

Inflammatory bowel disease pathobiology: the role of the interferon signature

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Abstract

The pathogenesis of inflammatory bowel disease (IBD) is still unclear, but includes both inflammatory and autoimmune reactions. Current methodological approaches could better elucidate the cytokine pathways and the genetics involved in the etiopathogenesis of this disease. Interferons (IFNs) are cytokines that play a key role in autoimmune/inflammatory disorders because of their pro- and anti-inflammatory properties as well as their immunoregulatory functions. An increased expression of IFN-regulated genes, widely known as an IFN signature, has been reported in blood and tissue from patients with autoimmune disorders. In this review, we present the function as well as the clinical and therapeutic potential of the IFN signature. Current data demonstrate that the IFN signature can be used as a biomarker that defines disease activity in autoimmune diseases, although this has not been thoroughly studied in IBD. Consequently, further investigation of the IFN signature in IBD would be essential for a better understanding of its actions.

Keywords Inflammatory bowel disease, interferon, interferon signature

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Inflammatory bowel disease (IBD)

IBD, including Crohn's disease (CD) and ulcerative colitis (UC), is a complicated, chronic, relapsing and heterogeneous disease induced by environmental, genomic, microbial, and immunological factors [1]. CD is a debilitating and incurable chronic idiopathic inflammatory disease of the intestine and is showing an increasing incidence in developing countries [2]. CD is characterized by ulceration and inflammation of the intestinal mucosa, which may affect the whole gastrointestinal tract, but mainly the distal small intestine. Typical characteristics of CD include discontinuous, transmural inflammation of the bowel wall, and the presence of granulomas, fistulas, strictures, and lymphoid aggregates [3]. UC is a chronic, idiopathic inflammatory disease that affects the colon. It is characterized by relapsing and remitting mucosal inflammation, starting in the rectum and extending to proximal segments of the colon.

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UC is limited to the colon and only affects its innermost lining, while CD can develop anywhere in the gastrointestinal tract in all the layers of the bowel walls [4].

IBD therapy aims to induce and maintain clinical and endoscopic remission. Current treatments include aminosalicylate drugs and antibiotics for mild-to-moderate IBD, conventional anti-inflammatory agents (corticosteroids), immunosuppressants (thiopurines and methotrexate) and biologic therapy for moderate-to-severe disease. Recent data, however, suggest that the early initiation of more aggressive treatment, such as biologic therapy, can modify disease progression and may lead to less damage. Immunomodulatory drugs are often used in combination with biologics in IBD patients with severe disease for the maintenance of remission [5]. Apart from these well-studied treatments, systemic administration of type I interferon (IFN), e.g., IFN- α , IFN- β) in IBD patients has been evaluated for the suppression of disease burden, with controversial results. Immunoregulatory therapy with IFN type I can inhibit production of tumor necrosis factor (TNF) and IFN- γ , antagonize the IFN- γ signaling pathway, and increase production of the anti-inflammatory cytokine interleukin (IL)-10 [6,7]. IFN- β also has an immunoregulatory action by enhancing regulatory T-lymphocyte and natural killer-cell activity [8,9].

IBD and immunity

IBD is characterized as an immune-mediated disease, although it still remains unknown whether this autoimmunity

has a direct pathogenic effect in CD or in UC, despite the presence of autoantibodies that react to bacterial antigens [10].

Innate immunity

The role of innate immunity in the pathogenesis of IBD has been described since the discovery of mutations in the *NOD2/CARD15* gene. The *NOD2/CARD15* gene is an intracellular bacterial sensor, with reduced expression in the presence of the 3020insC mutation, leading to a vulnerability to bacterial infections in IBD [11]. *NOD2/CARD15* mutations result in reduced α -defensin expression. On the other hand, β -defensin levels are increased as a result of enteric inflammation; this is not the case for CD regarding HBD-2 and HBD-3 [12,13]. The combination of *NOD2* mutations and the decreased defensin expression may lead to defective resistance against intestinal microorganisms and might result in inflammation of the mucosa [14].

Toll-like receptors (TLRs) also have an important role in innate immunity, through their ability to detect both normal and pathological microbes and to regulate the host's antimicrobial response [15]. Abnormal TLR expression or function has been implicated in the development or persistence of intestinal inflammation. TLR4 has been found to be upregulated in CD epithelial cells, while TLR3 is downregulated [16]. TLR4 and TLR9 polymorphisms have also been reported in IBD, but their functional significance is poorly understood [17,18].

Because of the involvement of both *NOD2* and TLRs in the recognition of and response to bacteria, they may have a reciprocal interaction that could be dysfunctional in IBD. Macrophages homozygous for *NOD2* mutations in CD patients show defective production of IL-1 and IL-8 when stimulated with muramyl dipeptide (MDP) or TNF- α [19]. In addition, peripheral blood mononuclear cells from double-mutant patients failed to interact with MDP and TLR ligands, leading to increased TNF- α and IL-1 β production [20]. In this way, the generalized inability of the innate immune response to control via pattern recognition receptors may contribute to IBD, particularly to CD [14].

Adaptive immunity

IBD is characterized by increased production of systemic and mucosal antibodies and an altered amount of immunoglobulin classes and subclasses due to the chronic inflammation of the intestine [21-23]. Additionally, IgG1 antibodies against epithelial cells in the colon are highly produced in UC, but not in CD, possibly demonstrating an autoimmune pathway in this case [24]. Lately, adaptive immunity in IBD has been focused on the subsets of T-helper (Th) cells (a lymphocyte subtype) and their soluble regulators, which are important elements of immune responses [25]. They are involved in the activation of other cells of the immune system and determine the specificity of antibodies secreted by B-cells [26]. Following proliferation, a Th cell is differentiated into Th1, Th2, or Th17 [27]. Th1 cells

mediate the production of proinflammatory cytokines, such as IFN- γ , TNF- α , and IL-12, whereas Th2 cells lead to the production of anti-inflammatory cytokines, including IL-4, IL-5, IL-6, and IL-10, which constitute the humoral immune response. There is an interaction between Th1 and Th2 lymphocytes. Th1 cytokines lead to the production of Th1 cells and inhibit Th2 cells. Conversely, Th2 cytokines lead to the production of Th2 cells and inhibit Th1 cells. In healthy individuals, there is an equilibrium between the quantities of Th1 and Th2 cells. The development of immune-mediated disorders such as CD is closely linked to a type 1 immune response causing chronic inflammation of the intestine. CD is characterized by the accumulation of Th1 cells and UC by the accumulation of Th2 cells [28]. The most recent class of Th cells to be revealed is Th17 cells, differentiated in the presence of IL-6, IL-1 β , IL-21, and IL-23 [29], and may secrete IL-17A, IL-17F, IL-21, IL-22, IL-26, and chemokine CCL20 [30]. The inflamed mucosa of CD patients is characterized by a multi-complex communication network between cytokines, responsible for the changes that occur in immune level [31]. An example of this complicated, unstable process has been described in CD, with the transition from the Th1 response to a mixed phenotype of Th1/Th17 [32].

A great number of types of cytokine dysregulation have been described, in which proinflammatory and immunoregulatory molecules are included [25]. In CD patients, intestinal CD4+ T cells produce increased numbers of IFN- γ , while the transcription factor of Th1 cells, T-bet, is also overexpressed [33]. Mucosal macrophages also produce remarkable levels of IL-12 and IL-18 [34,35]. Regarding UC, different immunological abnormalities have been observed, where natural killer T (NKT) cells produce large amounts of IL-13, and T cells of mucosa produce more IL-15, proliferate less and die more than healthy cells [36].

Genetics

Genome-wide association studies (GWAS) have been crucial in the recognition of over 230 disease loci linked to IBD [37]. The most strongly and consistently implicated loci are associated with intracellular bacteria killing, innate (*CARD15/NOD2*, *IRGM*, *IL-23R*, *LRRK2*, and *ATG16L1*) and adaptive immune responses (IL-23), and the Th17 cell pathway (*IL-23R*, *IL-12B*, *STAT3*, *JAK2*, and *TYK2*) [38]. Dendritic cells (DCs) followed by CD4 T, natural killer (NK), and NKT cells showed the highest enrichment of these susceptibility gene sets when tested in a panel of immune cell subsets, indicating a major role for these cells in CD pathogenesis [39].

Most of the loci are common for IBD, although some of them are unique for either CD or UC. NOD-like receptors (*NOD2*), autophagy genes (*ATG16L1*, *IRGM*) and intelectins (*ITLN1*) present high specificity for CD. Considering UC, gene loci involved in regulatory pathways, such as IL-10 and ARPC2, and in intestinal epithelial cell function, such as ECM1 and E3 ubiquitin ligase, seem to be disease-specific. Furthermore, the association of the human leukocyte antigen/major

histocompatibility complex region appears to be stronger with UC rather than CD, a genetic feature of IBD shared with several autoimmune diseases [40-42].

GWAS and the meta-analysis of loci have been crucial in the specification of over 230 genetic susceptibility loci linked to IBD [37]; some of these genes are involved in immunity and in barrier function [39]. Various single-nucleotide polymorphisms (SNPs) have been found in genes related to pathogenic cytokine pathways, for example the Th17/IL-23 pathway, IL-10 pathway, and type I IFN signaling [43]. The relevant pathways could not be precisely determined only from the genetic data, as most of the signaling mediators are shared between different cytokine signaling cascades.

Many of the IBD-associated genes are involved in the type I IFN signaling pathway. The rs2284553 SNP is associated with the *IFNGR2* gene and with the *IFNAR1*. SNPs in *JAK2*, *TYK2*, *STAT1* and *STAT3* genes affect the JAK/STAT signaling pathway, deregulating the action of several cytokines, such as IL-22, IL-10, and type I and type III IFN [39]. Moreover, *MDA5* or *IRF4* gene polymorphisms can modulate the production of type I and type III IFN [39]. Although studies in mice show that minor alterations in type I IFN may contribute to the imbalance of the immune response in the *lamina propria*, the exact role of type I IFN in IBD pathology remains unclear [44].

IFNs

IFNs are cytokines that have antiviral activity. They are classified into 3 categories: type I IFNs (IFN- α , IFN- β and other less explored members), type II IFNs (IFN- γ), and type III IFNs (IFN- λ 1, IFN- λ 2, IFN- λ 3 and IFN- λ 4 in humans) [45,46].

The type I multigene family consists of structurally related IFNs, such as IFN- α , IFN- β , IFN- ω , IFN- ϵ , IFN- κ , IFN- δ , IFN- ζ , and IFN- τ . [45]. The best-studied type I IFN is the IFN- α family, which is encoded by 13 homologous genes [47]. These cytokines are produced after the stimulation of pattern-recognition receptors, as part of the innate immune antiviral response [48]. Data indicate that the initial production of IFN- β and IFN- α 4 is dependent upon IRF3 phosphorylation and NF- κ B activation [49]. The primary wave of type I IFN then induces IRF7 phosphorylation, leading to a positive feedback loop to increase the release of type I IFN [50].

Type II IFN (also known as IFN- γ), is predominantly produced by NK and NKT cells, as well as by CD4 and CD8 T-lymphocytes. Along with its antiviral activity, IFN- γ also acts against intracellular bacterial infections and tumor progression [51]. There is also evidence to show that type I IFN, IL-12, IL-15 and IL-18 are able to induce production of IFN- γ by NK cells [52].

Type III IFNs are more similar in structure to the IL-10 family than to the other IFN subgroups, but functionally they are similar to type I and type II IFN, as they also contribute to antiviral responses and induce the activation of many common genes [53].

All type I IFN members bind to the same heterodimer, expressed on most cells: the type I IFN receptor (IFNAR).

IFNAR is composed of two subunits, IFNAR1 and IFNAR2 [47]. These receptors are endocytosed and activate their related tyrosine kinases, tyrosine kinase 2 (Tyk2) and Janus kinase 1 (JAK1), when bound to IFN type I [54]. The typical signaling cascade results in the phosphorylation of STAT1 and STAT2, which form a complex with IRF9, known as the IFN-stimulated gene factor 3 (ISGF3), leading to the expression of IFN-stimulated genes [54]. Apart from ISGF3, type I IFNs can induce phosphorylation and dimerization of STAT3, STAT4, STAT5 and STAT6 and activate Rap1, CrkL, Map kinases, IRS-1, IRS-2, Vav, RAC1 and PI3-kinase signal transduction pathways [54-59]. IFN- β has been shown to act via the IFNAR1, in an IFNAR2-independent way, through a non-canonical pathway [60].

The 2 other categories of the IFN family, type II and type III, display little similarity to type I IFNs and signal through their own cognate receptors. All IFNs act through various signal transduction pathways, with Janus kinases (JAK)/signal transducer and activator of transcription (STAT) pathway being the best-described [61]. Although type II IFN shares a similar classification with type I IFN, it activates different signal receptors that have other effects than those of type I IFN. IFN- γ signals through the IFN- γ receptor (IFNGR), composed of IFNGR1 and IFNGR2 subunits. In the classical signaling pathway, binding of IFN- γ to IFNGR activates JAK1 and JAK2 and leads to homodimerization and phosphorylation of STAT1 at tyrosine 701 [62]. However, like type I IFN, alternative signaling pathways have also been suggested for IFN- γ , such as STAT4, Erk1/2, Pyk2 and CrkL [63].

Type III IFNs bind to 2 receptors unique to this IFN type that have limited expression in epithelial cells: the low-affinity receptor subunit (IL-10R2) and the high-affinity receptor subunit (IFN- λ receptor 1, IFNLR1) [64]. These receptors trigger the same signaling JAK/STAT pathway as type I IFN receptors and induce a high number of ISGs [65]. All the types of IFNs are summarized in Table 1.

The role of IFNs has been widely studied in autoimmune diseases; however, there are not many data concerning IFNs and IBD. IFNs have multiple direct and indirect effects on adaptive immunity. IFN- α/β activates NK cells and DCs, with increased expression of major histocompatibility complex class I (MHC I) and other molecules, such as CD40, CD80 and CD86. Type I IFN affects DC targeting in peripheral lymphoid organs by inducing the production of several chemokines, including CXCL8, CXCL9, CXCL10, CXCL11 and their receptors. It boosts the production of IL-12, IL-15, IL-18 and IL-23 by DCs and the heightened expression of B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL). Furthermore, type I IFN stimulates macrophage development and inducible nitric oxide (NO) synthase expression in systemic lupus erythematosus (SLE) [66]. IFN- α overproduction has been described in SLE patients; immune complexes containing DNA or RNA in the serum of SLE patients may explain this increased production [67]. Immature plasmacytoid DCs produce increased levels of IFN that can also induce monocyte maturation into DCs [68].

The stimulatory or inhibitory role of type I IFN has been described in various other autoimmune disorders. For

Table 1 The types of interferons

IFN Type	Class	Receptor	Cellular source	Biological effect
I	$\alpha, \beta, \omega, \epsilon, \kappa, \delta, \zeta, \tau$	IFNAR1, IFNAR2	pDCs, Fibroblasts	Activates: NK cell, DC, macrophage development and chemokines production. Triggers/activates: Rap1, CrkL, Map kinases, IRS-1, IRS-2, Vav, RAC1 and PI3- kinase signal transduction pathways
II	γ	IFNGR1, IFNGR2	NK cells, CD4 and CD8 cells, macrophages, DCs, B cells	Triggers: JAK/STAT, STAT4, Erk1/2, Pyk2, CrkL pathway
III	$\lambda 1, \lambda 2, \lambda 3, \lambda 4$	IFNLR1	pDCs	Triggers JAK/STAT pathway, induces ISGs

IFN, interferon; IFNAR1, interferon α/β receptor subunit 1; IFNAR2, interferon α/β receptor subunit 2; IFNGR1, interferon-gamma receptor subunit 1; IFNGR2, interferon-gamma receptor subunit 2; IFNLR1, Interferon lambda receptor 1; pDCs, plasmacytoid dendritic cells; NK cells, natural killer cells; DC, dendritic cells; ISGs, interferon-stimulated genes

example, type I IFN has been suggested as a negative regulator in rheumatoid arthritis (RA), type I insulin-dependent diabetes mellitus, multiple sclerosis (MS), and acute encephalitis. However, IFN- β is used to treat relapsing/remitting forms of MS. Other examples are those of thyroiditis, some forms of autoimmune hemolytic anemia, and Behçet's disease [67].

Genetic studies in primary Sjögren's syndrome (pSS) report polymorphisms in the *IRF5* gene, whose transcripts may induce the stimulation of IFN- β [69]. A few studies have correlated the increased circulating IFN- α levels with autoimmune/autoimmune-featured diseases such as pSS, diffuse systemic sclerosis and interstitial lung disease [70]. In dermatomyositis, immunohistochemistry methods revealed that IFN- α/β induce the myxovirus resistance protein A in the perifascicular muscle fibers and in capillary cells [71]. IFN- α/β has also been detected in the synovial fluid and tissue of patients with RA. Subsequent treatment approaches using type I IFN have had controversial outcomes in both murine models and humans with RA [72].

It is known that, in healthy individuals, TNF downregulates IFN- α [73], and this leads to an initial theory that the reduction in TNF-mediated IFN- α secretion triggers autoimmunity. However, several studies showed that both IFN- α and TNF are increased in SLE patients and, furthermore, that their levels were indicative of the disease progression [74-78]. It seems that the increased levels of both TNF and IFN- α contribute to the development of autoimmunity [79].

There are studies indicating that type I IFN treatment often has an unpredictable outcome in IBD patients. Some pilot studies have shown that type I IFN may improve the condition of IBD patients [80,81], although some clinical trials found that there is no beneficial outcome of IFN- β 1a, IFN- α or IFN- β 1 treatment in terms of disease remission [82-84]. According to Mannon *et al*, UC patients characterized as responders to IFN- β 1a therapy presented significant lower levels of mucosal T-cell IL-13 production after treatment. Primary non-responders to IFN- β 1a treatment were associated with increased quantities of IL-17 and IL-6, while no other significant decrease in the production of inflammatory cytokines was noticed after clinically and endoscopically effective therapy [85]. We can conclude that, according to the current knowledge concerning type I IFN treatment, no statistical benefit in disease amelioration has been found, although the effect of the treatment seems to be associated with the Th profiles of each patient.

Proinflammatory and anti-inflammatory cytokines, type I IFN included, are significant players in the maintenance of gut microbiota, given their immunoregulatory effects on the growth and renewal of intestinal epithelial cells (IECs) [86-88]. Type I IFN is mainly expressed by *lamina propria* CD11c+ DCs in the intestine [89]; more specifically, these cells express IFN- α 5 and IFN- α 9 mRNA, but not IFN- α 4 [90]. Moreover, it has been found that CD11c+ DCs express type I IFN-induced genes, including 2'-5' oligoadenylate synthetase (OAS), OAS-like family members, IRF5, IRF7, CXCL10, RNase L and PKR, as well as IL-15 α [91].

IFN signature in IBD

An increased expression of IFN-regulated genes, widely known as an IFN signature, has been reported in blood and tissue from patients with autoimmune disorders. The IFN signature has been studied in multiple autoimmune diseases, such as SLE, subacute cutaneous lupus erythematosus (SCLE), discoid lupus erythematosus (DLE), myositis, pSS, systemic sclerosis (SSc), scleroderma, and RA [92-95].

In SLE, the IFN signature is correlated with disease activity and severity and can be modulated with appropriate therapy [94]. Bauer *et al* suggest that IFN-induced chemokines can be used as possible biomarkers for predicting SLE [96,97]. The IFN-regulated gene signature is increased in peripheral blood cells and is correlated with disease activity in SCLE and DLE [95]. Furthermore, higher expression levels of IFN- λ 1 in serum and tissues induce type I IFN-regulated genes in cutaneous lupus erythematosus [98]. The IFN type I signature also defines a subset of RA patients, with a specific biomolecular phenotype, represented by increased activity of the innate defense system, coagulation and complement cascades, and fatty acid metabolism [99]. Similarly, the IFN signature can identify only a subgroup of pSS patients: those who present higher activity of the disease and a more obvious activation of the immune system, including higher BAFF mRNA expression [100]. However, the IFN signature does not have such a strong association with dermatomyositis, polymyositis, SSc and RA, as with SLE [94,101].

Extended research by Smiljanovic *et al* studied the impact of a large group of cytokines regulated by IFNs and TNF- α in

SLE and RA. Specifically the IFN- α 2a signature included the upregulation of the following probe sets: *CCL2*, *CCL8*, *CD164*, *CXCL10*, *CXCL11*, *FAS*, *IFI16*, *IFI27*, *IFI44*, *IFI44L*, *IL-15*, *IL-15RA*, *MX1*, *MX2*, *OAS1*, *OAS2*, *OAS3*, *OASL*, *SIGLEC1*, *SSB*, *STAT1*, *STAT2*, *STAT3* and *TNFSF10*, and downregulation of the following probe sets: *CENTD2*, *CYP1B1*, *GPX4*, *ID2*, *IER3*, *IRS2*, *JUN*, *KLF13*, *KLF2*, *KLF4*, *PTAFR*, *TNFAIP2* and *TNFRSF10B* in SLE. A pronounced IFN- α 2a signature was also identified in most RA patients. The IFN- α 2a imprint in RA included the upregulation of *CD163*, *CD55*, *CITED2*, *IL6ST*, *FOSL2*, *MAFF*, *ATF3* and *MT2A* and the downregulation of *CCNG2*, *CXCR4*, *ICAM2*, *FADD*, *GPX3*, *NGRN*, *PURA*, *TNFSF8* and *TP53*. The network that characterizes an IFN- γ signature in SLE contains the following genes: *STAT1*, *STAT3*, *IFI16*, *IRF7*, *CXCL10* and *TNFSF10*. In contrast, the network that demonstrates an IFN- γ imprint in RA contains genes like *CCL3*, *CCL4*, *CXCR4* and *ATF3* [100].

Appendicitis and appendectomy (AA), when occurring at an early age, have been found to be protective against the development of colitis in adulthood [102]. Cheluvappa *et al* showed that AA influence the expression of IFN-associated genes using microarray and gene set enrichment analysis in an AA model [103], explaining its beneficial role in trinitrobenzenesulfonic acid (TNBS) colitis. In this study, the expression of 46 distal colonic, IFN activity-associated genes was measured 3 and 28 days after AA. At day 3 after AA, *IRF7* and *IFI35* were significantly upregulated, while *IFNK* and *IFRD2* were significantly downregulated. At day 28 after AA, *IFNZ*, *IFIT1*, *IFIT2*, *IFIT3*, *IRF9*, *IFIH1* and *IFI44* were found significantly upregulated. However, *IRF2BP1*, *IRF2BP2* and *IFI30* were significantly downregulated [104]. The only IFN gene that was upregulated at any time point was *IFNZ* [105]. The *IFNz* gene in mice exhibits immunomodulatory and antiviral effects, initiated by its IFN- α/β receptor binding [105]. These data agree with another study that showed imiquimod-induced colonic upregulation of IFN activity-associated genes or their gene sets (*IFIT1*, *IFIT2*, *IFIT3*, *IRF7*, *IFI44* and *IFIH1*) that provide protection against DSS colitis [106]. A similar study investigated the role of several chemokines in colitis after AA. At day 28 after AA, *CCL5* was significantly upregulated, whereas *CCL20* was significantly downregulated. Interestingly,

CXCL11 was found to be significantly upregulated at days 3 and 28 after AA [107]. The IFN-regulated genes in the IBD model, SLE and RA are presented in Table 2.

IFIT1, IFIT2, and IFIT3 are induced by IFNs, virus infections, and several molecular patterns, interfere with multiple protein-protein interactions, and present antiproliferative and immunoregulatory properties [108,109]. The IRF family of transcription factors that bind with DNA has the ability to recognize and bind to consensus gene sequences (IFN, stimulated response elements and virus-response elements), helping in IFN production, IFN/feedback-inhibition, management of cell growth, T-/B- lymphocyte activity and IFN-induced gene expression [110,111]. Specifically, IRF7 is a positive IFN regulator and a key mediator of the IFN positive feedback amplification loop, while IRF9 contributes toward a heterotrimeric complex, which induces IRF7 via JAK/STAT signaling, and autocrine IFN-receptor activation [110]. IFI44 binds intracellular GTP and prevents cells from proliferating [112], while IFI30 is an enzyme of lysosomal thiol reductase. It is expressed from antigen-presenting cells (APCs) and is responsible for processing the antigen through the decrease of bisulfide bonds of endocytosed proteins [113]. IFI35 is a leucine zipper protein, expressed in fibroblasts, macrophages and epithelial cells [114]. IFIH1 is an RNA helicase involved in induction of translation, in nuclear/mitochondrial splicing and ribosome assembly [115]. The IFN IFNz in mice exhibits immunoregulatory and antiviral effects, initiated by its IFN- α/β receptor binding [105]. Considering the chemokines involved in the IFN signature, the chemokine CCL5 is a chemoattractant for monocytes, memory Th cells, and eosinophils [116], and is induced by IFN- γ [117]. The chemokine CCL20 is also induced by IFN- γ [117] and is chemoattractant for lymphocytes and neutrophils, which can help lymphoid tissues of mucosa to attract lymphocytes and DCs to epithelial cells [118], while IFN- β and IFN- γ induce the chemokine CXCL11. CXCL11 is a chemoattractant for IL-activated T-cells [119].

There are not many studies concerning the correlation of the IFN-regulated gene expression and the response to anti-TNF therapy. The aforementioned study of Palucka *et al* suggests the upregulation of IFN- α regulated genes in circulating leukocytes

Table 2 Interferon (IFN)-regulated genes in the inflammatory bowel disease (IBD) model, Systemic lupus erythematosus (SLE) and Rheumatoid arthritis (RA)

Diseases	IFN signature	
	Upregulated genes	Downregulated genes
IBD model (after appendicitis and appendectomy)	<i>IRF7</i> , <i>IFI35</i> , <i>IFNZ</i> , <i>IFIT1</i> , <i>IFIT2</i> , <i>IFIT3</i> , <i>IRF9</i> , <i>IFIH1</i> , <i>IFI44</i> , <i>IFIT1</i> , <i>IFIT2</i> , <i>IFIT3</i> , <i>IRF7</i> , <i>IFI44</i> , and <i>IFIH1</i> , <i>CCL5</i> , <i>CXCL11</i>	<i>IFNK</i> , <i>IFRD2</i> , <i>IRF2BP1</i> , <i>IRF2BP2</i> , <i>IFI30</i> , <i>CCL20</i>
SLE	<i>CCL2</i> , <i>CCL8</i> , <i>CD164</i> , <i>CXCL10</i> , <i>CXCL11</i> , <i>FAS</i> , <i>IFI16</i> , <i>IFI27</i> , <i>IFI44</i> , <i>IFI44L</i> , <i>IL-15</i> , <i>IL-15RA</i> , <i>MX1</i> , <i>MX2</i> , <i>OAS1</i> , <i>OAS2</i> , <i>OAS3</i> , <i>OASL</i> , <i>SIGLEC1</i> , <i>SSB</i> , <i>STAT1</i> , <i>STAT2</i> , <i>STAT3</i> , <i>TNFSF10</i>	<i>CENTD2</i> , <i>CYP1B1</i> , <i>GPX4</i> , <i>ID2</i> , <i>IER3</i> , <i>IRS2</i> , <i>JUN</i> , <i>KLF13</i> , <i>KLF2</i> , <i>KLF4</i> , <i>PTAFR</i> , <i>TNFAIP2</i> , <i>TNFRSF10B</i>
RA	<i>CD163</i> , <i>CD55</i> , <i>CITED2</i> , <i>IL6ST</i> , <i>FOSL2</i> , <i>MAFF</i> , <i>ATF3</i> , and <i>MT2A</i>	<i>CCNG2</i> , <i>CXCR4</i> , <i>ICAM2</i> , <i>FADD</i> , <i>GPX3</i> , <i>NGRN</i> , <i>PURA</i> , <i>TNFSF8</i> , <i>TP53</i>

IFN, interferon; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis

of patients with systemic onset juvenile idiopathic arthritis who receive anti-TNF therapy [73]. A study performed in 33 RA patients revealed that increased IFN response gene activity is associated with a poor clinical response to TNF blockade, most evident 2 months after the initiation of treatment. Interestingly, the combination of five IFN response genes (*OAS1*, *LGALS3BP*, *Mx2*, *OAS2* and *SERPING1*) into one IFN response gene set improved the predictive accuracy compared to *OAS1* and *LGALS3BP* expression separately [120].

Although IBD is not considered as an autoimmune disease, it may trigger autoimmunity caused by the increased antigenic load and mucosal immune activation. It is well established that both innate and adaptive immunity play a major role in IBD development. Several genetic alterations are shared between IBD and autoimmune diseases. Furthermore, chronic intestinal inflammation presented in IBD could trigger autoimmunity. IBD-related inflammation consists of a variety of abnormalities in humoral and cell-mediated immunity, and a generalized enhanced reactivity against intestinal bacteria. The IFN signature in autoimmune diseases represents a useful tool as a biomarker of disease progression and treatment efficiency. Thus, the IFN signature in IBD could serve as an early predictor of disease activity and progression, as well as a supplementary therapeutic target [121,122].

Concluding remarks

Many autoimmune diseases present an IFN signature in cells from peripheral blood and tissues. Current data demonstrate that the IFN signature can be used as a biomarker that defines disease activity. In RA, the IFN signature may be used in the prediction of treatment response to some biological drugs, while inhibition of the IFN signature in other autoimmune disorders, such as SLE, could have a potential role in clinical practice. The IFN signature in IBD has not been thoroughly studied compared to autoimmune diseases. For this reason, further investigation of the IFN signature in IBD would be essential for a better understanding of its actions.

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