat2-T403* mutated to alanine (T403A) were highly susceptible to VSV and herpes simplex virus infection, whereas wild-type counterparts were protected. Compared with wild-type mice, *Stat2-T403A* knockin mice infected with VSV produced higher serum levels of IFN-β as well as proinflammatory mediators, CCL2 and CSF-1, compounded by accumulation of immune cells in the brain. It is unclear whether high IFN-β levels produced during VSV infection increased the protein expression levels of unphosphorylated STAT2-T403A or its stability and the formation of mutant STAT2/IRF9 complex to potentially drive the expression of CCL2, an ISG that can facilitate recruitment of inflammatory monocytes to the site of infection (Conrady and others 2013).

In humans, the discovery of a young child and infant sibling born with homozygous germline STAT2 deficiency who experienced severe viral illness has contributed vital information to the biological significance of STAT2 in antiviral immunity (Hambleton and others 2013). Of the 2, only the older sibling was vaccinated and developed disseminated vaccine-strain measles after routine immunization. In contrast, heterozygous relatives were unaffected. *In vitro* studies demonstrated that restoration of STAT2 in patient's fibroblasts restored type I IFN response and antiviral state.

After this initial report, more STAT2-deficient individuals have since been identified with similar and/or additional clinical manifestations with varying penetrance (Duncan and Hambleton 2021). For instance, 2 cases were reported with distinct homozygous STAT2 mutations that resulted in complete loss of STAT2 protein and presented with secondary HLH (Alosaimi and others 2019; Gothe and others 2020). HLH is a rare condition characterized by severe systemic hyperinflammation associated with high production of IFN-γ, where viral infection provokes a robust, destructive, and inefficient antiviral response (Rosado and Kim 2013). One patient developed secondary HLH upon infection with meningitis due to vaccine-strain mumps (Alosaimi and others 2019). Treatment with high doses of intravenous immunoglobulin enabled patient recovery. The exact viral trigger that led to HLH in the second patient who developed severe illness following MMR vaccination and subsequently fatal hyperinflammation could not be established (Gothe and others 2020), as there was no evidence of vaccine-strain viral replication.

The cause was postulated to be either influenza A or vaccination strain of Varicella (Freij and others 2021). In both cases of HLH, STAT2 deficiency was reflected by decreased expression of ISGs upon stimulation with IFN-α. Collectively, these 2 case studies demonstrate the far-reaching detrimental effects of STAT2 deficiency on functionality of the type I IFN response and patients' abilities to combat viral illness (Gothe and others 2022). Based on these findings, one could speculate that type III IFN signaling would also be impaired in individuals with STAT2 deficiency. The emerging trend is that all STAT2-deficient individuals share a susceptibility to viral illness during childhood, which becomes less recurrent when they reach adulthood. Interestingly, no increase in susceptibility to bacterial infections has been reported in STAT2-deficient individuals.

STAT2 in Bacterial Infections

Unlike viral infections, where type I and type III IFNs are protective, both display dual opposing roles in bacterial infection. Depending on the bacterial pathogen, IFNs can be protective or deleterious to the host (Lebreton and others 2011; Cohen and Prince 2013; Boxx and Cheng 2016; Kovarik and others 2016). To elucidate the role of IFN signaling in microbial pathogenesis, mice deficient in *Ifnar1, Ifnlr1*, and components of the ISGF3 complex are routinely used. However, the phenotypes of STAT2 or IRF9 deficiency may not mirror those of IFNAR1 deficiency. The absence of both STAT2 and IRF9 is rather expected to resemble double IFNAR1/IFNLR1 deficiency, suggesting that both factors have critical roles in bacterial infections that are yet to be fully characterized.

It is widely accepted that type I IFN contributes to the immunopathology of *Salmonella* Typhimurium, an intracellular Gram-negative enteric pathogen that evades the innate immune system by provoking severe inflammation. In contrast, the role of type III IFN in Salmonella infection is not entirely clear. *In vitro* studies show IFN-λ treatment safeguards the integrity of epithelial barriers from *Salmonella*-induced damage, whereas IFN-β provides minimal effect (Odendall and others 2017). Studies in *ifnlr1*-deficient mice would be needed to determine whether IFN-λ has antibacterial activity *in vivo*. What is known is that loss of *Ifnar1* prolongs host survival to *Salmonella* infection (Robinson and others 2012). Type I IFN induces cell death of *Salmonella*-infected macrophages by activating necroptosis, a form of inflammatory cell death. This type of cell death helps to evade the immune response and spread the infection to other organs (McComb and others 2014). Deficiency in RIP3 kinase, a key component of the necroptotic pathway, enhances bacterial clearance.

Similarly, macrophages lacking *IFN-a*, *Stat1*, *Stat2*, or *Irf9* were highly resistant to necroptosis. *Salmonella* infection was reported to drive necroptosis by upregulating the mitochondrial phosphatase Pgam5 that in turn sequestered the transcription factor NRF2 in the cytosol, preventing the expression of antioxidative genes. Ultimately, this led to the production of reactive oxygen species, energy depletion and cell death, which helps the organism evade the immune response (Hos and others 2017). Of note, STAT2 has been reported to increase mitochondrial mass in lipopolysaccharides (LPSs)-stimulated macrophages; such an increase in mitochondrial copy number is needed to support the proinflammatory differentiation of macrophages (Yu and others 2020).

Most recent literature shows that *Salmonella* flagellin activates the NLRC4 inflammasome to trigger pyroptosis and the synthesis of lysophospholipids to clear early

infection (Akhade and others 2020). However, as infection progresses, type I IFN represses NLRC4 and the lysophospholipid enzyme iPLA2. This results in reduced production of lysophospholipids that ultimately downregulates flagellin expression to enable *Salmonella* to switch to a flagellin-low phenotype to avert immunosurveillance. It is unclear if deletion of STAT1, STAT2, or IRF9 will rescue *Salmonella* flagellin expression and enhance bacterial clearance. Another study shows that type I IFN remodels lysosome localization and function, which is associated with enhanced *Salmonella* virulence (Zhang and others 2020).

The expression of a unique group of ISGs (*IFITM3, SLC15A3, and CNP*) localized to lysosomes after *Salmonella* infection of intestinal epithelial cells were identified by a combination of CRISPR/Cas9 screen and proteomic profile of lysosomes and found to be important in reducing the pH and protease activity of lysosomes. IFN-dependent lysosome acidification was associated with the expansion of *Salmonella*-containing vacuoles that is permissive for Salmonella replication, their rupture, and host cell death. Whether this is driven through ISGF3 or STAT2/IRF9 is yet to be determined.

The pathogenic role of STAT2 in S*almonella* infection was recently evaluated more closely. Similar to *Ifnar1*-deficient mice (Robinson and others 2012), our group found that *Stat2*-deficient mice were less susceptible to *Salmonella* infection and had impaired ISG expression, in contrast to wild-type mice (Wilson and others 2019). *Salmonella* needs a highly oxygenated environment to expand (Rivera-Chávez and others 2016). We observed that Stat2 deficiency limited the expansion of *Salmonella* by impairing neutrophil function (defect in generating superoxide anion), thus leading to the establishment of a hostile hypoxic environment in the intestinal lumen, which in turn decreased bacterial burden. Loss of STAT2 also prevented *Salmonella* from outcompeting the healthy microbiota thereby impeding dysbiosis. Based on these findings, we concluded that STAT2 generates a proinflammatory environment, which allows *Salmonella* to thrive by increasing luminal oxygenation driven by neutrophils. However, the specific mechanisms by which STAT2 promotes this inflamed state are yet to be elucidated.

Type I IFNs are also detrimental in infection with intracellular Gram-positive *Listeria monocytogenes,* a foodborne pathogen, by inducing lymphocyte death (Auerbuch and others 2004; O'Connell and others 2004). Induction of apoptosis-associated genes by type I IFN in a STAT1-dependent manner was first proposed as a mechanism to explain susceptibility to infection (Stockinger and others 2002). Subsequent studies showed *Listeria* infection triggers pyroptosis in macrophages, an inflammatory form of cell death marked by rupture of the plasma membrane, whereby inflammasome activation results in caspase 1/caspase 11 activation, cleavage of pro-IL1-β and pro-IL-18, and activation of pore-forming protein Gasdermin D (Cervantes and others 2008). IFN-γ controls *Listeria* infection, so a second mechanism was proposed, by which type I IFN antagonizes the antimicrobial effects of IFN-γ in macrophages (Rayamajhi and others 2010). As part of the probacterial effect of type I IFN, *Stat2*-deficient mice were also found to be more resistant to *Listeria* infection (Shaabani and others 2021).

Although type III IFN responses have yet to be determined, the possibility that it is detrimental in Listeria infection due to its dependence on STAT2 is plausible. In addition to functioning as a positive activator of type I IFN signaling, it is important to highlight that STAT2 is also a negative regulator of the type I IFN pathway. STAT2 functions as an adaptor molecule to USP18, an ISG, to desensitize cells to IFNs (Arimoto and others 2017). Paradoxically, USP18 expressed in dendritic cells was shown to promote the replication of *Staphylococcus aureus* and *Listeria* by inhibiting the production of antimicrobial IFN-γ and TNF-α (Shaabani and others 2021).

Previously, the intestinal microbiota was reported to affect the host transcriptional response to *Listeria* infection (Archambaud and others 2013). The microbiota inhibited the expression of several microRNAs (miRNAs) that were inversely correlated with the expression of protein-coding genes. The expression of 4 miRNAs, miR-143, miR-148a, miR-200b, and miR-200c, was downregulated in conventional mice upon *Listeria* infection. Among the 16 top protein-coding genes identified during Listeria infection, germ-free and conventional mice showed upregulation of STAT2 expression. Other ISGs were also identified that are known to be STAT2 dependent. The relationship between these ISGs and miRNAs to the probacterial effects of type I IFN may shed more light into the damaging effects of type I IFN signaling in certain bacterial infections.

Most recently, a link between STAT2 and METTL3 was reported to play a proinflammatory role in the pathogenesis of neonatal bacterial pneumonia (NP), a prevalent cause of neonatal morbidity and mortality (Li and others 2021). Bacterial LPSs induce lung inflammation in neonates (Cui and others 2020). METTL3 catalyzes the methylation of adenosine to N6-methyladenosine (m^6A) on mRNA transcripts, an important process in inflammatory responses. In the serum of NP patients and LPS-treated human lung fibroblasts, METTL3 was upregulated, whereas the expression of long noncoding RNA SNHG4 was downregulated. Silencing of METTL3 or overexpression of SNHG4 decreased m^6A levels of STAT2 mRNA causing a reduction in STAT2 protein levels and inhibition of LPS-induced production of inflammatory cytokines that were reversed by ectopic STAT2 overexpression. This finding provides insight into the role of STAT2 as a promoter of acute lung inflammation in the setting of bacterial infection.

Our group previously reported that mice lacking Stat2 were highly susceptible to LPS-induced sepsis, as opposed to mice missing components of type I IFN signaling that survived after LPS administration (Alazawi and others 2013). This observation suggested that Stat2 had a protective role. Lethality could not be explained by induction of a cytokine storm as no exaggerated increases were noted in the levels of classical cytokines and chemokines associated with sepsis. Serum levels of TNF-α, MCP-1, and IL-6 were lower than wild-type mice, whereas the levels of IFN-γ were similar between strains. We concluded that the Stat2 deficiency phenotype was due to a distinct mechanism that involved increased cellular transmigration of immune cells. This is in stark contrast to what others have reported regarding type I IFN signaling being responsible for lethality to LPS (Karaghiosoff and others 2003; Kamezaki and others 2004; Bosmann and others 2014) as well as driving TNF-α-induced systemic inflammatory response syndrome (Huys and others 2009) and sepsis in a model of cecal ligation and puncture (CLP) (Dejager and others 2014).

In these models, expression levels of several cytokines and chemokines were drastically reduced in *Ifnar1*-deficient mice. The latter coincided with reduced trafficking of immune cells in the blood and their migration into tissues. In the model of CLP, antibody-mediated neutralization of IFNAR1 was shown to enhance bacterial clearance by increasing the recruitment of neutrophils (Dejager and others 2014). Therefore, in animal models of sepsis, type I IFNs are detrimental by amplifying the production of proinflammatory mediators that lead to multiorgan failure, although STAT2 has a protective effect.

STAT2 in Superinfection

Superinfection is a secondary infection that occurs following an existing infection and the most common complication of influenza illness. Significant mortality in influenza A virus-infected patients is caused by a secondary bacterial pneumonia infection (Morens and others 2008). *S. aureus* is the most prominent bacterium in influenza bacterial superinfection. Induction of type I and type III IFNs' antiviral response against influenza enhances susceptibility to bacterial pneumonia infection (Lee and others 2015; Planet and others 2016). Different groups have shown that while influenza virus replicates better in *Ifnar1 and ifnlr1*-deficient mice, these mice are superior to wild-type mice in clearing *Staphylococcus* during superinfection (Li and others 2012; Planet and others 2016; Shepardson and others 2016, 2018). One study reported that administration of IFN-λ had the opposite effect with detrimental consequences as it increased bacterial burden due to host immune response to influenza (Rich and others 2019).

Infection by influenza inhibits a Th17-mediated protective response intended to clear bacterial pneumonia infection during influenza and bacterial superinfection (Kudva and others 2011). Bacterial superinfection subsequently antagonizes antiviral type I IFN signaling; STAT1/STAT2 dimerization becomes impaired, causing inhibition of ISG expression and enhanced viral replication (Warnking and others 2015), a finding that can be extended to type III IFN signaling. A recent study compared the outcome of influenza and influenza methicillin-resistant *S. aureus* superinfection between wild-type and *Stat2* null mice (Gopal and others 2018). As expected, influenza-infected *Stat2*-deficient mice had increased mortality, impaired viral clearance, and severe inflammatory response than wild-type mice. In the context of an influenza bacterial superinfection, *Stat2*-deficient mice survived and showed bacterial clearance. No discernable differences in perivascular inflammation were noted between wild-type and *Stat2*-deficient mice as well as in the levels of IL-17, IL-22, and IL-23 cytokines, known to be altered by influenza infection.

RNA-seq analysis revealed that expression levels of IFN-γ, IL-4, and IL-13 were increased in the lungs of *Stat2* null mice in comparison to wild-type mice during superinfection. *Stat2* null mice also showed elevated expression of chemokines, IFN-γ induced ISGs, and genes representing a dual phenotype of M1- and M2-type macrophages. Additionally, loss of Stat2 signaling was shown to enhance the uptake and killing of bacteria by macrophages. Furthermore, blocking IFN-γ in influenza-infected *Stat2*-deficient mice before bacterial infection decreased bacterial clearance.

Our most current global health challenge is coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Hu and others 2021). Other viruses that similarly cause dysregulated inflammation and acute respiratory disease are SARS-CoV-1 and MERS-CoV. Optimal and balanced activation of type I and type III IFN-dependent antiviral responses as the first line of defense can subvert SARS-CoV-2 infection. COVID-19 patients in critical condition, however, experience severe inflammation due to the induction of a pulmonary cytokine storm, defective type I IFN secretion, impaired/delayed type I IFN response (inhibiting the JAK/STAT pathway) and production of neutralizing autoantibodies to type I IFN.

All of these were associated with poor outcomes (Zhang and others 2021). SARS-CoV-2 utilizes the angiotensin-converting enzyme 2 (ACE2) as a receptor for virus entry and replication. ACE2 has been described as an ISG because of its induction by all 3 types of IFNs and virus infection (Chua and others 2020; Ziegler and others 2020; Salka and others 2021). However, recent studies invalidate that *ACE2* is an ISG. Rather, a spliced variant of *ACE2* (*dACE2*) is an ISG that is nonfunctional and unable to promote infection (Onabajo and others 2020; Blume and others 2021), indicating a protective effect by IFNs.

SARS-CoV-2 replicates poorly in wild-type and immunodeficient SCID mice that lack human ACE2 transgene. Also noted were mice deficient in *Ifnar1* presenting with mild lung pathology. However, some of these mice showed an increase in viral titers and peribronchial inflammation, indicating that these mice are not a suitable model to recapitulate the pathogenesis of COVID-19. Recently, a Syrian hamster model of SARS-CoV-2 infection (Chan and others 2020) was utilized to investigate the dual role of STAT2 signaling in the pathogenesis of the disease (Boudewijns and others 2020). Infected wild-type hamsters developed severe lung pathology marked by high infiltration of neutrophils, bronchopneumonia, and edema, all of which resemble the pathology seen in COVID-19 patients (Xu and others 2020). There were no differences in viral RNA levels in the lungs of WT, *Stat2*-deficient, and *IL28ra* (also known as *ifnlr1*)-deficient hamsters.

Nonetheless, when compared with wild-type, *Stat2*-deficient hamsters showed higher titers of infectious virus in the lung that disseminated to other organs, suggesting STAT2 was critical in controlling SARS-CoV-2 viral replication. In the absence of STAT2, bronchopneumonia and perivascular edema were drastically attenuated unlike that observed with *Il28ra* deficiency, which could be attributed to the overlapping antiviral effects of type I IFN mediated by STAT2 that remain intact in *ifnlr1*-deficient mice. Infection of *Stat2*-deficient hamsters also showed lower baseline expression of antiviral ISGs and inflammatory cytokines (IL-6, IP-10, IFN-λ, and Mx2) with no effect on ACE2 expression. Of note, critically ill COVID-19 patients have reduced IFN responses coupled with an enhanced IL-6 and TNF-α proinflammatory response (Hadjadj and others 2020).

Furthermore, COVID-19 patients have higher rates of co-infection or secondary bacterial infection than influenza patients (Shafran and others 2021). Two studies showed that COVID-19 mortality was associated with elevated expression of both type I and type III IFNs in the lung (Broggi and others 2020; Major and others 2020). These studies also revealed that excessive production of IFN-α, IFN-β, and IFN-λ (more robustly) in the lungs by synthetic viral RNA caused damage to the lung epithelium and hindered repair by inducing p53 to inhibit cell proliferation and differentiation during influenza recovery, which enhances susceptibility to lethal bacterial

superinfection. This inherently aggravates severity of disease and clinical outcomes. These findings indicate that STAT2 downstream type I and type III IFN signaling serves a dual function in controlling viral infections at the expense of causing unrestrained inflammation and severe pathologies.

STAT2 as an Inducer of Inflammatory Cytokines in Cancer

IL-6 is a major cytokine involved in the activation of the STAT3 oncogenic pathway that promotes tumor growth and metastasis (Johnson and others 2018). It was recently reported that metastatic colonization of colorectal tumor cells to the liver was reduced in *Il6*-deficient mice (Toyoshima and others 2019). Without IL-6, $CD11c^+$ dendritic cells that accumulated in the metastatic liver expressed high levels of *Ifna* and *Ifnb*. When blocking Ifnar1, metastatic colonization to the liver was restored.

STAT2 is widely recognized for its role in mediating the antitumor activities of type I IFN (Clifford and others 2003; Wang and others 2003; Yue and others 2015). To investigate this closer, we induced tumors in wild-type and *Stat2*-deficient mice employing chemical models of skin and colorectal cancer (Gamero and others 2010). In the absence of STAT2, mice not only developed fewer tumors but also presented with an attenuated inflammatory transcriptional signature that is found before the onset of cancer. These inflammatory signatures involve the expression of chemokines (*Ccl2, Ccl3, Ccl4, Cxcl9, Cxcl10*) and cytokines (*IL1a, Il1b, and Il6*), all of which were reduced. Loss of STAT2 decreased IL-6 secretion and STAT3 activation while reconstitution of STAT2 in an established STAT2-deficient cancer cell line rescued IL-6 production. This finding, thus, uncovered a new association between STAT2 and IL-6 in the setting of skin and colorectal cancer models.

IL-6 is induced weakly by ISGF3 in response to type I IFN, but is significantly enhanced by activators of the NF-κB signaling pathway (Nan and others 2018). Analysis of the *IL-6* promoter revealed an ISRE motif needed for activation and occupied by the IRF9/STAT2 complex when present at high levels in concert with the NF-κB subunit p65. STAT2 acts as a bridge whereby IRF9 binds the ISRE complex and the p65 binds the NF-κB DNA element, although STAT2 does not bind to DNA. Consequently, this generates a more robust response that further drives IL-6 transcription. Also, increased unphosphorylated STAT2 protein levels can drive the expression of additional chemokines and cytokines that are dependent on NF-κB. This study also underscored a relationship between STAT2 and lung cancer in which elevated STAT2 mRNA levels were associated with poor clinical outcome. It has yet to be determined if the protumorigenic effects of STAT2 is due to impaired type I and/or type III IFN signaling by the actions of IL-6 or other soluble factors.

STAT2 in Asthma

Asthma is a complex inflammatory disease characterized by narrowing of the airways of the lungs, eosinophilic inflammation, mucus hypersecretion, increased Th2 cytokines (IL-4, IL-5, and IL-13), elevated IgE production, shortness of breath, and wheezing (Hamid and Tulic 2009). The development and exacerbation of the disease is influenced by lifestyle, genetics, and environmental factors. Research has shown genetic variants of STAT6, STAT3, and STAT4 being strongly associated with this respiratory condition (Litonjua and others 2005; Korman and others 2008; Qian and others 2014). A more recent study further implicates the STAT family in progression of asthma by identifying a STAT2-related polymorphism directly linked to asthma susceptibility (Hsieh and others 2009). Proportions of genotypes at a single nucleotide polymorphism site in the STAT2 gene (rs2066807) were observed for both asthma and control patients.

Results indicated that the distribution of the genotypes CC/CG/GG were significantly different when these 2 groups were compared. Based upon statistical analysis, the study predicts that STAT2*C-associated variants could be correlated with increased asthma susceptibility. In this same study, TLR4 and CD40-related polymorphisms were found not to contribute to increased susceptibility to asthma. In the future, identification of STAT2 polymorphisms in the exons or promoter region will enable expansion of a database of markers and help with predicting disease susceptibility.

Type I and type III IFN levels are found increased in patients with asthma (da Silva and others 2017). Both types of IFNs have been shown to inhibit the development of Th2 cells and secretion of Th2 cytokines, which suppress allergic responses that in turn attenuate lung inflammation (Jordan and others 2007; Huber and others 2010). Intranasal delivery of IFN-λ1 was found to decrease severity of airway inflammation in an experimental model of ovalbumin-induced asthma (Li and others 2014b). A recent study looked at asthmatic children's peripheral blood mononuclear cells, which had elevated IFN-λ and STAT2 expression (Krug and others 2021). These cells were noted to have a degree of protection against rhinovirus infections. One study reported that 80%–85% of asthma exacerbations in children are associated with upper respiratory viral infections and rhinovirus being the most common (Johnston and others 1995).

Therefore, a decrease in type I and type III IFN response during viral infection in asthmatics can have detrimental effects in promoting asthma exacerbation by the inability of IFNs to restrict Th2 cytokine secretion. Collectively, these studies imply a protective anti-inflammatory effect of STAT2 and identifies a possible target for the induction of antiviral responses in asthmatic children.

Glucocorticoids are a first-line treatment in the prevention and symptomatic control of asthma. One study looked at the association of glucocorticoid usage among asthmatic children and rhinovirus infection. The study showed reduced type I IFN signaling among glucocorticoid-treated children and an association with rhinovirus replication (Marcellini and others 2021). Stimulation of rhinovirus-infected *Beas* 2b epithelial cells with IFN-β in the presence of the glucocorticoid, fluticasone propionate, decreased mRNA expression of ISGs. This reduction in ISG expression was due to impaired STAT1 and STAT2 tyrosine phosphorylation, thus preventing an antiviral response and enabling rhinovirus replication. This finding helps to explain why long-term use of inhaled corticosteroids in patients with asthma increases the risk of respiratory infections. Additionally, these data further solidify the role STAT2 plays in this process.

STAT2 in Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a chronic intestinal condition characterized by inflammation of the digestive

tract. IBD occurs in 2 forms: Crohn's Disease (CD) and Ulcerative Colitis (UC) (Friedrich and others 2019). Type I and type III IFNs have been studied in models of acute and chronic colitis and are considered a double-edged sword as they can reduce or intensify the severity of inflammation (Rauch and others 2014; McElrath and others 2021; Wallace and others 2021; Xu and others 2021).

A growing body of evidence shows that patients with active IBD displaying a high IFN response signature are poor responders to anti-TNF-α drugs (Andreou and others 2020; Mavragani and others 2020). In addition, IFN-λ is increased in the serum of CD patients with active disease (Günther and others 2019). Clinical trials of type I IFN therapy have produced mixed results (Musch and others 2002; Pena Rossi and others 2009); therefore, the beneficial effects of type I IFN therapy in treating IBD remain controversial. IFN-λ has not yet been tested to treat IBD but given the detrimental and beneficial effects seen in mouse models, like those with type I IFN, extreme caution is urged.

Today, hardly anything is known about STAT2 in IBD and no genetic association to UC or CD has been reported. Current knowledge regarding the role of STAT2 in IBD is limited to flow cytometric analysis of different STATs in lamina propria lymphocytes from healthy individuals and patients with active disease in which intracellular levels of STAT2 were decreased in both UC and CD patients (Mudter and others 2005). As the sample size of this study was small, more studies that use a larger cohort of patients would be required to elucidate the activation status of STAT2. In another study, IRF9 was found to be proinflammatory, in a type I and type III IFN independent noncanonical fashion, by forming a complex with STAT1 in an acute model of dextran sodium sulfate (DSS)-induced colitis (Rauch and others 2015). From this study, it was implied that STAT2, as part of the ISGF3 complex, is protective against acute colitis.

In a mouse model of CD, in which Caspase 8 is deleted in the intestinal epithelium ($Casp8^{\Delta IEC}$), mice spontaneously developed inflammatory lesions in the terminal ileum (Günther and others 2011). Administration of DSS resulted in colonic inflammation and necroptosis of Paneth cells, which produce antimicrobial peptides.

Treatment of $Casp8^{\Delta IEC}$ intestinal organoids with either IFN-β- or TNF-α-induced cell death (Stolzer and others 2021). This same study investigated the different contributions of STAT1 and STAT2 in this model. *In vivo*, STAT1 played no role in inducing inflammation and instead, partially contributed to the death of Paneth cells. In contrast, Paneth cell death occurred independently of STAT2. However, unlike STAT1, STAT2 contributed to the severity of inflammation. In a different study, expression of IFN-λ in $Casp8^{\Delta IEC}$ mice was lethal by promoting massive epithelial cell death and loss of immune homeostasis independently of TNF-α through STAT1 signaling (Günther and others 2019). However, the potential contribution of STAT2 in this context is still unclear. These findings highlighted the distinctive, nonoverlapping roles that STAT1 and STAT2 serve in intestinal inflammation.

STAT2 in Type I Interferonopathy

Unrestrained activation of type I IFN signaling pathway can result in a group of disorders defined as type I interferonopathy (Crow and Stetson 2021). Patients with type I interferonopathy often show signs of severe auto-inflammation such as cerebral calcifications and skin ulcerations, in addition to upregulation of IFN-α and aberrant induction of ISGs. Recent studies have implicated STAT2 in the pathogenesis of type I interferonopathies by demonstrating that STAT2 mutations that directly impact its interaction with USP18 interfere with the role of STAT2 as a key negative regulator of the type I IFN pathway.

Two independent studies identified children who died due to excessive type I IFN activity and severe inflammation caused by a homozygous germline missense mutation in STAT2. In the first study, a lethal germline homozygous variant of STAT2 at position c.442CC>T was identified in 2 children (Duncan and others 2019). This mutation resulted in an amino substitution at arginine 148 with tryptophan (R148W). As a result, this mutation affected the recruitment of USP18 to IFNAR2, causing desensitization to type I IFN stimulation. Dysfunction of the negative regulatory system, thus, caused prolonged tyrosine phosphorylation, nuclear localization of STAT2, heightened ISG expression, and hyperinflammation. In the second study, arginine at position 148 was replaced by glutamine (R148Q) at the site where USP18 binds (Gruber and others 2020).

This mutation does not interfere with ISGF3 activity, nor does it inhibit the interaction between USP18 and R148Q STAT2; however, it entirely impairs the ability of STAT2 to mediate USP18 trafficking to the receptor to turn off type I IFN signaling. Whether type III IFN contributes to this phenotype is unclear. Altogether, this contributed to the development of severe type I interferonopathy in the patient. Research that furthers our understanding of type I interferonopathies early in their development will prove valuable to efforts toward therapeutic treatments.

STAT2 in Psoriasis

Psoriasis is a chronic inflammatory skin disease that commonly results in the formation of lesional plaques, which appear as red, silvery, scaly patches on the skin. Pathogenesis of psoriasis is marked by the penetration and infiltration of immune cells, namely Th1 and Th17 cells, into superficial layers of the skin (Nograles and others 2008). While previous research had demonstrated increased expression of STAT1 and STAT3 in psoriatic skin, recent studies point to the involvement of STAT2 in the pathogenesis of the disease. Genome-wide association studies show STAT2 as a psoriasis susceptibility gene (Gupta and others 2014; Yin and others 2015; Fodil and others 2016). A recent study revealed activation of STAT2 signaling in skin lesions of patients with psoriasis (Johansen and others 2017). Paired skin biopsies taken from psoriasis patients with lesional and nonlesional skin as well as skin from healthy individuals were analyzed for STAT2 mRNA levels.

Only lesional psoriatic skin displayed elevated STAT2 mRNA expression when compared with normal and nonlesional skin. This increase in STAT2 expression also matched at the protein level. Psoriatic skin lesions not only had elevated STAT2 protein but also displayed activated STAT2. Curiously, no changes in STAT2 expression were detected in atopic dermatitis, a different inflammatory skin condition. This study also reported that human keratinocytes responding to type I IFN stimulation produced the

chemokines CCL5 and CXCL11, both of which required STAT2 but not STAT1 for their induction. These findings imply that STAT2 is involved in the recruitment of immune cells into the epidermal and dermal layers of the skin. In a different study, T cell lines generated from the skin of psoriasis patients showed increased sensitivity to type I IFN when compared with T cells from healthy subjects (Eriksen and others 2005).

The level and kinetics of STAT2 activation by IFN-β were elevated and prolonged when compared with STAT1 activation. Another study profiled transcriptomic changes in psoriatic keratinocytes isolated from paired lesional and nonlesional skin of psoriasis patients (Pasquali and others 2019). A subset of upregulated genes identified in psoriatic lesions contained binding sites for STAT2. The role of type III IFN in the pathogenesis of psoriasis is not entirely clear. Psoriatic lesions display elevated IFN-λ associated with an ISG signature (Wolk and others 2013) and psoriatic patients have elevated serum levels of IFN-λ (Cardoso and others 2016). Treatment of human keratinocytes with type III IFN induced chemokines CXCL10 and CXCL11 (Witte and others 2016). Of note, induction of CXCL11 is mediated by STAT2 in response to type I IFN. This hints at a shared response between these 2 cytokines and their overlapping contribution to the pathogenesis of psoriasis.

Current knowledge pertaining to psoriasis pathogenesis also encompasses our understanding of risk loci and variants that confer risk for psoriasis and psoriatic arthritis (PsA). PsA is a chronic inflammatory condition closely linked to psoriasis (Rahmati and others 2020). To date, all risk loci known to be associated with psoriasis also confer risk for PsA. Thus, identifying risk loci that distinguish risk for PsA from psoriasis can significantly aid in the development of treatments and processes by which patients at high risk for each inflammatory condition are identified. These data point to STAT2 as having an active deleterious role in psoriasis.

Concluding Remarks

Over the years, multiple studies have reaffirmed the essential role of STAT2 in activating the transcriptional response to type I and type III IFNs. It is becoming increasingly clear that STAT2 has distinct functions in pathogenic infections, autoimmune and autoinflammatory diseases as depicted in Fig. 2. STAT2 is protective against viral infections while deleterious in bacterial infections. Loss of STAT2 can lead to hyperinflammation and tissue injury in the setting of viral illness due to the failed attempt of the host to clear the virus. Severe inflammation is also observed in certain bacterial infections and in superinfections; however, in this case, STAT2 activates a damaging transcriptional inflammatory program. Similarly, severe inflammation is noted in patients with persistent type I and type III IFN signaling as observed in multiple human diseases (IBD, psoriasis, type I interferonopathies).

It is important to consider that STAT2 is multifaceted: initially, it assumes the role of an activator and later, functions as a suppressor of type I IFN signaling. This became apparent with the identification of individuals born with a primary immunodeficiency disorder characterized by a STAT2 deficiency.

During childhood, they experienced recurrent viral infections and others born with a lethal homozygous STAT2 variant (R148W/Q), which cannot restrict type I IFN signaling and led to severe inflammation. In that regard, STAT2 can be viewed as an immune rheostat. However,

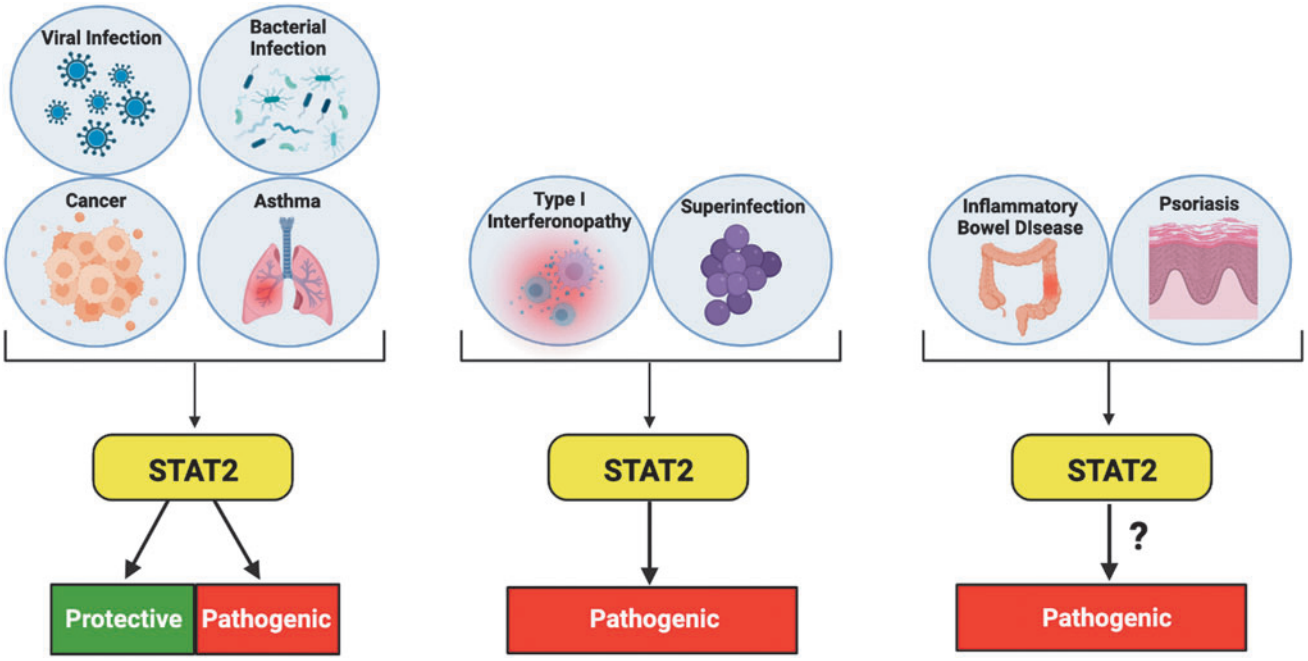

FIG. 2. STAT2 plays a dual role as a transcription factor involved in promoting proinflammatory and anti-inflammatory activities. Unrestrained STAT2 signaling due to uncontrolled infection, tissue injury, or heightened IFN-I production can lead to detrimental and severe inflammation. Shown are the various diseases to which STAT2 can be associated as either protective or pathogenic or both.

whether the inflammatory effects of STAT2 are driven solely by a secondary transcriptional response mediated by unphosphorylated STAT2/IRF9 complex and if this operates independently of type I or type III signaling, is still unknown. Already, STAT2 has been shown to promote the expression of protumorigenic cytokines, IL-6 and TNF-α. This may aid in explaining the contribution of STAT2 in promoting cancer. Nevertheless, mechanistic studies are warranted to understand mechanistically how STAT2 promotes hyperinflammation and whether this feature is regulated by post-translational modifications and association with other proteins. Insight into these inquiries will prompt the development of treatments that target key factors in a myriad of inflammatory diseases assumed to be linked to STAT2.

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Authors' Contributions

A.M.G. conceptualized, wrote, and approved the final version of the article. P.D., G.S., and O.C. contributed to the writing and editing of the article. J.C. made the illustrations and helped with editing.

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References

Akhade AS, Atif SM, Lakshmi BS, Dikshit N, Hughes KT, Qadri A, Subramanian N. 2020. Type 1 interferon-dependent repression of NLRC4 and iPLA2 licenses down-regulation of *Salmonella* flagellin inside macrophages. Proc Natl Acad Sci USA 117(47):29811–29822.

Alazawi W, Heath H, Waters JA, Woodfin A, O'Brien AJ, Scarzello AJ, Ma B, Lopez-Otalora Y, Jacobs M, Petts G, Goldin RD, Nourshargh S, Gamero AM, Foster GR. 2013. Stat2 loss leads to cytokine-independent, cell-mediated lethality in LPS-induced sepsis. Proc Natl Acad Sci U S A 110(21):8656–8661.

Alosaimi MF, Maciag MC, Platt CD, Geha RS, Chou J, Bartnikas LM. 2019. A novel variant in STAT2 presenting with hemophagocytic lymphohistiocytosis. J Allergy Clin Immunol 144(2):611–613.e3.

Andreou NP, Legaki E, Gazouli M. 2020. Inflammatory bowel disease pathobiology: the role of the interferon signature. Ann Gastroenterol 33(2):125–133.

Archambaud C, Sismeiro O, Toedling J, Soubigou G, Bécavin C, Lechat P, Lebreton A, Ciaudo C, Cossart P, Miller JF. 2013. The intestinal microbiota interferes with the microRNA Response upon Oral *Listeria* Infection. mBio 4(6):e00707–13.

Arimoto K-i, Löchte S, Stoner SA, Burkart C, Zhang Y, Miyauchi S, Wilmes S, Fan J-B, Heinisch JJ, Li Z, Yan M, Pellegrini S, Colland F, Piehler J, Zhang D-E. 2017. STAT2 is an essential adaptor in USP18-mediated suppression of type I interferon signaling. Nat Struct Mol Biol 24(3): 279–289.

Auerbuch V, Brockstedt DG, Meyer-Morse N, O'Riordan M, Portnoy DA. 2004. Mice lacking the type I interferon receptor are resistant to Listeria monocytogenes. J Exp Med 200(4):527–533.

Banninger G, Reich NC. 2004. STAT2 Nuclear Trafficking*. J Biol Chem 279(38):39199–39206.

Blaszczyk K, Nowicka H, Kostyrko K, Antonczyk A, Wesoly J, Bluyssen HA. 2016. The unique role of STAT2 in constitutive and IFN-induced transcription and antiviral responses. Cytokine Growth Factor Rev 29:71–81.

Blaszczyk K, Olejnik A, Nowicka H, Ozgyin L, Chen Y-L, Chmielewski S, Kostyrko K, Wesoly J, Balint Balint L, Lee C-K, Bluyssen Hans AR. 2015. STAT2/IRF9 directs a prolonged ISGF3-like transcriptional response and antiviral activity in the absence of STAT1. Biochem J 466(3):511–524.

Blume C, Jackson CL, Spalluto CM, Legebeke J, Nazlamova L, Conforti F, Perotin J-M, Frank M, Butler J, Crispin M, Coles J, Thompson J, Ridley RA, Dean LSN, Loxham M, Reikine S, Azim A, Tariq K, Johnston DA, Skipp PJ, Djukanovic R, Baralle D, McCormick CJ, Davies DE, Lucas JS, Wheway G, Mennella V. 2021. A novel ACE2 isoform is expressed in human respiratory epithelia and is upregulated in response to interferons and RNA respiratory virus infection. Nat Genet 53(2):205–214.

Bosmann M, Strobl B, Kichler N, Rigler D, Grailer JJ, Pache F, Murray PJ, Müller M, Ward PA. 2014. Tyrosine kinase 2 promotes sepsis-associated lethality by facilitating production of interleukin-27. J Leukoc Biol 96(1):123–131.

Boudewijns R, Thibaut HJ, Kaptein SJF, Li R, Vergote V, Seldeslachts L, Van Weyenbergh J, De Keyzer C, Bervoets L, Sharma S, Liesenborghs L, Ma J, Jansen S, Van Looveren D, Vercruysse T, Wang X, Jochmans D, Martens E, Roose K, De Vlieger D, Schepens B, Van Buyten T, Jacobs S, Liu Y, Martí-Carreras J, Vanmechelen B, Wawina-Bokalanga T, Delang L, Rocha-Pereira J, Coelmont L, Chiu W, Leyssen P, Heylen E, Schols D, Wang L, Close L, Matthijnssens J, Van Ranst M, Compernolle V, Schramm G, Van Laere K, Saelens X, Callewaert N, Opdenakker G, Maes P, Weynand B, Cawthorne C, Vande Velde G, Wang Z, Neyts J, Dallmeier K. 2020. STAT2 signaling restricts viral dissemination but drives severe pneumonia in SARS-CoV-2 infected hamsters. Nat Commun 11(1):5838.

Boxx GM, Cheng G. 2016. The roles of type I interferon in bacterial infection. Cell Host Microbe 19(6):760–769.

Broggi A, Ghosh S, Sposito B, Spreafico R, Balzarini F, Cascio AL, Clementi N, Santis MD, Mancini N, Granucci F, Zanoni I. 2020. Type III interferons disrupt the lung epithelial barrier upon viral recognition. Science 369(6504): 706–712.

Cardoso PRG, de Andrade Lima EV, de Andrade Lima MM, de Melo Rêgo MJB, Marques CDL, da Rocha Pitta I, Duarte ALBP, da Rocha Pitta MG. 2016. Clinical and cytokine profile evaluation in Northeast Brazilian psoriasis plaque-type patients. Eur Cytokine Netw 27(1):1–5.

Cervantes J, Nagata T, Uchijima M, Shibata K, Koide Y. 2008. Intracytosolic Listeria monocytogenes induces cell death through caspase-1 activation in murine macrophages. Cell Microbiol 10(1):41–52.

Chan JF-W, Zhang AJ, Yuan S, Poon VK-M, Chan CC-S, Lee AC-Y, Chan W-M, Fan Z, Tsoi H-W, Wen L, Liang R, Cao J, Chen Y, Tang K, Luo C, Cai J-P, Kok K-H, Chu H, Chan K-H, Sridhar S, Chen Z, Chen H, To KK-W, Yuen K-Y. 2020. Simulation of the Clinical and pathological manifestations of coronavirus disease 2019 (COVID-19) in a golden syrian hamster model: implications for disease pathogenesis and transmissibility. Clin Infect Dis 71(9):2428–2446.

Chua RL, Lukassen S, Trump S, Hennig BP, Wendisch D, Pott F, Debnath O, Thürmann L, Kurth F, Völker MT, Kazmierski J, Timmermann B, Twardziok S, Schneider S, Machleidt F, Müller-Redetzky H, Maier M, Krannich A, Schmidt S, Balzer F, Liebig J, Loske J, Suttorp N, Eils J, Ishaque N, Liebert UG, von Kalle C, Hocke A, Witzenrath M, Goffinet C, Drosten C, Laudi S, Lehmann I, Conrad C, Sander LE, Eils R. 2020. COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis. Nat Biotechnol 38(8):970–979.

Clifford JL, Yang X, Walch E, Wang M, Lippman SM. 2003. Dominant negative signal transducer and activator of transcription 2 (STAT2) protein: stable expression blocks interferon alpha action in skin squamous cell carcinoma cells. Mol Cancer Ther 2(5):453–459.

Cohen TS, Prince AS. 2013. Bacterial pathogens activate a common inflammatory pathway through IFNλ regulation of PDCD4. PLoS Pathog 9(10):e1003682.

Conrady CD, Zheng M, Mandal NA, van Rooijen N, Carr DJJ. 2013. IFN-α-driven CCL2 production recruits inflammatory monocytes to infection site in mice. Mucosal Immunol 6(1): 45–55.

Crow YJ, Stetson DB. 2021. The type I interferonopathies: 10 years on. Nat Rev Immunol [Epub ahead of print]; DOI: 10.1038/s41577-021-00633-9.

Cui TX, Brady AE, Fulton CT, Zhang Y-J, Rosenbloom LM, Goldsmith AM, Moore BB, Popova AP. 2020. CCR2 mediates chronic LPS-induced pulmonary inflammation and hypoalveolarization in a murine model of bronchopulmonary dysplasia. Front Immunol 11:579628.

da Silva J, Hilzendeger C, Moermans C, Schleich F, Henket M, Kebadze T, Mallia P, Edwards MR, Johnston SL, Louis R. 2017. Raised interferon-β, type 3 interferon and interferon-stimulated genes–evidence of innate immune activation in neutrophilic asthma. Clin Exp Allergy 47(3):313–323.

Dejager L, Vandevyver S, Ballegeer M, Van Wonterghem E, An LL, Riggs J, Kolbeck R, Libert C. 2014. Pharmacological inhibition of type I interferon signaling protects mice against lethal sepsis. J Infect Dis 209(6):960–970.

Duncan CJA, Hambleton S. 2021. Human disease phenotypes associated with loss and gain of function mutations in STAT2: viral susceptibility and type I interferonopathy. J Clin Immunol 41(7):1446–1456.

Duncan CJA, Thompson BJ, Chen R, Rice GI, Gothe F, Young DF, Lovell SC, Shuttleworth VG, Brocklebank V, Corner B, Skelton AJ, Bondet V, Coxhead J, Duffy D, Fourrage C, Livingston JH, Pavaine J, Cheesman E, Bitetti S, Grainger A, Acres M, Innes BA, Mikulasova A, Sun R, Hussain R, Wright R, Wynn R, Zarhrate M, Zeef LAH, Wood K, Hughes SM, Harris CL, Engelhardt KR, Crow YJ, Randall RE, Kavanagh D, Hambleton S, Briggs TA. 2019. Severe type I interferonopathy and unrestrained interferon signaling due to a homozygous germline mutation in STAT2. Sci Immunol 4(42):eaav7501.

Eriksen KW, Lovato P, Skov L, Krejsgaard T, Kaltoft K, Geisler C, Ødum N. 2005. Increased sensitivity to interferon-α in psoriatic T cells. J Invest Dermatol 125(5):936–944.

Fodil N, Langlais D, Gros P. 2016. Primary immunodeficiencies and inflammatory disease: a growing genetic intersection. Trends Immunol 37(2):126–140.

Freij BJ, Hanrath AT, Chen R, Hambleton S, Duncan CJA. 2021. Life-threatening influenza, hemophagocytic lymphohistiocytosis and probable vaccine-strain varicella in a novel case of homozygous STAT2 deficiency. Front Immunol 11: 624415.

Friedrich M, Pohin M, Powrie F. 2019. Cytokine networks in the pathophysiology of inflammatory bowel disease. Immunity 50(4):992–1006.

Fu XY, Kessler DS, Veals SA, Levy DE, Darnell JE, Jr. 1990. ISGF3, the transcriptional activator induced by interferon alpha, consists of multiple interacting polypeptide chains. Proc Natl Acad Sci USA 87(21):8555–8559.

Fu XY, Schindler C, Improta T, Aebersold R, Darnell JE. 1992. The proteins of ISGF-3, the interferon alpha-induced transcriptional activator, define a gene family involved in signal transduction. Proc Natl Acad Sci USA 89(16):7840–7843.

Gamero AM, Young MR, Mentor-Marcel R, Bobe G, Scarzello AJ, Wise J, Colburn NH. 2010. STAT2 contributes to promotion of colorectal and skin carcinogenesis. Cancer Prev Res (Phila) 3(4):495–504.

Gopal R, Lee B, McHugh KJ, Rich HE, Ramanan K, Mandalapu S, Clay ME, Seger PJ, Enelow RI, Manni ML, Robinson KM, Rangel-Moreno J, Alcorn JF. 2018. STAT2 signaling regulates macrophage phenotype during influenza and bacterial super-infection. Front Immunol 9:2151.

Gothe F, Hatton CF, Truong L, Klimova Z, Kanderova V, Fejtkova M, Grainger A, Bigley V, Perthen J, Mitra D, Janda A, Fronkova E, Moravcikova D, Hambleton S, Duncan CJA. 2020. A novel case of homozygous interferon alpha/beta receptor alpha chain (IFNAR1) deficiency with hemophagocytic lymphohistiocytosis. Clini Infect Dis 74(1):136–139.

Gothe F, Stremenova Spegarova J, Hatton CF, Griffin H, Sargent T, Cowley SA, James W, Roppelt A, Shcherbina A, Hauck F, Reyburn HT, Duncan CJA, Hambleton S. 2022. Aberrant inflammatory responses to type I interferon in STAT2 or IRF9 deficiency. J Allergy Clin Immunol [Epub ahead of print]; DOI: 10.1016/j.jaci.2022.01.026.

Gruber C, Martin-Fernandez M, Ailal F, Qiu X, Taft J, Altman J, Rosain J, Buta S, Bousfiha A, Casanova J-L, Bustamante J, Bogunovic D. 2020. Homozygous STAT2 gain-of-function mutation by loss of USP18 activity in a patient with type I interferonopathy. J Exp Med 217(5):e20192319.

Günther C, Martini E, Wittkopf N, Amann K, Weigmann B, Neumann H, Waldner MJ, Hedrick SM, Tenzer S, Neurath MF, Becker C. 2011. Caspase-8 regulates TNF-α-induced epithelial necroptosis and terminal ileitis. Nature 477(7364): 335–339.

Günther C, Ruder B, Stolzer I, Dorner H, He G-W, Chiriac MT, Aden K, Strigli A, Bittel M, Zeissig S, Rosenstiel P, Atreya R, Neurath MF, Wirtz S, Becker C. 2019. Interferon lambda promotes paneth cell death via STAT1 signaling in mice and is increased in inflamed ileal tissues of patients with Crohn's disease. Gastroenterology 157(5):1310–1322.e13.

Gupta R, Debbaneh MG, Liao W. 2014. Genetic epidemiology of psoriasis. Curr Dermatol Rep 3(1):61–78.

Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, Péré H, Charbit B, Bondet V, Chenevier-Gobeaux C, Breillat P, Carlier N, Gauzit R, Morbieu C, Pène F, Marin N, Roche N, Szwebel T-A, Merkling SH, Treluyer J-M, Veyer D, Mouthon L, Blanc C, Tharaux P-L, Rozenberg F, Fischer A, Duffy D, Rieux-Laucat F, Kernéis S, Terrier B. 2020.

Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 369(6504): 718–724.

Hambleton S, Goodbourn S, Young DF, Dickinson P, Mohamad SMB, Valappil M, McGovern N, Cant AJ, Hackett SJ, Ghazal P, Morgan NV, Randall RE. 2013. STAT2 deficiency and susceptibility to viral illness in humans. Proc Natl Acad Sci USA 110(8):3053–3058.

Hamid Q, Tulic M. 2009. Immunobiology of asthma. Annu Rev Physiol 71:489–507.

Ho J, Pelzel C, Begitt A, Mee M, Elsheikha HM, Scott DJ, Vinkemeier U. 2016. STAT2 is a pervasive cytokine regulator due to its inhibition of STAT1 in multiple signaling pathways. PLoS Biol 14(10):e2000117.

Hofer MJ, Li W, Manders P, Terry R, Lim SL, King NJ, Campbell IL. 2012. Mice deficient in STAT1 but not STAT2 or IRF9 develop a lethal CD4+ T-cell-mediated disease following infection with lymphocytic choriomeningitis virus. J Virol 86(12):6932–6946.

Hos NJ, Ganesan R, Gutiérrez S, Hos D, Klimek J, Abdullah Z, Krönke M, Robinson N. 2017. Type I interferon enhances necroptosis of Salmonella Typhimurium–infected macrophages by impairing antioxidative stress responses. J Cell Biol 216(12):4107–4121.

Hsieh YY, Wan L, Chang CC, Tsai CH, Tsai FJ. 2009. STAT2*C related genotypes and allele but not TLR4 and CD40 gene polymorphisms are associated with higher susceptibility for asthma. Int J Biol Sci 5(1):74–81.

Hsu Y-L, Wang M-Y, Ho L-J, Lai J-H. 2016. Dengue virus infection induces interferon-lambda1 to facilitate cell migration. Sci Rep 6(1):24530.

Hu B, Guo H, Zhou P, Shi Z-L. 2021. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 19(3):141–154.

Huber JP, Ramos HJ, Gill MA, Farrar JD. 2010. Cutting edge: Type I IFN reverses human Th2 commitment and stability by suppressing GATA3. J Immunol 185(2):813–817.

Huys L, Van Hauwermeiren F, Dejager L, Dejonckheere E, Lienenklaus S, Weiss S, Leclercq G, Libert C. 2009. Type I interferon drives tumor necrosis factor–induced lethal shock. J Exp Med 206(9):1873–1882.

Johansen C, Rittig AH, Mose M, Bertelsen T, Weimar I, Nielsen J, Andersen T, Rasmussen TK, Deleuran B, Iversen L. 2017. STAT2 is involved in the pathogenesis of psoriasis by promoting CXCL11 and CCL5 production by keratinocytes. PLoS One 12(5):e0176994.

Johnson DE, O'Keefe RA, Grandis JR. 2018. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol 15(4):234–248.

Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, Toole SO, Myint SH, Tyrrell DAJ, Holgate ST. 1995. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ 310(6989):1225–1229.

Jordan W, Eskdale J, Srinivas S, Pekarek V, Kelner D, Rodia M, Gallagher G. 2007. Human interferon lambda-1 (IFN-λ1/IL-29) modulates the Th1/Th2 response. Genes Immunity 8(3):254–261.

Kamezaki K, Shimoda K, Numata A, Matsuda T, Nakayama K, Harada M. 2004. The role of Tyk2, Stat1 and Stat4 in LPS-induced endotoxin signals. Int Immunol 16(8):1173–1179.

Karaghiosoff M, Steinborn R, Kovarik P, Kriegshäuser G, Baccarini M, Donabauer B, Reichart U, Kolbe T, Bogdan C, Leanderson T, Levy D, Decker T, Müller M. 2003. Central role for type I interferons and Tyk2 in lipopolysaccharide-induced endotoxin shock. Nat Immunol 4(5):471–477.

Korman BD, Kastner DL, Gregersen PK, Remmers EF. 2008. STAT4: genetics, mechanisms, and implications for autoimmunity. Curr Allergy Asthma Rep 8(5):398–403.

Kotenko SV, Durbin JE. 2017. Contribution of type III interferons to antiviral immunity: location, location, location. J Biol Chem 292(18):7295–7303.

Kovarik P, Castiglia V, Ivin M, Ebner F. 2016. Type I interferons in bacterial infections: a balancing act. Front Immunol 7:652.

Krug J, Kiefer A, Koelle J, Vuorinen T, Xepapadaki P, Stanic B, Chiriac MT, Akdis M, Zimmermann T, Papadopoulos NG, Finotto S. 2021. TLR7/8 regulates type I and type III interferon signalling in rhinovirus 1b-induced allergic asthma. Eur Respir J 57(5):2001562.

Kudva A, Scheller EV, Robinson KM, Crowe CR, Choi SM, Slight SR, Khader SA, Dubin PJ, Enelow RI, Kolls JK, Alcorn JF. 2011. Influenza a inhibits Th17-mediated host defense against bacterial pneumonia in mice. J Immunol 186(3): 1666–1674.

Le-Trilling VTK, Wohlgemuth K, Rückborn MU, Jagnjic A, Maaßen F, Timmer L, Katschinski B, Trilling M, Jung JU. 2018. STAT2-dependent immune responses ensure host survival despite the presence of a potent viral antagonist. J Virol 92(14):e00296-18.

Lebreton A, Lakisic G, Job V, Fritsch L, Tham TN, Camejo A, Matteï P-J, Regnault B, Nahori M-A, Cabanes D, Gautreau A, Ait-Si-Ali S, Dessen A, Cossart P, Bierne H. 2011. A bacterial protein targets the BAHD1 chromatin complex to stimulate type III interferon response. Science 331(6022): 1319–1321.

Lee B, Robinson KM, McHugh KJ, Scheller EV, Mandalapu S, Chen C, Di YP, Clay ME, Enelow RI, Dubin PJ, Alcorn JF. 2015. Influenza-induced type I interferon enhances susceptibility to gram-negative and gram-positive bacterial pneumonia in mice. Am J Physiol Lung Cell Mol Physiol 309(2): L158–L167.

Leung S, Qureshi SA, Kerr IM, Darnell JE, Jr., Stark GR. 1995. Role of STAT2 in the alpha interferon signaling pathway. Mol Cell Biol 15(3):1312–1317.

Li S-X, Yan W, Liu J-P, Zhao Y-J, Chen L. 2021. Long noncoding RNA SNHG4 remits lipopolysaccharide-engendered inflammatory lung damage by inhibiting METTL3–Mediated m6A level of STAT2 mRNA. Mol Immunol 139:10–22.

Li W, Hofer MJ, Jung SR, Lim S-L, Campbell IL. 2014a. IRF7-dependent type I interferon production induces lethal immune-mediated disease in STAT1 knockout mice infected with lymphocytic choriomeningitis virus. J Virol 88(13): 7578–7588.

Li W, Moltedo B, Moran TM. 2012. Type I interferon induction during influenza virus infection increases susceptibility to secondary *Streptococcus pneumoniae* infection by negative regulation of γδ T Cells. J Virol 86(22):12304–12312.

Li Y, Gao Q, Yuan X, Zhou M, Peng X, Liu X, Zheng X, Xu D, Li M. 2014b. Adenovirus expressing IFN-λ1 (IL-29) attenuates allergic airway inflammation and airway hyperreactivity in experimental asthma. Int Immunopharmacol 21(1): 156–162.

Litonjua AA, Tantisira KG, Lake S, Lazarus R, Richter BG, Gabriel S, Silverman ES, Weiss ST. 2005. Polymorphisms in signal transducer and activator of transcription 3 and lung function in asthma. Respir Res 6(1):52.

Lukacikova L, Oveckova I, Betakova T, Laposova K, Polcicova K, Pastorekova S, Pastorek J, Tomaskova J. 2015. Antiviral effect of interferon lambda against lymphocytic choriomeningitis virus. J Interferon Cytokine Res 35(7):540–553.

Major J, Crotta S, Llorian M, McCabe TM, Gad HH, Priestnall SL, Hartmann R, Wack A. 2020. Type I and III interferons disrupt lung epithelial repair during recovery from viral infection. Science 369(6504):712–717.

Marcellini A, Swieboda D, Guedan A, Farrow SN, Casolari P, Contoli M, Johnston SL, Papi A, Solari R. 2021. Glucocorticoids impair type I IFN signalling and enhance rhinovirus replication. Eur J Pharmacol 893:173839.

Martinez-Moczygemba M, Gutch MJ, French DL, Reich NC. 1997. Distinct STAT Structure Promotes Interaction of STAT2 with the p48 Subunit of the Interferon-α-stimulated Transcription Factor ISGF3*. J Biol Chem 272(32):20070–20076.

Mavragani CP, Nezos A, Dovrolis N, Andreou NP, Legaki E, Sechi LA, Bamias G, Gazouli M. 2020. Type I and II interferon signatures can predict the response to Anti-TNF agents in inflammatory bowel disease patients: involvement of the microbiota. Inflamm Bowel Dis 26(10):1543–1553.

McComb S, Cessford E, Alturki NA, Joseph J, Shutinoski B, Startek JB, Gamero AM, Mossman KL, Sad S. 2014. Type-I interferon signaling through ISGF3 complex is required for sustained Rip3 activation and necroptosis in macrophages. Proc Natl Acad Sci USA 111(31):E3206–E3213.

McElrath C, Espinosa V, Lin J-D, Peng J, Sridhar R, Dutta O, Tseng H-C, Smirnov SV, Risman H, Sandoval MJ, Davra V, Chang Y-J, Pollack BP, Birge RB, Galan M, Rivera A, Durbin JE, Kotenko SV. 2021. Critical role of interferons in gastrointestinal injury repair. Nat Commun 12(1):2624.

Morens DM, Taubenberger JK, Fauci AS. 2008. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis 198(7):962–970.

Mudter J, Weigmann B, Bartsch B, Kiesslich R, Strand D, Galle PR, Lehr HA, Schmidt J, Neurath MF. 2005. Activation pattern of signal transducers and activators of transcription (STAT) factors in inflammatory bowel diseases. Am J Gastroenterol 100(1):64–72.

Musch E, Andus T, Malek M. 2002. Induction and maintenance of clinical remission by interferon-β in patients with steroid-refractory active ulcerative colitis—an open long-term pilot trial. Aliment Pharmacol Ther 16(7):1233–1239.

Nan J, Wang Y, Yang J, Stark GR. 2018. IRF9 and unphosphorylated STAT2 cooperate with NF-kappaB to drive IL6 expression. Proc Natl Acad Sci U S A 115(15):3906–3911.

Nograles KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suárez-Fariñas M, Cardinale I, Khatcherian A, Gonzalez J, Pierson KC, White TR, Pensabene C, Coats I, Novitskaya I, Lowes MA, Krueger JG. 2008. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. Br J Dermatol 159(5):1092–1102.

O'Connell RM, Saha SK, Vaidya SA, Bruhn KW, Miranda GA, Zarnegar B, Perry AK, Nguyen BO, Lane TF, Taniguchi T, Miller JF, Cheng G. 2004. Type I interferon production enhances susceptibility to listeria monocytogenes infection. J Exp Med 200(4):437–445.

Odendall C, Voak AA, Kagan JC. 2017. Type III IFNs are commonly induced by bacteria-sensing TLRs and reinforce epithelial barriers during infection. J Immunol (Baltimore, MD.: 1950) 199(9):3270–3279.

Onabajo OO, Banday AR, Stanifer ML, Yan W, Obajemu A, Santer DM, Florez-Vargas O, Piontkivska H, Vargas JM, Ring TJ, Kee C, Doldan P, Tyrrell DL, Mendoza JL, Boulant S, Prokunina-Olsson L. 2020. Interferons and viruses induce a novel truncated ACE2 isoform and not the full-length SARS-CoV-2 receptor. Nat Genet 52(12):1283–1293.

Ou R, Zhou S, Huang L, Moskophidis D. 2001. Critical role for alpha/beta and gamma interferons in persistence of lymphocytic choriomeningitis virus by clonal exhaustion of cytotoxic T cells. J Virol 75(18):8407–8423.

Palma-Ocampo HK, Flores-Alonso JC, Vallejo-Ruiz V, Reyes-Leyva J, Flores-Mendoza L, Herrera-Camacho I, Rosas-Murrieta NH, Santos-López G. 2015. Interferon lambda inhibits dengue virus replication in epithelial cells. Virol J 12(1):150.

Park C, Li S, Cha E, Schindler C. 2000. Immune response in Stat2 knockout mice. Immunity 13(6):795–804.

Pasquali L, Srivastava A, Meisgen F, Das Mahapatra K, Xia P, Xu Landen N, Pivarcsi A, Sonkoly E. 2019. The keratinocyte transcriptome in psoriasis: pathways related to immune responses, cell cycle and keratinization. Acta Derm Venereol 99(2):196–205.

Pena Rossi C, Hanauer SB, Tomasevic R, Hunter JO, Shafran I, Graffner H. 2009. Interferon beta-1a for the maintenance of remission in patients with Crohn's disease: results of a phase II dose-finding study. BMC Gastroenterol 9(1):22.

Perry ST, Buck MD, Lada SM, Schindler C, Shresta S. 2011. STAT2 mediates innate immunity to dengue virus in the absence of STAT1 via the type I interferon receptor. PLoS Pathog 7(2):e1001297.

Pestka S, Krause CD, Walter MR. 2004. Interferons, interferon-like cytokines, and their receptors. Immunol Rev 202:8–32.

Planet PJ, Parker D, Cohen TS, Smith H, Leon JD, Ryan C, Hammer TJ, Fierer N, Chen EI, Prince AS. 2016. Lambda interferon restructures the nasal microbiome and increases susceptibility to *Staphylococcus aureus* superinfection. mBio 7(1):e01939-15.

Platanitis E, Demiroz D, Schneller A, Fischer K, Capelle C, Hartl M, Gossenreiter T, Müller M, Novatchkova M, Decker T. 2019. A molecular switch from STAT2-IRF9 to ISGF3 underlies interferon-induced gene transcription. Nat Commun 10(1):2921.

Qian X, Gao Y, Ye X, Lu M. 2014. Association of STAT6 variants with asthma risk: a systematic review and meta-analysis. Hum Immunol 75(8):847–853.

Qureshi SA, Leung S, Kerr IM, Stark GR, Darnell JE, Jr. 1996. Function of Stat2 protein in transcriptional activation by alpha interferon. Mol Cell Biol 16(1):288–293.

Rahmati S, Tsoi L, O'Rielly D, Chandran V, Rahman P. 2020. Complexities in genetics of psoriatic arthritis. Curr Rheumatol Rep 22(4):10.

Rauch I, Hainzl E, Rosebrock F, Heider S, Schwab C, Berry D, Stoiber D, Wagner M, Schleper C, Loy A, Urich T, Müller M, Strobl B, Kenner L, Decker T. 2014. Type I interferons have opposing effects during the emergence and recovery phases of colitis. Eur J Immunol 44(9):2749–2760.

Rauch I, Rosebrock F, Hainzl E, Heider S, Majoros A, Wienerroither S, Strobl B, Stockinger S, Kenner L, Müller M, Decker T. 2015. Noncanonical effects of IRF9 in intestinal inflammation: more than type I and type III interferons. Mol Cell Biol 35(13):2332–2343.

Rayamajhi M, Humann J, Penheiter K, Andreasen K, Lenz LL. 2010. Induction of IFN-alphabeta enables Listeria monocytogenes to suppress macrophage activation by IFN-gamma. J Exp Med 207(2):327–337.

Rich HE, McCourt CC, Zheng WQ, McHugh KJ, Robinson KM, Wang J, Alcorn JF, Bäumler AJ. 2019. Interferon lambda inhibits bacterial uptake during influenza superinfection. Infect Immunity 87(5):e00114-19.

Rivera-Chávez F, Zhang Lillian F, Faber F, Lopez Christopher A, Byndloss Mariana X, Olsan Erin E, Xu G, Velazquez Eric M, Lebrilla Carlito B, Winter Sebastian E, Bäumler Andreas

J. 2016. Depletion of butyrate-producing clostridia from the gut microbiota drives an aerobic luminal expansion of salmonella. Cell Host Microbe 19(4):443–454.

Robinson N, McComb S, Mulligan R, Dudani R, Krishnan L, Sad S. 2012. Type I interferon induces necroptosis in macrophages during infection with *Salmonella enterica* serovar Typhimurium. Nat Immunol 13(10):954–962.

Rosado FG, Kim AS. 2013. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. Am J Clin Pathol 139(6):713–727.

Salka K, Abutaleb K, Chorvinsky E, Thiruvengadam G, Arroyo M, Gomez JL, Gutierrez MJ, Pillai DK, Jaiswal JK, Nino G. 2021. IFN stimulates ACE2 expression in pediatric airway epithelial cells. Am J Respir Cell Mol Biol 64(4):515–518.

Schindler C, Shuai K, Prezioso VR, Darnell JE. 1992. Interferon-dependent tyrosine phosphorylation of a latent cytoplasmic transcription factor. Science 257(5071):809–813.

Shaabani N, Vartabedian VF, Nguyen N, Honke N, Huang Z, Teijaro JR. 2021. IFN-beta, but not IFN-alpha, is responsible for the pro-bacterial effect of type I interferon. Cell Physiol Biochem 55(3):256–264.

Shafran N, Shafran I, Ben-Zvi H, Sofer S, Sheena L, Krause I, Shlomai A, Goldberg E, Sklan EH. 2021. Secondary bacterial infection in COVID-19 patients is a stronger predictor for death compared to influenza patients. Sci Rep 11(1): 12703.

Shepardson KM, Larson K, Johns LL, Stanek K, Cho H, Wellham J, Henderson H, Rynda-Apple A. 2018. IFNAR2 is required for anti-influenza immunity and alters susceptibility to post-influenza bacterial superinfections. Front Immunol 9: 2589.

Shepardson KM, Larson K, Morton RV, Prigge JR, Schmidt EE, Huber VC, Rynda-Apple A. 2016. Differential type I interferon signaling is a master regulator of susceptibility to postinfluenza bacterial superinfection. mBio 7(3):e00506-16.

Steen HC, Gamero AM. 2013. STAT2 phosphorylation and signaling. JAKSTAT 2(4):e25790.

Steen HC, Kotredes KP, Nogusa S, Harris MY, Balachandran S, Gamero AM. 2016. Phosphorylation of STAT2 on serine-734 negatively regulates the IFN-α-induced antiviral response. J Cell Sci 129(22):4190–4199.

Steen HC, Nogusa S, Thapa RJ, Basagoudanavar SH, Gill AL, Merali S, Barrero CA, Balachandran S, Gamero AM. 2013. Identification of STAT2 serine 287 as a novel regulatory phosphorylation site in type I interferon-induced cellular responses. J Biol Chem 288(1):747–758.

Stockinger S, Materna T, Stoiber D, Bayr L, Steinborn R, Kolbe T, Unger H, Chakraborty T, Levy DE, Müller M, Decker T. 2002. Production of type I IFN sensitizes macrophages to cell death induced by Listeria monocytogenes. J Immunol 169(11):6522–6529.

Stolzer I, Dressel A, Chiriac MT, Neurath MF, Günther C. 2021. An IFN-STAT axis augments tissue damage and inflammation in a mouse model of Crohn's disease. Front Med (Lausanne) 8:644244.

Tavares LP, Teixeira MM, Garcia CC. 2017. The inflammatory response triggered by Influenza virus: a two edged sword. Inflamm Res 66(4):283–302.

Teijaro JR, Ng C, Lee AM, Sullivan BM, Sheehan KCF, Welch M, Schreiber RD, de la Torre JC, Oldstone MBA. 2013. Persistent LCMV infection is controlled by blockade of type I interferon signaling. Science (New York, N.Y.) 340(6129): 207–211.

Testoni B, Vollenkle C, Guerrieri F, Gerbal-Chaloin S, Blandino G, Levrero M. 2011. Chromatin dynamics of gene activation and repression in response to interferon alpha (IFN(alpha)) reveal new roles for phosphorylated and unphosphorylated forms of the transcription factor STAT2. J Biol Chem 286(23):20217–20227.

Toyoshima Y, Kitamura H, Xiang H, Ohno Y, Homma S, Kawamura H, Takahashi N, Kamiyama T, Tanino M, Taketomi A. 2019. IL6 modulates the immune status of the tumor microenvironment to facilitate metastatic colonization of colorectal cancer cells. Cancer Immunol Res 7(12):1944–1957.

Wallace JW, Constant DA, Nice TJ. 2021. Interferon lambda in the pathogenesis of inflammatory bowel diseases. Front Immunol 12:767505.

Wang J, Pham-Mitchell N, Schindler C, Campbell IL. 2003. Dysregulated Sonic hedgehog signaling and medulloblastoma consequent to IFN-{alpha}-stimulated STAT2-independent production of IFN-{gamma} in the brain. J Clin Invest 112(4):535–543.

Wang W, Yin Y, Xu L, Su J, Huang F, Wang Y, Boor PPC, Chen K, Wang W, Cao W, Zhou X, Liu P, van der Laan LJW, Kwekkeboom J, Peppelenbosch MP, Pan Q. 2017a. Unphosphorylated ISGF3 drives constitutive expression of interferon-stimulated genes to protect against viral infections. Sci Signal 10(476):eaah4248.

Wang Y, Nan J, Willard B, Wang X, Yang J, Stark GR. 2017b. Negative regulation of type I IFN signaling by phosphorylation of STAT2 on T387. EMBO J 36(2):202–212.

Wang Y, Song Q, Huang W, Lin Y, Wang X, Wang C, Willard B, Zhao C, Nan J, Holvey-Bates E, Wang Z, Taylor D, Yang J, Stark GR. 2021. A virus-induced conformational switch of STAT1-STAT2 dimers boosts antiviral defenses. Cell Res 31(2):206–218.

Warnking K, Klemm C, Löffler B, Niemann S, van Krüchten A, Peters G, Ludwig S, Ehrhardt C. 2015. Super-infection with *Staphylococcus aureus* inhibits influenza virus-induced type I IFN signalling through impaired STAT1-STAT2 dimerization. Cell Microbiol 17(3):303–317.

Wilson RP, Tursi SA, Rapsinski GJ, Medeiros NJ, Le LS, Kotredes KP, Patel S, Liverani E, Sun S, Zhu W, Kilpatrick L, Winter SE, Gamero AM, Tükel Ç. 2019. STAT2 dependent type I interferon response promotes dysbiosis and luminal expansion of the enteric pathogen Salmonella Typhimurium. PLoS Pathog 15(4):e1007745.

Witte E, Kokolakis G, Witte K, Warszawska K, Friedrich M, Christou D, Kirsch S, Sterry W, Volk HD, Sabat R, Wolk K. 2016. Interleukin-29 induces epithelial production of CXCR3A ligands and T-cell infiltration. J Mol Med (Berl) 94(4):391–400.

Wolk K, Witte K, Witte E, Raftery M, Kokolakis G, Philipp S, Schönrich G, Warszawska K, Kirsch S, Prösch S, Sterry W, Volk H-D, Sabat R. 2013. IL-29 is produced by Th17 cells and mediates the cutaneous antiviral competence in psoriasis. Sci Transl Med 5(204):204ra129.

Xu P, Becker H, Elizalde M, Pierik M, Masclee A, Jonkers D. 2021. Interleukin-28A induces epithelial barrier dysfunction in CD patient-derived intestinal organoids. Am J Physiol Gastrointest Liver Physiol 320(5):G689–G699.

Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang F-S. 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 8(4):420–422.

Yin X, Low HQ, Wang L, Li Y, Ellinghaus E, Han J, Estivill X, Sun L, Zuo X, Shen C, Zhu C, Zhang A, Sanchez F, Padyukov L, Catanese JJ, Krueger GG, Duffin KC, Mucha S, Weichenthal M, Weidinger S, Lieb W, Foo JN, Li Y, Sim K, Liany H, Irwan I, Teo Y, Theng CT, Gupta R, Bowcock A, De Jager PL, Qureshi AA, de Bakker PI, Seielstad M, Liao W, Stahle M, Franke A, Zhang X, Liu J. 2015. Genome-wide meta-analysis identifies multiple novel associations and ethnic heterogeneity of psoriasis susceptibility. Nat Commun 6: 6916.

Yu W, Wang X, Zhao J, Liu R, Liu J, Wang Z, Peng J, Wu H, Zhang X, Long Z, Kong D, Li W, Hai C. 2020. Stat2-Drp1 mediated mitochondrial mass increase is necessary for pro-inflammatory differentiation of macrophages. Redox Biol 37: 101761.

Yue C, Xu J, Tan Estioko MD, Kotredes KP, Lopez-Otalora Y, Hilliard BA, Baker DP, Gallucci S, Gamero AM. 2015. Host STAT2/type I interferon axis controls tumor growth. Int J Cancer 136(1):117–126.

Zhang H, Zoued A, Liu X, Sit B, Waldor MK. 2020. Type I interferon remodels lysosome function and modifies intestinal epithelial defense. Proc Natl Acad Sci USA 117(47):29862–29871.

Zhang J, Zhao C, Zhao W. 2021. Virus caused imbalance of type I IFN responses and inflammation in COVID-19. Front Immunol 12:633769.

Zhao W, Cha EN, Lee C, Park CY, Schindler C. 2007. Stat2-dependent regulation of MHC class II expression. J Immunol 179(1):463–471.

Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, Cao Y, Yousif AS, Bals J, Hauser BM, Feldman J, Muus C, Wadsworth MH, 2nd, Kazer SW, Hughes TK, Doran B, Gatter GJ, Vukovic M, Taliaferro F, Mead BE, Guo Z, Wang JP, Gras D, Plaisant M, Ansari M, Angelidis I, Adler H, Sucre JMS, Taylor CJ, Lin B, Waghray A, Mitsialis V, Dwyer DF, Buchheit KM, Boyce JA, Barrett NA, Laidlaw TM, Carroll SL, Colonna L, Tkachev V, Peterson CW, Yu A, Zheng HB, Gideon HP, Winchell CG, Lin PL, Bingle CD, Snapper SB, Kropski JA, Theis FJ, Schiller HB, Zaragosi L-E, Barbry P, Leslie A, Kiem H-P, Flynn JL, Fortune SM, Berger B, Finberg RW, Kean LS, Garber M, Schmidt AG, Lingwood D, Shalek AK, Ordovas-Montanes J, lung-network@humancellatlas.org HCALBNEa, Network HCALB. 2020. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell 181(5): 1016–1035.e19.

Zimmermann A, Trilling M, Wagner M, Wilborn M, Bubic I, Jonjic S, Koszinowski U, Hengel H. 2005. A cytomegaloviral protein reveals a dual role for STAT2 in IFN-γ signaling and antiviral responses. J Exp Med 201(10):1543–1553.

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