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[Review] The Landscape of Interferons in Health and Disease

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Abstract

Interferons (IFNs) were the original prototype cytokine system discovered in 20th century research. As the name interferon implies (derived from the Latin interfere-on), these proteins have immunostimulatory, primarily antiviral and antitumour properties and are synthesised and secreted between cells. Due to technological advances, processes and variable factors involved in IFN regulation can be comparatively explained by proteins expressed and genes expressed. In this review, we provide a brief introduction and background on the history of IFN research. We then provide an overview of type I IFNs, associated cells, and their receptors and outline the characteristics of type I IFN subtypes. We distinguished between the three types of IFN in the immune system of higher mammals and the associated cellular signalling mechanisms of IFNs together with IFN–inducible transmembrane proteins (IFITM) during viral infection. Additionally, we elucidated the role of IFN in viral diseases, as well as type II IFN and immunological disorders, in infections and deficiency followed by type I IFN subtypes. Errors in the IFN signal transduction and activator of transcription (STAT) protein signalling pathway during disease were analysed. This paper concludes with an examination of the role of type I/II/III interferon signalling since the discovery of the timing of interferon synthesis within immune cell pathways, examining autoantibodies, interferons and errors, and finally closing with the current understanding of interferon and immunotherapy regulation in cancer.

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Introduction and brief history of type I IFN

Interferons (IFNs) are cellular secreted glycoproteins with historically unique antiviral activity, as well as oncological regulatory properties induced by the regulation, maturation, development or chemotaxis of immune cells (e.g., dendritic cells, DCs). Different types of IFN proteins were discovered after 1957 to stimulate the innate/adaptive compartments of the immune system through pleiotropic proteins synthesised and released by immune cells. It was discovered by Alick Isaacs and Jean Lindenmann, two scientists who described the first IFN in 1957 [1]. These effects are suppressed by cytokine interleukins (ILs), chemokine receptors or ligands (C-C-Rs or C-X-C-Ls), which act as specific cellular autocrine/paracrine signals in a hormonal manner [1].

The nomenclature of IFN has historically been derived as alpha (α, from leukocytes), beta (β, from fibroblasts), or gamma (γ, from mitogen–activated lymphocytes) stimulated to proliferate [1]. Following initial IFN discovery, three main types of IFN are now known: type I (α or β) and type II (γ), with the recent discovery of type III (λ) in 2003 and other subtypes. Each has distinct anti–proliferative and/or antiviral activities through cellular signalling affecting immune cell phenotypes migrating through epithelial and endothelial cellular layers [1]. Upon initiation of IFN signalling, differentially expressed genes (DEGs), which are transcribed and translated through IFN regulatory factors (IRFs) as well as other proteins, are produced. This process occurs in both healthy and disease states and is regulated by IFN-stimulated genes (ISGs), IFN-inducible proteins (IFIs), and IFI transmembrane proteins (IFITMs) [2][3][4][5]. Differential cellular concentrations of either natural or recombinant IFN can stimulate innate/adaptive immune system branches and hone the immune response [6].

Foundations of IFN research originated when haemagglutination was measured, with IFN then known as an inhibitory factor (IF) able to inhibit virus-induced pathological effects. This occurred before and after the predominant 20th century influenza epidemics and pandemics [6][7][8]. It is known that the influenza virus expresses hemagglutinin/neuraminidase (HA/NA) proteins that affect immune cells inhibited by IFN [9]. This occurs together with T-cell synthesis and natural killer (NK) cell synthesis of type II IFN–γ, resulting in the activation of other antigen–presenting cells (APCs), such as macrophages (Mϕs), with variable phenotypes [2]. Pathogenic antigens are sensed through pattern recognition receptors (PRRs), and more cellular endosomal expressed Toll–like (TLR) receptors have since been discovered. Cancer pathologies also respond to type II IFN–γ-cell synthesis, while viral evolution may affect the homeostatic balance of all three type I/II/III IFNs on immune cell function [10][11][12]. This aspect of viral epidemics/pandemics is considered, as evidenced by Dengue fever virus (DENV) and, recently, Monkeypox virus (MPXV) [13][14].

It is plausible that IFN regulation is modulated, affecting early therapeutic and/or clinical disease onset–delaying effects during viral–evoked diseases caused by influenza A virus (IAV), measles virus (MeV), and human immunodeficiency virus (HIV), while other lower respiratory tract bacterial infections caused by *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus aureus* also cause diseases [10][15]. IFN is also crucial in some oncological disorders,

such as melanoma [10][15]. Other reviews have shown that IFN proteins can be affected by *Flaviviridae* (e.g., DENV), *Coronaviridae*, and *Ebolaviridae* (EBOV) viral proteins (VPs) [14][16][17]. Individual pathogens express different proteins with a human host recognising fragment epitopes, known as antigens, utilising phagocytes (APCs) that digest self and non–self antigens affected through many cellular protein sensors. These include cytosolic PRR proteins surrounding organelles such as the nucleus or mitochondria (e.g., retinoic acid–inducible gene I (RIG–I) or mitochondrial antiviral signalling proteins (MAVS)) [2][14]. Therefore, since the first single-cell RNA (scRNA) sequencing in 2009, pathogenic antigens affect many sensors and IFN factors within host cells, necessitating further clarification [18]. The activity of synthetic type I IFN–α2 was observed in 2002 in more than 40 countries where recombinant type I IFN–α2 began to be used as a therapeutic in leukemia (B/T-cell lymphomas) treatment [19][20]. As recently as 2022, a notable longitudinal study of nonrelated acute/chronic inflammatory conditions further demonstrated that IFN expression gradually decreased in early-onset rheumatoid arthritis (RA) patients (n = 191) [21]. IFN types are usually constitutively expressed in humans, and type IV IFN–υ subtypes were discovered in 2022, only in lower vertebrates such as zebrafish and the African clawed frog but also newly discovered in the mallard duck. It is hypothesised that type IV IFNs bind to an IFN domain receptor composed of two subunit domains, IFN–υR1 and IL–10R2 [22][23].

Therapeutics and immunisations have historically targeted IFN for therapeutic benefit measured during disease from preclinical development through phases 1-3 and beyond. This occurs through the overall safety profile and therapeutic benefit evaluated through regulatory and monitoring agencies such as the United States Food and Drug Administration Agency, the European Centre for Disease Control, and other organisations such as the European Medicines Agency (see Supplementary Materials). Regulation of the rate of synthesis of type I/II/III IFNs can have detrimental and/or beneficial effects on the immune system during pathology. The subtypes of IFN produced influence both innate and adaptive immune responses. Each IFN fulfils unique host immunological roles during five types of pathology, including viral, fungal, bacterial, mycobacterial and oncogenic diseases. Therefore, the present study analysed the effects of current genetic, molecular, and cellular type I IFNs on health and deficiency.

Overview of type I IFNs, cells and receptors

Subtypes of type I IFNs

The three types of IFN have differential inhibitory or stimulatory effects on the immune system and are aetiologic in lysing infectious viruses effectively through stimulating effector immune cell activity. IFN receptors (IFNRs) affect this process through their expression within the cell surface plasma membrane (PM), acting as a restrictive barrier. At least 18 types of IFN bind to combinations of six IFNR protein subunit domains. For example, IFNR is expressed by dendritic cells (DCs) and other cells with variable phenotypes. IFNRs are expressed by B lymphocytes, as well as APCs, including monocytes, which can reversibly differentiate into both DCs and Mφs of two types (M1φ/M2φ) [2][24]. IFNR is expressed by the cellular membranes of glial cells, neurons, and other cells. IFNRs are a cellular restriction barrier that initiates downstream/upstream cellular effects and regulates the rate of T-cell secretion of type II IFN–γ upon pathogen

infection [25]. Plant products also generate IFN-stimulating proteins[26]. The timing and rate of cellular IFN synthesis and cellular secretion affect viral infection, propagation, and replication, with subtypes of IFNs affecting pathogen cellular lysis in organs, tissues and cell systems by regulating other cell cycle proteins, such as p38 [27]. Immunodeficiency disorders or individual host single nucleotide polymorphism (SNP) changes may cause errors in IFN/IFNR signalling throughout development. Type I IFN proteins are synthesised/secreted by translation through cellular nuclear transcription factors, such as nuclear factor kappa–light–chain–enhancer of activated B cells **(**NF–κB), resulting in varying antiviral activity.

Each IFN is known as a small molecular weight (MW) protein in humans; for example, type I IFN–α1/13, IFN–α2, IFN–α8 and IFN–α21 are composed of 187-189 amino acids (aa), while type III IFN–λ is within the MW range of 179-200 aa (see Supplementary Materials). Chemokines are smaller-MW proteins (e.g., CCL2, 99aa), with pleiotropic effects directing immune cell migration throughout tissues. Each small-MW IFN protein is translated after cellular transcription through at least six types of RNA differentially modified earlier in response to pathogenic antigens both inside and outside the cell [28]. IFN subtypes can be synthesised by myeloid cells, similar to plasmacytoid DCs (pDCs), which produce higher concentrations of type I IFN (IFN–α/IFN–β), affecting antiviral responses in hosts but also within skin epithelial cell tissues through tumor necrosis factor (TNF)-related apoptosis–inducing ligand (TRAIL), together with at least 10 intra/extracellular PM and vesicular TLRs [29].

On the other hand, type II IFN–γ is secreted predominantly by two effector cells (NK/T cells), which can affect antigen–presenting protein expression through MHC upregulation of class II together with two antigen–presenting cells (DCs and Mφs), each with different phenotypes characterised by cluster of differentiation (CD) molecules [30][31][32]. Type III IFNs also influence host immune responses within epithelial layers. It is considered that each IFN performs unique roles through regulating cellular cycle function, with type I IFN–β potentially regulating the alveolar Mφ cell cycle (M1φ/M2φ) and metabolism [33], while type I IFN–α could be considered to play a similar role in the regulation of homeostatic function and is commonly observed in health, inflammatory and autoimmune (AI) disorders.

Type I IFNs include IFN–β, IFN–δ, IFN–ε, IFN–κ, IFN–τ, IFN–ω, and IFN–ζ, among others, whereas type III IFNs are composed of IFN–λ (IFN–λ1, IFN–λ2, IFN–λ3, IFN–λ4), known originally as interleukins (ILs, denoted as IL29, IL28A, and IL28B), with IFN–λ4 discovered in 2014 [34]. Two types of type III IFNs (λ2 and λ3) are considered to have 96% aa homology [34]. Other subtypes exist, and most of these subtypes vary between host animal species and are encoded by IFN genes. To clarify, human IFN consists of at least 18 subtypes, some of which are type I IFN–α4, IFN–α7, and IFN–α14; at the same time, in pigs and bats, the diversity of IFN–ω is worthy of more consideration, with less type I IFN–α described, as discussed further [35][36][37]. Among the type I IFN–α subtypes, a recombinant IFN–α2b therapeutic version has been utilised in humans [38][39]. Research in 2015 indicated that IFN–α2 is non–glycosylated and missing one aspartic acid aa at position 44 in humans without functional changes [40]. Furthermore, two recombinant type I IFN–α2α/IFN–α2β preparations contain a neutral lysine and alanine substitution at position 23 because type I IFN–α2 is conserved in humans and less prone to mutations [40][41][42].

Recently, it was shown that type I IFNs may contain proinflammatory glycans that affect the binding of the predominant antibody (IgG) to immune cell fragment crystallizable (FcγR) PM receptors (CD16/CD32/CD64), all of which influence the

immune system [42][43]. As a result, this further affects more than 3 branches of the adaptive T-cell response through helper (T_H), cytotoxic (T_C), and natural killer (NK) cells. Modulation of sialic acid residues present in other receptors, such as the specific intercellular adhesion molecule 3-grabbing non–integrin (DC–SIGN or CD209) or fucose residues, may also occur. Therefore, the overall homeostatic properties of type I IFN can be considered further.

Before and after 2019, studies of the pharmacokinetic properties of recombinant type I IFN–α2 engineered strains indicated that the synthetic IFN production vector could affect the pharmacokinetic half–life when glycoengineering indicated *Pichia pastoris* as an option, together with the purification method of recombinant IFN, whereas all subtypes of type I IFN–β are N–glycosylated [44][45][46]. In comparison, others have shown that the addition of a glycosyl group to IFN–λ4 may increase its anti–inflammatory effects and antiviral efficacy [47]. Notably, research on glycosylated IFNs, which vary in stability and display antimicrobial effects, is in its infancy [48][49]. Glycosylated IFNs bind to carbohydrates and PM receptors with higher/lower binding affinities to IFNRs. Respective IFNRs include type I IFN receptors (IFNAR1/2), type II IFN receptors (IFN–γR1/IFN–γR2), and type III IFN receptors (IFN–λR1/IL10R2), each composed of two subunit domains [50][51]. Some share signalling pathways with cytokines, such as IL–10, with each signalling through the cellular signal of transduction and activator of transcription (STAT) proteins reviewed elsewhere and discussed below [52]. Below is a depiction of two type I IFNs (see Figure 1).

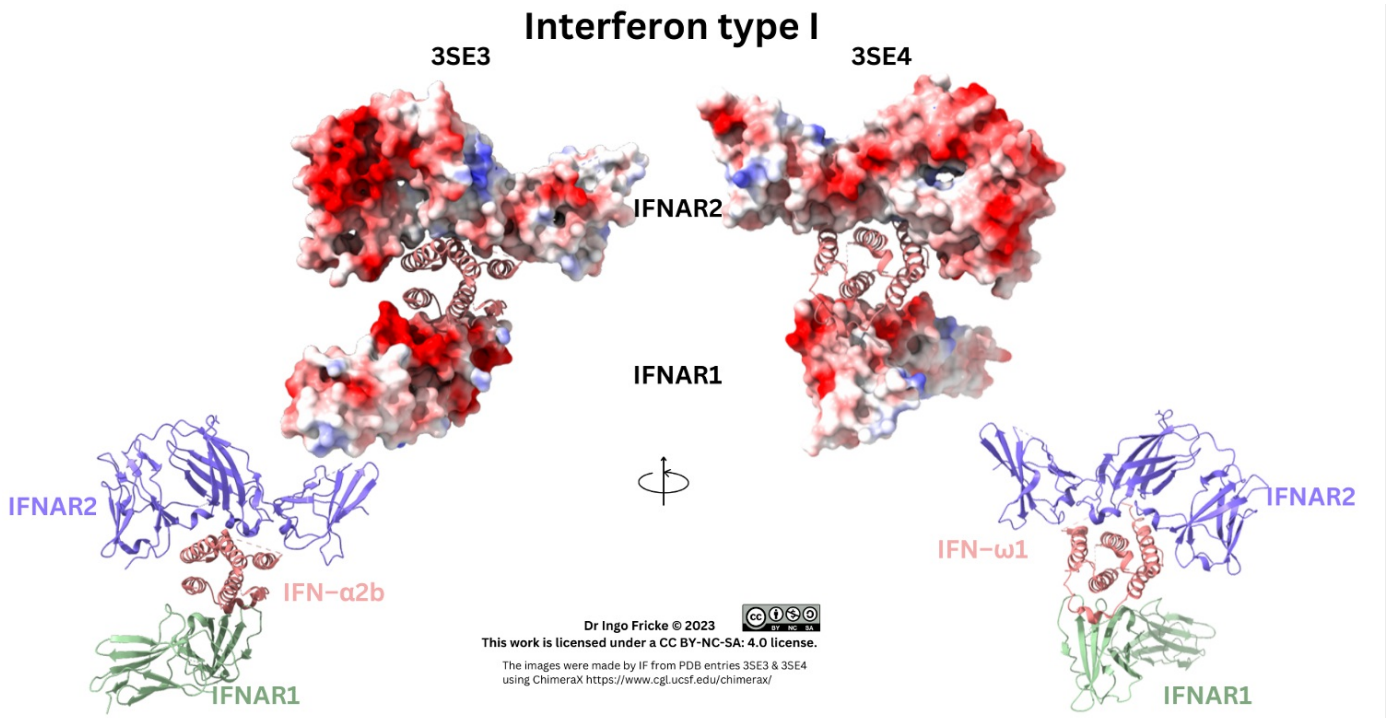

Figure 1. Type I IFN receptor/ligand binding. Pictures were made in ChimeraX (https://www.cgl.ucsf.edu/chimerax/) using existing PDB files, namely, 3SE3 and 3SE4, depicted as ribbons, and ribbons with surfaces of the receptor, with electrostatic potential.

As described above, the IFN/IFNR binding complex was identified in 2011 without nuclear magnetic resonance (NMR) imaging, while comparisons of type I IFN–α assays allowed type I IFN–α receptor binding studies to show that binding to IFNAR1 could occur with higher (μm) affinity, although binding to IFNAR2 occurred with lower affinity in a smaller (nm)

range [53]. At the same time, the literature appears to show that during the hepatitis C virus (HCV) infection cycle, more type I IFN–α2 could stimulate IFNAR1 (IFN–α2: 116 fM compared to IFN–ω: 37 fM); however, a mutant type I IFN–α2 (Q61S YNS) appeared to have a substantially greater (60×) binding affinity to IFNAR1 (in phage display) [54][55]. *In vitro in vitro,* cell culture of type I IFN–α10 together with type I IFN–α14 was indicated to have the lowest antiproliferative and antiviral effects, while type I IFN–ω was indicated to have the lowest activity *in vitro* on B cells, T cells and monocytes, but possibly more recent *in vivo* research indicates the reverse [56]. The binding affinity of type I IFNs for IFNAR1 varies by subtype and mutation within the pathways described below [54][55]. However, IFN–β and type III IFN–λ are produced by various cells, although type I IFN–α is generally synthesised by immune cells, specifically pDCs, early during infection [16][32]. Other reviews establish that type I IFN synthesis can be downregulated, while research into type III IFNs is in its early stages; however, some authors suggest that type III IFNs may have further biological mechanisms, as discussed in other papers [57][58][59]. Specific data on the effects of type I IFN therapy are available through national clinical trials (NCTs) conducted throughout history before/after the first cloning of IFN receptors approximately 1990 together with the production of recombinant type I IFN–α2 [60]. During the recent pandemic, type I IFNs were shown to have some effect on reducing the severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) host viral genome load, but further details are required [61][62][63][64]. Much of what is known about type I IFN stems from herpes simplex viruses (HSVs), as well as both sensory and immune cell tropism, as discussed elsewhere [65][66][67][68].

The three types of IFNs in the immune system of higher vertebrates

Type III IFN–λ was first discovered in 2003, and four subtypes of type III IFN–λ1, IFN–λ2, IFN–λ3, and IFN–λ4 were subsequently confirmed. Early observations revealed that type III IFN–λ could influence immune cell (monocyte) development into DCs, as several cytokines (e.g., IL–2) differentially induce T_{REG} cell development through STAT protein and IFN signalling [69]. The mechanism by which type III IFN–λ affects intracellular signal transduction through IFN–λR1/IL10RB2 binding is unclear. Shortly thereafter, in 2010, this was further clarified when genomic analysis revealed that one gene for *IL28RA* (*IFNLR1*) was common to many animals, including humans, monkeys, mice, horses and chickens [70]. The gene transcript was subsequently found to be expressed not only by LNs and testis but also by germinal centre B cells and in various types of cancer (lymphoma, acute lymphoblastic leukaemia, and head and neck cancer) but also at high concentrations within tissues such as the pancreas (thyroid, skeletal muscle, and heart tissues), indicating that these tissues could respond to type III IFN synthesis [70]. Interestingly, the authors postulated that the three important adaptive arms of the immune system responsive were NK cells and T_C cells, which promoted the other T_H1 cell response phenotype [70].

Before and after type III IFN discovery, the lymphoid transcription factor gene regulator of B/T-cell differentiation (*LyF*) was described as having a transcriptional binding site within the *IFNLR1* domain encoding one part of the type III IFN receptor[2][71]. Furthermore, activator protein 2 (AP–2), c–Jun and a p53 binding site within 1 kilobase of the start of the transcription sequence on *IFNLR1* in humans were described [70][71]. In 2011, the first report presented evidence of another key gene transcript for type I IFN synthesis, *ISG56*, as well as *RIG–I* induced by synthetic IFN–λ2 *in vitro* in *P. alecto* bats [72]. As type III IFN research unfolded, in 2014, it was clarified that JAK2 was essential for regulating the signal

transduction of type III IFN–λ1 when *in vitro Listeria monocytogenes* was observed to potentiate type III IFN–λ1 signalling around peroxisomes [73]. The new type III IFN–λ4 was investigated at the same time using transcriptome sequencing (RNA–seq) to determine how liver hepatocytes and primary human airway epithelial cells (pHAEs) could be affected [74]. This comparison and others note that the gene encoding type III IFN–λ4 is more polymorphic, changing cellular function after protein translation with frameshift mutations disrupting translation of IFN–λ4 mRNA [75]. In 2016, no difference in IFN/ISG gene expression according to clinical asthma severity (n = 66) was detected among individuals. It was observed that neutrophilic patients with asthma overexpress both type I/III IFN (IFN–β, IFN–λ1) rather than eosinophilic patients with asthma, but not IFN–λ2 or IFN–λ3 [76]. More recently, since 2020, research on systemic lupus erythematosus (SLE) has further confirmed the unclear mechanisms of type III IFN in which IFN–λR1 may correlate with B-cell proliferation signalling through TLR7/8 PM receptors. It was suggested that increased IgM production could occur outside the lymphatic follicular environment, where B-cell antibody clonal selection and isotype switching usually occur [77]. However, during the timeframe of type III IFN–λ4, there has been further clarification of extrafollicular B and T-cell phenotypes in autoimmune disease (RA), indicating that type I IFN–α clearly induces T cells together with IL–12 and CXCL13 production [78][79][80]. In contrast to type I IFNAR, type III IFN–λR1/IL–10RB is considered to be expressed by neutrophils, pDCs, Mϕs and lymphocytes, although this expression can vary within mucosal barriers [81]. The cellular effects of IFNs on immune system cells vary with the affinity of the three main types of IFN and IFN subtypes through six protein subunit domains encompassing the three IFN receptors differentially expressed in organs, systems, tissues and cells. In brief, type I IFN–α research to date indicates unusual variance during host infections, with evidential beneficial/detrimental effects regulating the differentiation and maturation of myeloid cell lineages such as B cells, T cells, and natural killer (NK) cells via metabolism and secretion during homeostasis. This training of immune responses occurs through inhibition as well as DC stimulation of immune cell maturation/differentiation by regulating various checkpoint markers, such as CD80/CD86, increasing MHC antigen presentation, and stimulating T-cell phenotypes expressing adhesion molecules (e.g., CD62) [3]. The tolerogenic and maturation phenotypes of DCs are known to occur from pDCs to three conventional types of DCs (cDC1s, cDC2s, and cDC3s) [82]. These cells reversibly differentiate into myeloid/monocytic lineages during inflammatory processes such as endothelial cell insult, injury, or cancer [83]. Immune system modulation and/or evasion can be considered evolutionary developments within animal host immune systems and can vary.

Recently, two additional types of cellular signalling pathways have been identified alongside IFN cytokines, which include other cytokines (ILs) and chemokines (CCs/CXCs). Individual cellular expression is stimulated by many pathogens as well as viral-induced pathology. Viral mutations occur in DNA/RNA viruses, such as the positive–sense single–stranded RNA virus (+ssRNA) influenza A (Alphainfluenzavirus), which has 198 potential subtype combinations of hemagglutinin/neuraminidase (HA/NA) protein antigens that can differentially affect immune cell phenotypes. Three types of Gram–negative (–ve) bacteria (e.g., *Haemophilus influenzae*) are also known to shed intracellular/extracellular protein membranes during infection (A, F or non–capsulated (ncHI)).

In comparison, type II IFN–γ is produced by only host cells of the immune system, primarily induced by APCs phagocytosing pathogens through adaptive NK and T_C cells expressing MHC class II proteins to effect cytolysis. Two primary T-cell phenotypes also produce type II IFN–γ, with the majority expressing CD4 and/or CD8 proteins [84]. During

2020, further clarification revealed that the effector role of type I IFN in inhibiting cytokine (e.g., IL–10) secretion by monocytes could stimulate a T-cell response [85]. This is mediated through the suppressor of cytokine signalling–1 (SOCS–1) protein. IFN transduction occurs independently through the second IFN receptor (IFNAR2) through conserved phosphotyrosine residues on tyrosine kinase (TYK) enzymes to regulate cell antiviral/anti–proliferative activity [86][87][88]. Historically, type II IFN has been used as a measure of T-cell activity. The activity of each type I/II/III IFN since 2009 can also be observed through gene transcript expression during scRNA research. For example, RNA for the other type III IFN receptor (*IL10R2*) is currently considered to be present not only in the lungs, intestines, and liver but also in B cells, neutrophils, Mφs and pDCs but not in NK cells [89]. Additionally, type III IFN is considered to have a greater affinity for one subunit (IFN–λR1) but less affinity for the other subunit (IL10R2), possibly explaining some of the differential activity of IL–10, which shares this receptor [89]. In the past, type III IFN was considered to be predominantly expressed by non–haematopoietic cells (e.g., intestinal epithelial cells). Type III IFNs have a lower affinity for binding to their respective receptors than type I IFNs [90]. Other reviews have examined the relevance of SNP mutations in type III IFN pathways during disease [90][91]. The relevance of type III IFN has become clearer since *in vivo* research in 2006 revealed that during type III IFN–λ (IL28A) deficiency, there is an effect on three crucial immune system branches [92]. Specifically, in germinal B-cell centre formation, B cells develop and secrete immunoglobulins (Igs) of four dominant types (IgM, IgG, IgA, and IgE) present in blood sera, but IFN can also affect the adaptive immune system through increased activity of the adaptive T_H ($CD4^+$) and T_C ($CD8^+$) cell phenotypes [2]. Moreover, type III IFN–λ3 is similarly highlighted as relevant to B-cell proliferation and antibody production [59].

An effective increase in pathogen antigen circulation may inhibit or stimulate/sensitise the immune system, affecting the lysis of infectious viruses through regulatory host IFN synthesis or unknown metabolic factors. The three shared methods of immune system kinetics include pathogenic DNA/RNA 5’ capping through the incorporation of a methyl (CH3–) group into the 5’ genome even if RNA viruses activate both TLRs and retinoic acid–inducible gene I (RIG–I)–like receptors (RLRs) [93]. Second, cellular mitochondrial metabolic changes affect the synthesis rate of reactive oxygen species (ROS), while pathogens also utilise intercellular channels such as nanotubes or porous membranes [94]. The third could be that the modulation of type I/III IFN is affected by the rate of host cell IFN synthesis, although type I IFN is a historically well–researched therapeutic that has initiated remission during oncological disorders [95].

Cellular signalling mechanisms of IFNs

IFN cellular action occurs through transmembrane protein receptors, as described above, utilising predominantly Janus kinase (JAK) enzymes, together with the STAT protein phosphorylation activation pathway SNP [96]. Seven STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6) are described in mammals as central to immune cell regulation, with STAT1/STAT2 pertinent to IFN signalling [96]. The IFN–λR1/IL–10RB receptors for IFN–λ are notably shared with IL–22, which is implicated in disease [97]. Less is known about type III IFN since the discovery of subtypes in 2003-2014. www.proteinatlas.org showed that the IFN–λ receptor (IFN–λR1) is preferentially expressed by both pDCs and B cells, with IFNAR1 expressed by both neutrophils and three monocyte phenotypes (classical, intermediate and non–classical), exactly as IFNAR2 is evenly distributed on all immune cells [52][96].

During the 1990s, STAT proteins were found to bind to JAK proteins. Various laboratories were known when three scientists, including James Darnell, George Stark, and Ian Kerr, discovered their molecular basis [98]. In 1992, these enzymes were further classified into additional relevant enzyme types (JAK1, JAK2, and JAK3), and Velazquez reported that TYK2 enzymes bridge the gap between the JAK/STAT proteins required for type I IFN signalling [52]. Thereafter, two pathways were described, including the initial “canonical” or high–affinity binding of type I IFNs to IFNAR2 to form a trimer with IFNAR1 [52]. The second pathway, described as “noncanonical”, refers to three independent kinase enzyme pathways, including activation of MAP kinase (MAPK), mammalian target of rapamycin (mTOR), and phosphatidylinositol 3–kinase (PI3K), a serine/threonine kinase [52]. In the canonical model, the activation and phosphorylation of JAK1/TYK2 occurs via phosphorylation to form a STAT1/STAT2 trimer with other IFN regulator factors (e.g., IRF1/3/7/9), resulting in the translocation of IFN-stimulating growth factors (e.g., ISGF3) to nuclear IFN sensitive response elements (ISREs) that affect IFN synthesis [97]. However, the original “noncanonical” pathway is considered to be where STAT1 or other proteins, such as MAPK or PI3K, homodimerise. STAT proteins contain a conserved DNA binding domain, SH2, which recognises the phosphotyrosine motifs of cytokine receptors [52]. The overall IFN signalling pathways are shown below (see Figure 2).

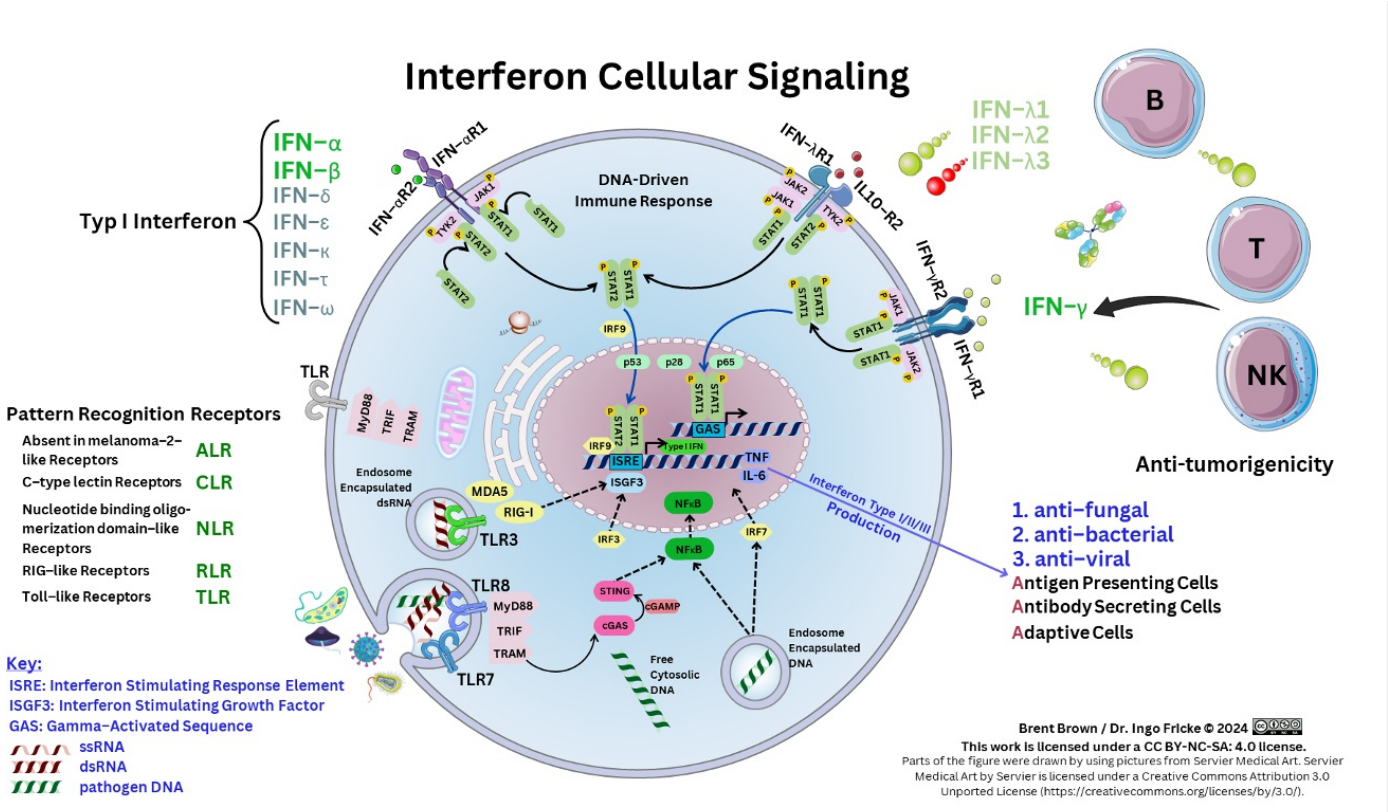

Figure 2. Systemic IFN signalling; parts of the figure created with Servier Medical Art (https://smart.servier.com), licenced under a Creative Commons Attribution 4.0 International (CC BY 4.0) Licence; cyclic guanosine monophosphate adenosine monophosphate (cGMP–AMP) synthase (cGAS); STING: cytoplasmic stimulator of IFN gene; MDA5: melanoma differentiation–associated protein 5; TRIF: Toll/IL–1R domain–containing adaptor–inducing type I IFN–β; TRAM: TRIF–related adaptor molecule; MyD88: myeloid differentiation primary response 88.

The activity of type I IFN occurs via activation of nitric oxide synthase (NOS) and inactivation of the enzyme protein kinase

R (PKR), which is regulated by cellular viral DNA/RNA. Further activation of the enzyme oligoadenylate synthetase (OAS) along with peptide presentation by class I/II (MHC–I/II) occurs [99][100]. However, VP fragments are also metabolised with short aa peptide chains presented as epitopes to immune cell receptors (e.g., T cells expressing CD4/CD8) [101]. There are four OAS enzymes, three of which (OAS1/2/3) produce 2′–5′–linked oligoadenylates and a similar OAS ligand (OASL) that binds to a ribonuclease (RNase L), regulating the degradation of viral or cellular RNA [99][100]. Activation of adenosine deaminase 1 (ADAR1), a dsRNA binding protein, is also known to catalyse the process of adenosine deamination, which is usually involved in viral RNA replication, as well as the maturation and development of leukocytes to affect the apoptosis of infected cells [99][100]. PKR downregulates the translation of viral RNA encoding pathogenic protein domains, whereas OAS activation can degrade and lyse RNA with ADAR1, enabling RNA editing. Viral nonstructural proteins (NSPs) may activate the phosphatidylinositol 3–kinase (PI3K) pathway, inhibiting type I IFN synthesis and activating cellular stress–response proteins (e.g., heat–shock proteins) involved in cell proliferation regulation, survival, and differentiation as well as immune cell regulation. Therefore, temporal initial inhibition of regulatory apoptotic pathways can occur while a pathogen replicates before the induction of innate immune system host cells regulated by IFN [102]. In brief, STAT1 proteins are also regulators of cell cyclin–dependent kinase inhibitors (CDKIs), p21 and p27, as well as caspases (1/3/11), which sense and are activated during cellular apoptosis [52]. However, the activation and phosphorylation of STAT1 are also involved in antigen presentation and B-cell development through the regulation of the CD95 (Fas) and B-cell lymphoma 2 (Bcl–2) proteins, which affect granulocyte development [52]. In an immunological context, STAT1 is activated by three cytokines (IL–2, IL–6, TNF) and IFN. Second, STAT2 does not homopolymerise but can be activated by type I IFN. Third, STAT3 is activated by the IL–6/IL–10 family of cytokines regulated by CD95, which act as molecular switches controlling immune cell differentiation, growth and apoptosis, as observed in certain cancer types [103]. STAT3 is constitutively transcribed in certain cancer types, such as head and neck cancer, as well as hematological tumors, among others [52][104][105]. STAT3 inhibition has been shown to affect the expression of the cytokine receptor IL–4Rα by naïve CD4 T cells expressing the adhesion molecule CD62L, which is required for the transverse of endothelial cell membrane layers [105]. Gene knockout experiments of CD95 have also shown that the overexpression of STAT1 inhibits the transcription of the *IL17a* promoter gene transcript, which is necessary for facilitating the synthesis of IL–17 in T_H17 cells; however, to date, the mechanism by which this occurs is largely unknown [106]. Conversely, *in vivo*, the role of STAT3 is intertwined with that of STAT5. The overexpression of STAT5 together with granulocyte–macrophage colony–stimulating factor (GM–CSF) may activate the differentiation of both types of neutrophils while inhibiting myeloid lineages (monocyte/Mϕs) [104].

Therefore, pathological antagonism of IFN is affected by a multitude of extraneous factors as well as cellular PM and vesicular TLRs that could plausibly also have mutations leading to a sensitised and/or delayed immune system response dependent on the homeostatic function of IFN proteins. This was exemplified in one project (n = 1288), where five individuals were indicated to have an autosomal recessive (AR) disorder within IFN pathways [107]. These differences may result from deficiencies in the genes involved in IFN regulation (*OAS1/OAS2/RNASEL*), with type II IFN *in vitro* able to upregulate the expression of OAS1/2/3 in the myeloid cell lineage required to synthesise IFN through nuclear transcription of IFN and viral antigen presentation [107][108]. In a subset of multi-inflammatory syndrome-associated disorders, in

children without COVID–19 pneumonia but with antibodies to SARS–CoV–2, mononuclear phagocyte function relies on IFN signalling [107]. The last key protein to be considered, ISG15, which is derived through the transcription and translation of IFN–stimulated gene 15 *(ISG15*), is also an intracellular/extracellular protein described as “ubiquitin–like”[109]. The protein ISG15 has been found only in vertebrates; it is induced by a range of cellular–associated injury or infection (bacterial/viral) factors and can initiate cytokine release (e.g., IL–1β) or retinoic acid during hypoxia or DNA damage, affecting type I/II/III IFN synthesis [109]. The function of ISG15 in relation to immune cells was described several years ago to direct three cellular factors. First, monocyte cytotoxicity increases, second, type II IFN synthesis is stimulated, and third, DC and NK cell maturation are induced [109]. The mechanism underlying the variability of ISG15 exocytosis remains largely unknown, although ISG15 is likely localised in neutrophil vesicle exosomes in TLR3–activated endothelial cells during apoptosis [109]. Other authors have shown that ISG15 can bind to leukocyte function antigen 1, although inducing IL-10, which is known to affect both NK and T-cell differentiation, is induced by type I IFNs [109][110]. The *ISG15* gene has two ISREs in its promoter region that bind to the IRF3/9 ISRE. Of these, IRF9 interacts with STAT1/2 to form the ISGF3 complex that induces ISG nuclear transcription, although other IRFs (e.g., IRF4) can also induce *ISG15* transcription and translation [109][110]. It has been suggested that type III IFN–λ could be regulated by *ISG15* transcription and encode the respective ISG15 protein at early/late stages after hepatocyte cell stimulation, with different inhibitory effects on type I IFNs. *In vitro* studies using immortalised hepatocytes have shown that this process occurs independently of IRF1, but IFN–β is maintained for 24-72 hours after viral infection [111]. In 2012, when cellular *in vitro* stimulation was employed, more details of monocyte-derived phenotypes secreting variable type I/III IFN subtypes arose. Differential IFN arises from APCs (DCs or M1ϕ/M2ϕ), with type I IFN–β and type III IFN–λ1 synthesised by divergent phenotypes; this process is followed by type III IFN–λ2/λ3 secretion in both monocyte/myeloid-derived lineages [112].

IFN–inducible transmembrane proteins during viral infection

Other IFN proteins induced by IFN are relevant and can be affected during pathology. For example, the IFN–induced proteins with tetratricopeptide repeats (IFIT) family of proteins includes five members that regulate viral replication. Some consider IFIT proteins (IFIT1, IFIT3 and IFIT5) to regulate viral replication [113]. Various other IFITM proteins (also called the Dispanin protein family) intracellularly sequester viral ss/dsRNA and unmethylated RNA present during host cellular pathogen infection [114]. During the 2009 influenza (H1N1) pandemic, as described above, the roles of IFITM1/2 became clearer, as IFITM1/2 potentially limits the rate of VP synthesis through type I IFN synthesis, as in other viral infections, such as West Nile virus and DENV [115]. The third IFITM protein, IFITM3, is estimated to constitute 50-80% of the total IFITM proteins present on T-cell PMs and can differentially regulate IFN synthesis through concurrent inhibition of ubiquitination and methylation with SNPs in different tyrosine residues (e.g., Y20) [5][116]. Like STAT proteins, tyrosine phosphorylation can be inhibited, preventing endocytosis and ubiquitination through E3–ubiquitin ligase (E3L) [117]. At approximately this time, the CD225 domain of IFITM proteins was shown to be required for the inhibition of both influenza virus and DENV replication [118]. Indeed, IFITM3 was recently shown to be upregulated in severely affected individuals with influenza, further indicating that IFITM3 is a potential restriction factor of viral replication in tissues [117]. Therefore, IFITM3 could be considered important for influenza infection immunisation responses, while it has been confirmed to be present during SARS–CoV–2 infections as a regulatory checkpoint *in vivo,* as observed in gene knockout nonhuman

primates (NHPs) in the pulmonary tract [119]. Finally, this class of IFIT/IFITM3 proteins has also been implicated in modulating amyloid plaques during Alzheimer's disease [120][121].

IFN in infections and deficiency

Type I IFN subtypes in viral diseases

First, it is necessary to examine the expression of type I IFN subtypes synthesised by human cells. IFN regulation occurs in bodily tissue cellular systems regulated by metabolism. Research before 2009 examined chronic hepatitis C virus (HCV) infection and revealed that all type I IFN subtypes were inhibited by viral replication; however, three IFN–α subtypes exhibited increased activity (α17, α7, and α8) [122]. Even two years later, during human metapneumovirus infection (HMPV), four subtypes of type I IFN (α5, α6, α8, and α10) appeared to exhibit increased antiviral potency [123]. In comparison, after 2012, investigations into Mumps virus (MuV) revealed that 12 subtypes of human type I IFN–α could be synthesised [124]. It was then postulated that viral mutations could affect IFN affinity for IFNAR1. Increased synthesis of specific subtypes of type I IFN (α5, α8, α17, and α21) in comparison to less induction of five subtypes of type I IFN (α2, α4, α6, α7, and α16) was observed [124]. Genetic MuV mutations are characterised by the synthesis of more type I IFN–α10 and IFN–α14 in response to varying MuV strains [124]. In 2020, type I IFN synthesis variability was also observed *in vitro* with influenza virus infection of human respiratory epithelial cells compared to *in vivo* infection, revealing the induction of four subtypes of type I IFN (α1, α6, α14, and α16), although three subtypes of type I IFN (α5, α8, and α21) were found to be pertinent to lesser virulent strains [125]. Nonstructural proteins (NSPs) are produced by other *Flaviviridae* [e.g., Zika virus (ZIKV)] and are packaged in vesicles within the endosomal/exosomal cellular pathway after translation in host cells, which may affect the transcription of either host type I//II/III IFN gene [126]. This molecular event may occur with some SARS–CoV–2 NSPs, where the viral replication rate together with the IFN synthesis rate is therefore a crucial consideration. In comparison, other viruses, such as monkeypox virus (MPXV), as well as *Henipaviridae,* such as Nipah virus (NiV), can affect host cell nuclear activity by antagonising the synthesis and exocytosis of type I and possibly type III IFNs, but these effects remain unexplored [127]. For example, with respect to the translation of viral proteins, IFN-encoding mRNAs may be cleaved, or IFN gene transcription may be altered [2][13][125][127]. During *Filoviridae* (EBOV, as well as Marburg virus) infection, comparisons were made between the functions of VP24/VP35, which appear to affect the rate of IFN synthesis in specific cell types more than others [14][128][129][130][131]. Whereas the EBOV VP35 protein did not suppress IFN production in pDCs, sensitised type I IFN–mediated immune responses could attenuate EBOV virulence [14][128][130][132] [71][72]. Investigators induced a loss–of–function (LOF) mutation in the EBOV gene encoding VP35 to observe EBOV antigens with decreased virulence [133]. However, during infection with ZIKV, type I IFN–ε expression within both mucosal and glandular epithelial cells is suggested to be protective [134]. Research involving type I IFN–β seems to involve mycobacterial research on leprosy, implying that this dsDNA mycobacterial species differentially activates cGAS but can antagonise the OASL required for IFN signalling [134]. Moreover, during retroviral (HIV–1) infection, type I IFN synthesis and cellular transmission can be suppressed by the production of a viral infectivity factor

(Vif). This occurs by triggering STING by interacting with cellular tyrosine (Tyr/Y) phosphatase enzymes known as Src homology region 2 domain–containing phosphatase–1 (SHP–1) within STAT pathways regulating various IRFs [97][135][136]. STING can be dephosphorylated at the Y162 position[137]. Therefore, IFN regulation can be compared.

More recent developments seem to indicate that type I IFN subtypes (α6, α8, and α14) are pertinent to the regulation of HIV infection *in vitro* and *in vivo* [38]. However, type I IFNs (α5, α8, and α21) can potently inhibit influenza (IBV with other IFN–α1, IFN–α9, and IFN–α15) H1N1 influenza in respiratory epithelial layers [125]. However, in 2023, type I IFNs affecting STAT2 proteins were shown to affect the adaptive branch of the immune system through effector memory (T_{EM}) T cells alongside classical monocytes through defective IFN signalling as well as potentially through IFNAR2 [56][138][139][140]. Conversely, changes in the expression of the other type I IFN–β used in therapeutics, differentially expressed genes (DEGs), were examined. Together with TNF–α expression during *in vitro* stimulation of monocytes and T cells, metabolic changes were found to occur in specific immune cells expressing CD protein receptors [141]. Further clarification revealed that type I IFN–β could modify two immune cell checkpoint proteins, CD38 and CD83, through upregulation of monocytic cells at two days but not T cells, confirming that type I IFN–β can modify the STAT3 signalling pathway [141].

Type II IFN and immunological disorders

Cellular IFN signalling and synthesis can be influenced by many factors, including genetic mutations or cellular transcription/translation through transcription factors. These changes can affect the resultant immune cell secretion of type II IFN–γ as well as naturally produced auto–antibodies (aAbs). Changes can exhibit pathological consequences in individuals during either an ineffective immune response (e.g., immunodeficiency) or an overactive immune response.

For instance, Mendelian susceptibility to mycobacterial disease (MSMD) was first reported in 1996 as an inherited human IFN–γR1 and IFN–γR2 genetic mutational deficiency [142], with a resultant effect on less type II IFN receptor signalling and less effective immune responses, as described above. Since 2000, reports of two individuals have shown that type II IFN production through MSMD research can be affected by a number of other point mutations in many genes encoding IRF proteins and cytokines (e.g., *IL–12*) together with STAT1 (e.g., *IFNGR1*, *IFNGR2*, *IRF8*, *IL–12RB*, *IL–12RB1*, and *STAT1*), each of which is crucial to the cellular IFN signalling pathway [143]. Type II IFN–γ production influences outcomes during mycobacterial infection or other infections. Type II IFN is a crucial NK and T-cell cytokine that is naturally produced in a host. In 2020, gene mutations in genes affecting type II IFN–γ signalling through IFN–γR1/IFN–γR2 were reported in two patients [141]. Mutations in this trimer of type IFN–γ signalling through IFN–γR1/IFN–γR2 can be deficient and abrogate nuclear cellular transduction signals. This synthesis by both NK and T cells in some cases may be independent of circulating viral antigens [141]

However, in 2012, STAT1 (LOF) was also detected within the IFN pathway, indicating that MSMD could occur as one of four inherited phenotypes [144]. Research shows that increased host susceptibility to viral, bacterial, and mycobacterial infections is associated with the resulting immune responses [144]. Furthermore, two cases in 2012 corroborated that granulocytes could display reduced production of IFN-stimulated gene 15 (ISG15) protein, resulting in fewer type II IFN–γ

lymphocyte responses with recurrent mycobacterial illness [145]. It was subsequently suggested and hypothesised that cellular *ISG15* and serum ISG15 could have cytokine-like properties and be synthesised by B cells as well as monocytes in the sera of healthy individuals [145]. More recently, in 2021, a categorisation was proposed for other type I interferonopathies in which unrelated inherited diseases can cause inflammation due to dysregulation of this crucial IFN pathway [146]. With regard to type II IFN–γ, genetic variations also affect proteins encoding human leukocyte antigens (HLAs) that produce alternative protein-processing antigens, such as MHC I/II surface receptors, which vary between populations. As recently as 2021, anti–type II IFN–γ autoantibodies (AIAAs) were suggested to be affected by HLA antigens in some diagnosed patients (n = 600), which could explain differential immune responses to infections such as mycobacteria [147]. Specifically, it was suggested that the following alleles encoding MHC type II peptide-presenting molecules could be variable: HLA–DRB1*16:02–DQB1*05:02 and HLA–DRB1*15:02–DQB1*05:01 [147][148]. Therefore, each of these factors will be discussed further.

Type III IFN and immunological disorders

Type III IFN–λ was first discovered in 2003 with subsequent confirmation of four subtypes of type III IFN–λ1, namely, IFN–λ1, IFN–λ2, and IFN–λ3, together with IFN–λ4 [149]. Early observations revealed that type III IFN–λ can influence immune cell (monocyte) development into DCs through several cytokines (e.g., IL–2). This process was noted to differentially induce T_{REG} cell development through STAT protein and IFN signalling [69]. In the course of 2010, genomic analysis revealed that one gene for *IL28RA* (*IFNLR1*) was common to many animals, including humans, monkeys, mice, horses and chickens [150]. The gene transcript was subsequently found to be expressed not only in lymph nodes (LNs) and testes but also in germinal centre B cells and various types of cancer (lymphoma, acute lymphoblastic leukaemia, and head and neck cancer) but also at high concentrations within tissues such as the pancreas (thyroid, skeletal muscle, and heart tissues), suggesting that these tissues could respond to type III IFN synthesis [70]. Interestingly, the authors postulated that the three important adaptive arms of the immune system were responsive to NK cells and T_C cells through the promotion of the other T_H1 cell response phenotype [70].

In early 2011, research described a lymphocyte–specific DNA–binding protein, which is encoded by*LyF* and is described as having a transcriptional binding site within the *IFNLR1* domain encoding one part of the type III IFN receptor[71]. Additionally, an activator protein 2 (AP–2) complex together with c–Jun and a p53 binding site within 1 kilobase of the start of the transcription sequence of *IFNLR1* in humans was described [70]. In 2011, the first report revealed the other key gene transcript for type I IFN synthesis, *ISG56*, as well as *RIG–I* induced by synthetic IFN–λ2 *in vitro* in *P. alecto* bats [72]. As type III IFN research unfolded, further illumination in 2014 highlighted that JAK2 was essential for regulating signal transduction of type III IFN–λ1 when it was observed *in vitro* that *Listeria monocytogenes* potentiated type III IFN–λ1 signalling around peroxisomes [73]. The new type III IFN–λ4 was simultaneously investigated using transcriptome sequencing (RNA–seq) to understand how liver hepatocytes and primary human airway epithelial cells (pHAEs) could be affected [74]. This comparison and others note that the gene encoding type III IFN–λ4 is more polymorphic, changing cellular function after protein translation with frameshift mutations disrupting translation of IFN–λ4 mRNA [151]. In 2015 and following EBOV outbreaks, details on the newly discovered type III IFN in immune cells emerged, revealing that gene

transcripts during disease severity were detected (*IL28A*/*IL28B*) within DCs [14][130]. In 2016, based on clinical asthma severity in individuals (n = 66), no difference in IFN/ISG gene expression was detected. It was observed that neutrophilic asthmatics overexpress both type I/III IFN (IFN–β, IFN–λ1), rather than eosinophilic asthmatics, but not type III IFN–λ2 or IFN–λ3 [76]. During HCV infection, it was observed that STAT2 could change ISG15 synthesis through*MX1* transcription, which is required for type I IFN synthesis in Mϕs, with type III IFN phosphorylating JAK2, suggesting that STAT2 may heterodimerise [152]; subsequently, an increase in PKR and IRF9 was observed in cells deficient in these proteins stimulated by type I IFN [152]. These results confirmed that type III IFN–λ1 transduction was dependent on STAT1/STAT2. IFN can also reduce replication and inhibit HCV, while STAT1 is essential for type II IFN synthesis [153]. The paradoxical role of IFN–λ4, the most studied polymorphic IFN, indicates that during HCV infection, type III IFN–λ4 is secreted at lower concentrations from a stressed endoplasmic reticulum. This effect attenuated HCV-specific peptide presentation to $^{CD8+}$ T cells through MHC class I peptide-dependent presentation [153].

More recently, since 2020, research in SLE has further confirmed the unclear mechanisms of type III IFN and that IFN–λR1 may be correlated with double–negative (DN) B-cell proliferation signalling through TLR7/8 PM receptors [77]. It was plausibly suggested that increased IgM production could occur outside the lymphatic follicular environment, where B-cell antibody clonal selection and isotype switching usually occur [77]. Nevertheless, during the timeframe of type III IFN–λ4, there has been further presentation of extrafollicular B and T-cell phenotypes in AI disease (RA), revealing that type I IFN–α induces T cells in conjunction with IL–12 and CXCL13 production [78][79][80]. In contrast to IFNAR, IFN–λR1/IL10R2 is considered to be expressed by neutrophils, pDCs, Mϕs and lymphocytes, although it is prevalent within mucosal cellular layers [81][154].

In comparison, supporting evidence of the suppression of type III IFN–λ synthesis during rotavirus infection and porcine epidemic diarrhea virus (PEDV) infection similarly remains under investigation [155][156][157][158]. In pigs in 2019, just before the recent pandemic, *in vitro* experiments compared the transcriptional profile of porcine epithelial cells and revealed that type III IFN–λ3 upregulated at least 983 DEGs [159]. This STRING database analysis indicated that 7x as many type III DEGs in comparison to type I IFNs could be upregulated, illustrating the diversity of type III IFNs. These observations remain pivotal for the potential antiviral inhibition of porcine epidemic diarrhea virus (PEDV) infection. Although they cause different viral infections, type III IFNs are historically considered to be suppressive of bacteria at mucosal barriers [81]. This was one of the initial projects that revealed that relevant STAT protein-encoding gene transcripts affected by IFN–λ3 upregulation could be related to STAT2/JAK2, given that the effects of STAT proteins and JAK enzymes can potentially be activation/inhibition therapeutic targets [156].

Current 2022 investigations imply that IFN–λR1 is expressed within gingival keratinocytes, with*in vitro* IFN–λ1 stimulation at low doses activating RIG–I/TLR3, with both PRRs recognising viral RNA without evoking high expression of proinflammatory cytokines, such as IL–6, and therefore may be of consideration as antiviral agents [160]. Additionally, IFN–λ3 expression in a vector is being investigated to counter a variety of dog–affecting pathogens, such as canine coronavirus (CCoV), parvovirus (CPV), and distemper virus (CDV) [161]. In 2020, *in vivo* expression of a recombinant type III IFN (IFN–λ2, IFN–λ3) during rabies virus (RABV) infection was shown to result in an antiviral response after intranasal

administration and a reduction in the viral load of a neurotropic virus [162]. Overall, these observations were accompanied by the expression of type I IFN-related proteins (IFN–α4, IFN–α5, IFN–β, STAT1, and IFIT2) that can change vascular blood–brain barrier permeability [162]. Recent kinetic reports indicate *the in vitro potency* of the more polymorphic IFN–λ4 in hepatic cell lines, which is seemingly translated before 24 hours after cellular infection, instigating STAT1/STAT2 phosphorylation earlier [151]. This was also characterised by gene transcripts (*MX1*, *ISG15*, *OAS2*, *RIG–I*, and *STAT1),* while IFN–λ3 was sustained after 24 hours, in contrast to other reports [151]. Conversely, during human papillomavirus infection, which is implicated in cervical cancer, the differential expression of mucosal epithelial cell type III IFN gene transcripts (*λ1, λ2*, *λ3*) was upregulated in individuals (n = 56) with low-risk HPV infection[163]. Furthermore, utilising *in vitro* HPV18 expression in cell lines revealed that type I IFN–β and type III IFN–λ1 in basal epithelial cells could be inhibited by DNA ligand stimulation and through suppression of the cGAS–STING pathway necessary for IFN synthesis [164].

Errors in IFN-STAT pathway signalling during disease

Initially, four errors in STAT1 signalling were defined as genetic factors affecting protein production and immune system function. These were defined as follows: “AR complete” STAT1 deficiency, along with “autosomal dominant (AD)” but also “partial”, along with “gain of function (GOF)” and observed in pathological reports (n = 6) in children [143]. In the course of 2006, errors in TYK signalling within this pathway emerged in a single patient who was observed to have recurrent viral and mycobacterial infections along with increased levels of IgE susceptible to bacterial staphylococcal infections [165][166]. In 2015, further cases surfaced (n = 7), indicating that IFNAR1 could be downregulated, in addition to two cytokine receptors (IL–10R2 and IL–12Rβ1) being affected, accompanied by reduced expression of the IFNLR subunit affecting both IL–12 and IL–23 receptors during mycobacterial infection [167][168]. The aforementioned reports thus indicated that type I IFNs affect the synthesis or production of the crucial cytokine IL–12. Conversely, isolated reports from 2015 looking into chronic mucocutaneous candidiasis (CMC) confirmed that mutations in STAT1 are independent of STAT3, affecting T_H17 cell differentiation and producing IL–17 [169]. In 2020, only one additional case of a family with a heterozygous deficiency of the type I IFN receptor (IFNAR2) was reported, exhibiting a clinical pathology similar to that of hemophagocytic lymphohistiocytosis [170]. This indicates that type I IFN–α affects NK degranulation and function and controls the inhibition of type II IFN–γ [170]. Interestingly, the same donor cells were used *in vitro* to confirm that STAT1 phosphorylation is required for IFN signalling. Flow cytometric analysis of monocytes for this project revealed that IFN signalling did not occur because type I IFN gene transcripts were nearly completely abrogated (*IFI44*, *ISG15*, *CXCL10*, *IFI27*). This included other genes, such as the virus inhibitory protein endoplasmic reticulum–associated IFN inducible gene (*VIPERIN*, also known as *RSAD2),* sialic acid binding Ig like lectin (*SIGLEC1*), and type II IFN–γ-regulated genes [170][171]. More recently, reports have indicated that TLR3 deficiency may also occur as an AR disorder found during influenza infection in children (n = 3) [172].

Moreover, in 2020, the function of STAT1 in monocytes was shown to play dual roles in abrogating or reducing type II IFN–γ and type I IFN–α function during infection. These can result in serious complications immunologically through the LOF of monocytes, with recurrent infections independent of type III IFN–λ [173]. More recently, within the Shigella bacterial

species outer surface protein C (OspC) member, OspC2-mediated inhibition of type III IFN–λ1 synthesis was observed during infection [154]. In 2021, one report revealed through enterovirus infection of individuals (n = 2) that deficiencies in cytoplasmic TLR3 together with a RIG-I-like receptor, named MDA5, may explain why activation of TLR3 is required for endosomal sensing of type I/III IFN and that MDA5 is independently required for cytoplasmic pattern recognition [174]. Previously, STAT1 signalling was examined in individuals with GOF or overactive STAT1 signalling in diagnosed CMC individuals (n = 8) to impair STAT3 [169]. Considering the paucity of previous reports, it can be posited that further clarification is needed. Summary reviews from 2020 detail the complexity of errors in IFN signalling, affecting type I/II IFN signalling through gamma–activated sequences (GAS) responsible for delivering an effective immune response to infections and cell cycle regulation in cancer through adaptive T-cell phenotypes [173]. The role of type II IFN cannot be equally understood, as three types of IFN regulate and signal through STAT proteins.

Deficiencies in many STAT proteins affect all aspects of an effective immunological response. Recently, studies employing scRNA genomics quantified STAT2 deficiency in individuals (n = 23), which further elucidated the relationship between IFNAR2 and STAT1/STAT2 IFN signalling [138][175]. These findings suggest that STAT2 deficiency results in a loss of sensitivity to type I IFN. Gene transcription at the single-cell level showed that STAT2 deficiency affects specific T cells known as effector memory (T_{EM}) cells [138][175][176]. The genes with reduced expression of a number of gene transcripts included myxovirus resistance protein genes (e.g., *MX1*) in addition to *IRF9*, *ISG15* and ubiquitin–specific peptidase 18 (*USP18,* also known as *ISG43)*. Concurrently, two other gene factors (*STAT1*/*IRF1*) and one intercellular adhesion molecule (*ICAM1*) can affect IFN signalling in the classical monocyte response to and adhesion to viral inflammatory disorders, such as influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and enterovirus, as well as other viruses, such as herpes simplex virus (e.g., HSV-1) [138][175][176]. Furthermore, since 1966, STAT3 deficiency was also described in 2007 as a cause of hyper–immunoglobulinemia E, but its source is obscure [165]. The protein STAT3 was suggested to be involved in sporadic cases in individuals (n = 98) with another rare AD disorder (Job's syndrome) characterised by dermatitis and increased serum IgE [165]. In this instance, IL–6 stimulation resulted in less CCL2 synthesis by leukocytes and was suggested as a possible explanation [165]. The role of STAT3 in the immune system is shown below (Figure 3).

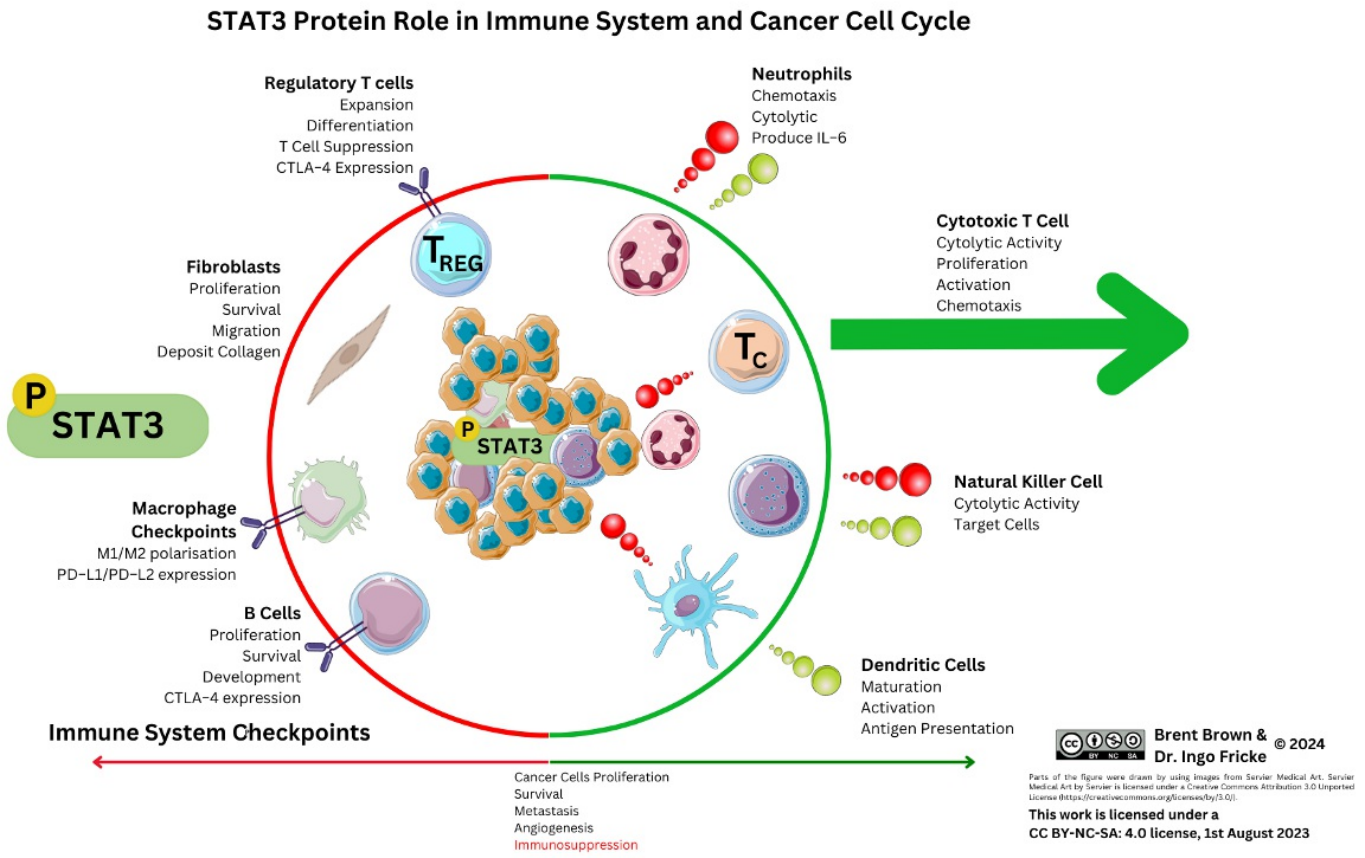

Figure 3. Role of the STAT3 protein in the immune system and cancer. Positive (green half of the circle) and negative (red half of the circle) effects exerted in the shown immune cells are depicted; CTLA–4: cytotoxic T–lymphocyte associated protein 4; PD–L1: programmed death–ligand 1.

The fungal and T_H17 cell immune responses during recurrent infection remain unknown, and further studies on DCs are needed. In 2023 DC analysis, through comparison of monocyte–derived DCs (moDCs) to tolerogenic DCs (tDCs), it is surmised that tDCs may express fewer immune cell checkpoint regulatory proteins (CD80, CD83, and CD40), while moDC phenotypes express other inhibitory receptors, such as PD–L1 [177]. However, PD–L1, which has dual effects on T-cell immunoglobulin (Ig) and mucin domain–containing protein (TIM3), was characterised as a receptor expressed on both T-cell types ($CD4^+/CD8^+$) that produce type II IFN–γ. Both checkpoint proteins remain targets of cancer therapeutics [178][179].

Other types of IFN regulation pathways

The other three crucial STAT proteins (STAT4/5/6) have recently been investigated. As recently as 2021, other authors concur that STAT4 has not been extensively examined and remains mysterious. STAT4 is constitutively expressed by hematopoietic cells (HPSCs), including both NK/T cells, and is involved in health and disease [180].

In 2020, it was shown that STAT4 is encoded by two additional gene transcripts (*α/β*), with the STAT4α subunit being able to induce the cellular production of more type II IFN–γ, whereas the STAT4β subunit was more responsive to IL–12 stimulation [181]. STAT4 is a pertinent potential protein modulator of tumor suppression during hepatocellular carcinoma (HCC) but is also correlated with serum hepatitis B antigen (HBsAg) levels [181][182][183][184]. An additional role for various

AI diseases, such as Sjøgren's syndrome (SS), SLE, psoriasis, type 1 diabetes (T1D), and rheumatoid arthritis (RA), as well as both asthma and atherosclerosis, has been suggested but discussed elsewhere [181][182][183]. Of the remaining two STAT proteins, STAT5 is essential for NK cell development and harbours two types of protein domains [52]. This approach was recently shown to utilise mouse cytomegalovirus (MCMV) infection *in vitro* in human cells [150]. STAT5 expression is upregulated in memory NK cells but not in naïve NK cells [150]. Furthermore, this was induced by IL–12 in cooperation with the two cytokines IL–2 and IL–15 to produce granzyme A, possibly affecting the apoptotic PI3K pathway [150][185]. However, STAT5 is also composed of 2 protein domains with varying functions. Overexpression of STAT5A *in vitro* in $CD4^+$ T cells stimulated with type I IFN–β suppressed CD279 (PD–1) induction, in turn regulating other coinhibitory receptors [186]. In comparison, STAT5B deficiency results in reduced numbers of T_{REG} cells, while STAT5A does not change [104][187][188]. Furthermore, STAT5B deficiency can manifest during lymphopenia together with a reduction in γδ T cells, as well as NK cells [187]. Deficiency of STAT5B in individuals has been associated with other AI diseases, such as idiopathic arthritis, thyroiditis, and thrombocytic purpura, with an undisclosed role of T_{REG} cells [150][185]. Finally, the dimer STAT6 can be activated by phosphorylation and is considered to transduce signals from cytokines required for Mϕ maturation (IL–4/IL–13), B-cell–driven maturation and various subtypes of Ig maturation in GCs [52]. STAT6 can be activated independently by viruses but also recruits APCs and T cells, which play a part in innate immunity during allergic conditions and immunity to helminthic parasites during T_H2 cell–driven responses [189]. The relevance of other genes translated into extracellular cytokine–like proteins induced by type I IFN, such as ISG15, is of consideration. During deficiency, the encoded protein appears to play a role in regulating type II IFN mycobacterial immune responses and is expressed in acute arthritic conditions [145]. The overall role of STAT proteins is depicted below (see Figure 4).

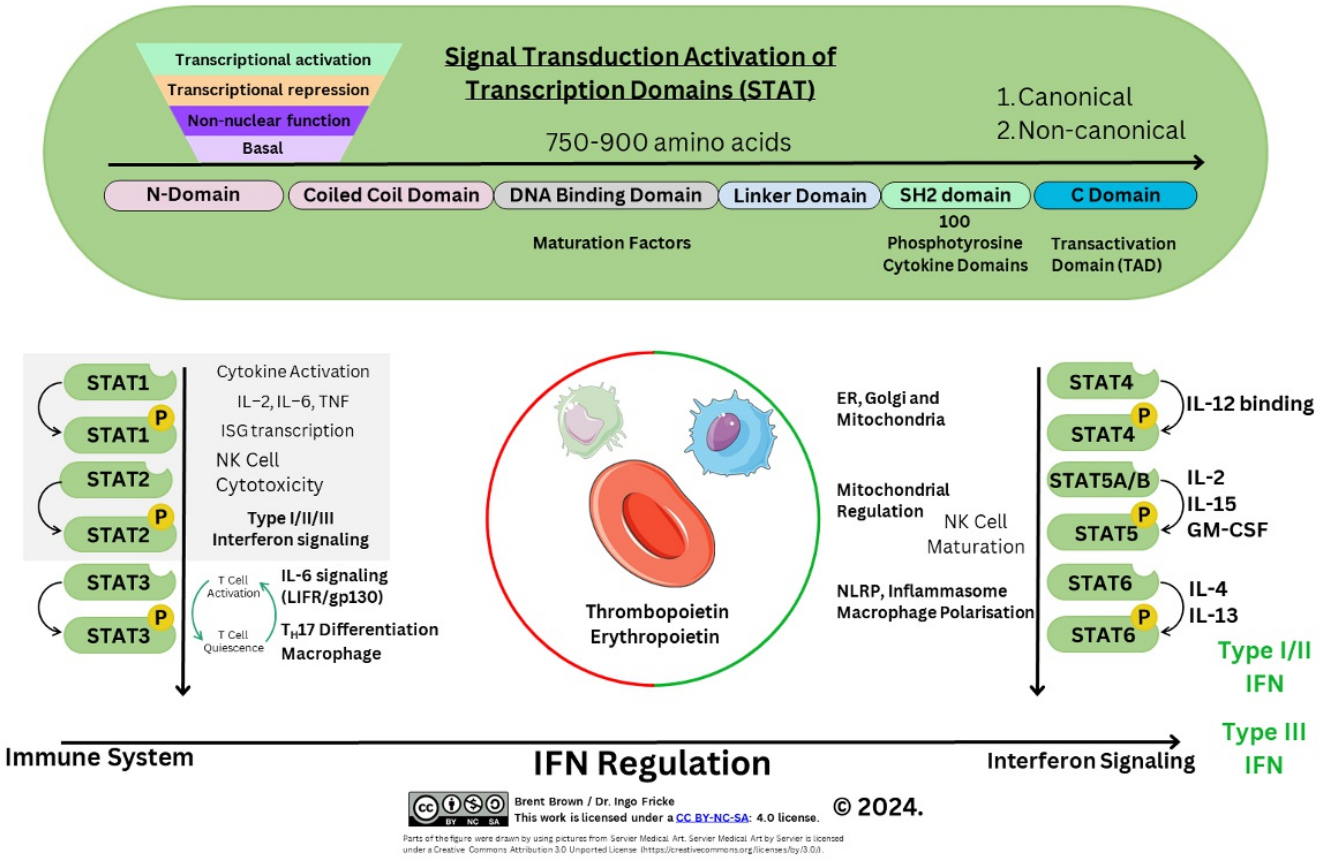

Figure 4. Protein and cytokine STAT interaction summary known today; NLRP: Nucleotide-binding oligomerization domain, **leucine-**rich **repeat** and **pyrin** domain.

Errors and effects of type I IFN and aAb production

Timing of IFN synthesis and immune cell pathways

The chronology of IFN signalling postcellular infection can be affected in three stages. Initial early IFN synthesis from DCs, followed by a delayed response, and, third, an absent IFN response through various cellular and nuclear factors. The first can occur with temporal viral load regulation, enhanced regulation of proinflammatory responses in the acute/chronic phase, as in many bacterial and viral diseases (e.g., EBOV/COVID–19). The second pathway is followed by a dysregulated DC maturation process, T-cell maturation, or antigen presentation by other cells during acute/chronic inflammation (e.g., DCs, monocytes/Mϕs); this process is affected by IFN signalling and subsequent secretion through respective receptors and STAT proteins (e.g., STAT1/STAT3/STAT5) [52]. The third may occur through either inborn genetic errors unknown or the production of autoantibodies (aAbs), which can affect the availability and transduction of IFN receptor pathways during pathogen infections (e.g., *H. pylori*). Currently, the homeostatic early synthesis of type I IFN, which affects the regulation of the immune system, underpins many of the current research therapeutics.

Autoantibodies, IFN and errors

Systemic production of aAbs, including those against type I IFN, for example, has long been known to occur in different pathologies. During AI polyendocrinopathy syndrome type I (APS–I), this AR syndrome occurs through immune cells affecting endocrine function, resulting in adrenal candidiasis insufficiency. In this case, point mutations in the AI regulator gene (AIRE) affect the tolerogenic profile development of T cells [177]. Notably, in population studies in 2017, aAb titres against type I IFN–ω were particularly high, varying across populations with IFN–α2 [190][191]. Subsequently, a notable study in 2017 (n = 8972) examined other aAbs against type I IFNs, including IFNα2, and found that aAbs occur naturally in 86% of people when combined with four other cytokines measured (IL–1α, IL–6, IL–10, GM–CSF) to determine their natural occurrence in younger adults [190][191]. Conversely, other studies in 2023 examining this phenomenon during non–COVID–19 acute respiratory failure in individuals indicated (n = 284) that 1.1% were positive for antibodies against IFN–α2, similar to recent findings for type III IFN [192][193].

Furthermore, SNP mutations also occur in other IFN signalling proteins, such as STAT2, or other AR individuals, with pathological consequences. This includes hemophagocytic lymphohistiocytosis, bronchiolitis, and recurrent respiratory syncytial virus, among others [175]. Causal factors in aAb production resulting in disease as a genetic trait were observed in investigating type II IFN research. Exemplified in 2019, a population study (n = 74) in Southeast Asia indicated that aAbs against type II IFN–γ do vary between populations and may be present as a risk factor for nontuberculous mycobacteria (NTM), in addition to other opportunistic infections such as *Salmonella*, *Histoplasma and Cryptococcus* [194].

During the recent COVID–19 pandemic, extensive research indicates variability and unknowns with regard to aAbs. Approximately 10%–25% of those who have chronic COVID–19 pneumonia possess aAbs to type I IFNs (type I IFN–α2 or IFN–ω) aged over 25 years, with less to the other subtypes of type I IFN–α but not type I IFN–β [195][196]. In other viral infections, such as WNV, aAbs to type I IFN (IFN–α/IFN–ω) were detected in a cohort (n = 441), occurring in males over 65 years of age at a prevalence range of 0.3%– 1.0% and in one-third of individuals hospitalised [197]. Although SARS–CoV–2 is a well–characterised virus, at least three types of type I IFNs possess antiviral regulatory properties (IFN–α8, IFN–β, IFN–ω), with type I IFN–ω having the most potent inhibitory activity against SARS–CoV–2 B.1.351 lineages circulating up to 2021 [63]. For reasons explained below, this was an oversite area of research, as another type I IFN–ε protein alongside type III IFN–ω proteins was also observed at higher concentrations in infant nasopharyngeal samples (n = 192) [198]. This was concurrently observed in population studies showing variance in the decrease in IFN subtype inhibition ability between four strains of SARS–CoV–2 showing less type I IFN antiviral activity [56]. In combination with genome–wide association studies, gene set enrichment analysis revealed that the type I IFN pathway could be associated with COVID–19 severity (n = 466) [199]. Authors correctly pointed out there are few if any global population studies that examine human leukocyte antigen (HLA) polymorphisms which are key in tissue typing. The HLA gene encodes two functional protein complexes required to present antigens (MHC class I/II) that are polymorphic proteins other than IFN proteins, as described above.

IFN and immunotherapy regulation in cancer

IFNs play roles in many pathologies. Both type I/II IFNs have long been considered immune cell regulators affecting both

the cell cycle and cancer cell proliferation, with partial protective roles during tumorigenesis through the expression of CD274 (PD–L1), while tissue cells can produce the suppressive cytokine IL–10 but also the metabolite indoleamine–pyrrole 2,3–dioxygenase (IDO1/2), which limits tryptophan catabolism. The regulatory effects of IFN rely on interactions between metabolic and cytokine factors affecting immune cell function (Figure 5).

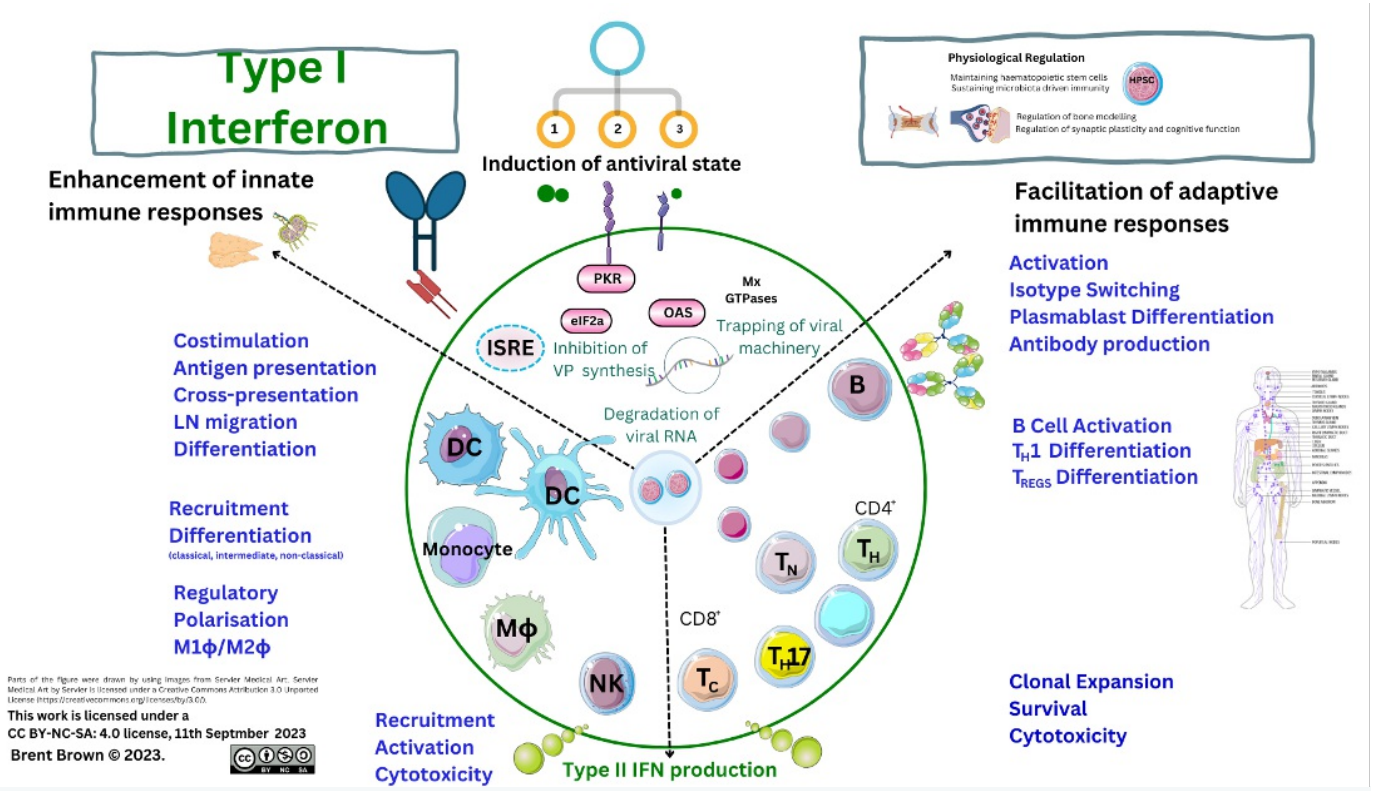

Figure 5. The role of type I IFN in the immune system.

These include tryptophan and its metabolite kynurenine, which affect the metabolism of immune cells such as Mϕ (M1ϕ/M2ϕ) and activate T_C ($CD8^+$) cells. Effector immune cell function relies on the production of perforin, granzymes and other cytolytic enzymes from both T_C/NK cells in the tumor microenvironment (TME), where other cell cycle proteins are involved [84]. Other reviews have identified therapeutic agents involved in clinical trials targeting type I IFN pathways, such as TLR agonists, STING agonists, chemotherapeutics, oncolytic viruses and cancer-targeting agents [200]. However, the overexpression of IRF7 proteins also affects cancer and acute myeloid leukemia (AML) progression [201]. Similarly, inhibition of vascular endothelial cell adhesion molecules (VCAM) and vascular leukocyte antigens (e.g., VLA–4) may reduce intracerebral invasion during AML *in vivo* [201]. In the past 2020, it was known that type II IFN–γ induces CD274 (PD–L1), a ligand of CD279 (PD–1), as well as IDO1 and is a checkpoint of T-cell activity in tumours. Thus, STAT1 upregulation and JAK2, as well as tryptophan degradation and NK cell suppression, remain targets of IFN therapy. It is considered that the T-cell response is affected by the concentration of type II IFN–γ within the TME, in addition to Mϕ phenotypes and tumor–associated antigens (TAAs), as well as type I/III IFNs [84]; moreover, escape from type II IFN–γ immune cell detection can regulate tumorigenesis [200][202]. As recently as 2021, other early IFN therapeutic (e.g., ProIFN) data *in vivo* indicate that the upregulation of CXCL9/CXCL10 in combination with more T cells expressing CD8 and fewer

T_{REG} cells is promising for infiltrating the TME[39]. Additionally, CD274 (PD–L1) can be upregulated on APCs, allowing infiltration of hot tumours, presumably because the ligands of CXCL9/CXCL10 allow more DC antigen cross–presentation but also have a receptor, CXCR3, on DCs [203].

Discussion

Since the 20th and 21st centuries pandemics, ongoing IFN research and receptor cloning have clarified some of the complexities of IFN. Type I IFN–α synthesis can affect viral replication, while type II IFN–γ is historically considered to be beneficially secreted from activated adaptive immune cells, training and a measure of the immune system response to pathologies, including cancer. Overall, the future effects of IFN subtypes on cells could be explored further. Malignant tumours and neurodegenerative disorders can be affected through type II IFN–γ-cellular secretion. The effects of a naturally produced human chemical remain a therapeutic development target subject to *in vitro*/*in vivo* methodology with toxicological profiling, although other recent developments in other cancer immunotherapeutics, including cytokine modulators, have occurred. Type II IFN–γ plays a key role and can be cytostatic and apoptotic and may prevent cellular proliferation within the TME.

In a recent 2022 study, the relevant IFN gene signatures were similar to those discussed above (*ISG15, IFI44L, OAS1, IFI6, MxA*) [21]. Type I IFN synthesis and exocytosis from tumor cells also represent essential steps in the adequate signalling of tumor cells to immune cell components implicated in both angiogenesis and oncological diseases [95]. Furthermore, the rate of type I IFN synthesis could be affected by LINE–1 retrotransposon viral inhibition [204]. Type II IFN is considered to be predominantly produced by T_H1 cells expressing CD4. In three cancer types (metastatic melanoma, head and neck squamous cell carcinoma, and gastric cancer patients), IFN gene signatures may also correlate with the activity of checkpoint inhibitor proteins through M1ϕ selectively activated to overcome tumor progression within the TME [84].

Questions arise as to when and how synthetic type I and type III IFNs can be better utilised to mimic naturally synthesised proteins that can cause complete cancer remission. Together with 2016 developments, type III IFNs (encoded by *IFNL1*, *IFNL2,* and *IFNL3)* indicate that type III IFN–λ4 may be associated with decreased cellular antiviral activity[205]. This has been observed during rotavirus infections [157]. Observations in other studies indicate that a type II IFN–γ gene, as well as an IL *serum* transcript *(IFNG/IL1A),* were upregulated, together with various chemokines *(CCL2/CCL3/CCL8)* [62]. The *level of* type II IFN–γ *(IFNG)* could be unchanged in *the* lungs [62]. This *finding* further *indicated* that T-cell production of type II IFN–γ could be independent of type I/III IFN. Strikingly, type I/III IFN variation across lung cell types and variable gene expression between myeloid cells (monocytes/Mϕs/neutrophils/cDCs) could be affected by temporal reductions (lymphopenia) in specific immune cells of lymphoid origin (B/T cells or pDCs) as well as other immune cell phenotypes [63][206]. The expression of one cytokine, TNF–α, can be reduced by altering other T-cell phenotypes (T_N/T_{EM}/T_H17/T_{REG} cells), as can that of NK cells and Tc cells. IFN pathways can affect STAT1/STAT3 signalling and immune cell differentiation through type I IFN regulation, but the other IFN signalling pathway, STAT5, may not [62].

Interestingly, it would thus appear that if IFN gene transcripts are present, unidentified T-cell phenotypes could affect this balance together with the rate of IFN/TNF synthesis [207][208][209]. However, Sposito et al.[63] showed that subtypes of type I IFN (*IFNβ1*, *IFNA2, and IFNA4*), as well as type III IFN gene transcripts, can be upregulated in the upper respiratory tract during COVID–19. The gene transcripts specifically shown were type III IFNs (*IFNL1, IFNL2, and IFNL3*), which are significantly correlated with the SARS–CoV–2 viral load, but the levels of *IL1B* and *IL–6* were also unusually increased in the control group, with the above IFNB being overexpressed during lower respiratory tract infection, as measured in bronchoalveolar fluid [63]. These results would therefore imply that neutrophils may not be causal during chronic COVID–19, which remains obscure [63]. Type III IFNRs can be differentially expressed and have utility as therapeutic targets[63]. This finding indicates that nuclear IFN subtype transcription differs between viral pathogens and affects metabolic and cytosolic pathways or nuclear pathway protein translocation. Such other factors are becoming evident with investigations into multisystem inflammatory syndrome (MIS–C), another pathology not yet understood. Although various theories circulate regarding the origins of SARS–CoV–2, it is important to note that there is a semblance of superantigen–like properties. Other studies indicate that a combined diagnostic approach could be utilised, exemplified by a combined CD64/CD169 diagnostic, to differentiate between bacterial/viral infections in which neutrophils and monocytes are affected [210]. The role of cellular membrane Fc receptors that bind Abs in effector cell function requires further clarification [211].

Before the COVID–19 pandemic, CD64 was suggested as a diagnostic marker of sepsis, even as CD169 could be considered an activation marker in other viral pathologies [210]. However, the IFN gene signatures evoked during type I IFN homeostatic responses in the early onset of arthritis appear to be similar and mirror human type I IFN gene signatures, as well as inhibiting lyssaviruses [212]. Further details on other AI conditions and therapeutic developments, such as those described above, require further development [213][214][215][216].

In this century, the bat gene transcripts affected by type I IFN response*in vivo* appear to include *Mx1*, *ISG15, IFIT3,* and *ISG56* and could be individually unique to type I IFN–w uncharted[217]. Type I IFN–w was described as antigenically distinct, understandably because the genetic regulation of different species can vary among species. However, Guo et al. [56] clearly showed that type I IFN–w, together with both IFN–α8 and IFN–β, was the most potent inhibitor of the SARS–CoV–2 viral load *in vitro* using quantitative PCR in conjunction with human alveolar type II epithelial cells (A549) transduced with the angiotensin–converting enzyme 2 (ACE2) receptor. Few studies have documented which species–specific pDCs are able to potentially produce IFN subtypes [130]. Type III IFN–λ is likely a major player in the DC–mediated immune response downstream of the activation of STING (encoded by the transmembrane protein 173 gene). It would be interesting to investigate the mechanisms by which type III IFNs regulate and induce STING in DCs and DC apoptosis [218].

Limitations

The assay scales used for measuring host type I/III IFN vary with regard to the early stage of research concerning potential further prophylactic/early therapeutic effects highlighted in 2019 [219]. A common problem of clinical trial

completion is a lack of funding with insufficient participants. Likewise, the bioavailability of natural or recombinant IFNs has an impact on the severity of multiple diseases. Adverse effects of recombinant IFN were noted in pharmacokinetic studies [220]; however, other studies indicate that the production vectors used could effectively deliver the appropriate pharmacokinetic profile further using other synthetic IFN derivatives [44][221][222].

Conclusion

In conclusion, pathogenic microbes and humans coexist and will evolve regardless of first–line human immunity. Many pathogens and oncological processes, as well as protein mutations discovered during development, affect the homeostatic immune system balance affected by IFN synthesis. Some pathogens and inherent genetic disorders may impair the IFN system. Given the above findings and the results from the NCT data, type I/III IFN therapy is worthy of further investigation as a potential prophylactic treatment. The type I IFN subtypes vary as described above, and type III IFNs can restrict the viral load in the respiratory epithelial tract. Developments in scRNA sequencing have provided greater insights into where type I/III IFN is expressed and by which cells and above are discussed where type III IFN could be a factor during the host immune response. Therefore, the outline above should serve as a complete analysis of current IFN subtypes in health and disease. The IFN gene regulatory pathways have been described in detail. Type I IFN was heavily researched before the pandemic and during oncogenic pathologies and utilised as a therapeutic. SARS–CoV–2 viral proteins affect the complexities of type I/II/III IFN subtype regulation. Therefore, this additional layer of immune cell regulation requires further research. Furthermore, studies appearing since 2022, although small cohorts, have consistently shown a reduction in type I IFN in patients during the pandemic, which could be due to other disorders. Further administration of type I IFN from NCTs revealed that other type I IFNs, such as IFNα–2b and IFN–w, as well as type III IFN–λ1, IFN–λ2 and IFN–λ3 in hosts, may counteract cellular infection to stimulate a robust and natural immune response against viral/neoplastic or other pathologies. Likewise, this intervention fits the definition of a traditional immunogen.

The variability in IFN synthesis in both immunodeficient patients and the current knowledge of IFN subtypes, together with the complexities of STAT proteins throughout pathologies, are discussed above, some of which were considered only in the 21st century during information technology (IT) development. This report should therefore serve academics, clinicians and researchers as a holistic overview of the roles of IFN in health and disease.

Abbreviations

- aa: amino–acid
- APC: antigen-presenting cell
- DC: Dendritic cell
- DENV: Dengue fever virus
- EBOV: Ebola virus
- IFI: interferon-induced

- IFIT: interferon–induced **protein** with tetratricopeptide repeats
- IFITM: interferon–inducible transmembrane proteins
- IFN: interferon
- IFNα: type I interferon
- IFN–λ: type III interferon
- IFNR: interferon receptor
- IFNAR: type I IFN receptor
- IFN–λR1/IL–10R2: type III IFN receptor
- LOF: loss of function
- MW: molecular weight
- PI3K: phosphatidylinositol 3–kinase
- PM: plasma membrane
- NK: natural killer cell
- STAT: signal transduction and activator of transcription
- SLE: systemic lupus erythematosus
- T_C: cytotoxic T-cell
- T_H: helper T-cell
- T_{REG}: regulatory T-cell
- TLR: Toll–like receptor

Supplementary Materials

The supplementary material for this article is available upon request.

Statements and Declarations

Author contributions

BB: Conceptualisation, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing–original draft, review & editing, Validation, Visualisation. CI: Data curation, Formal analysis, Methodology, Investigation, Writing–review, Software. IF: Data curation, Formal analysis, Investigation, Methodology, Writing–review & editing, Resources, Visualisation, Software, Supervision.

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