Review

Dr Jekyll and Mr Hyde: From Two Branches of Immune Response to Three Types of Interferon Response

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Dr Jekyll and Mr Hyde: From Two Branches of Immune Response to Three Types of Interferon Response

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Abstract: Interferons were the original prototype cytokine system discovered during research of the 20th century. As the name suggests these were originally considered to be synthesised and secreted between cells. However, technological advancements since dictate processes involved in secreting these proteins can be extensively explained through both genetic and biochemical pathways comparatively clearer. Interferon (IFN) discovery occurred when genetic research was in its infancy. Simultaneous discovery by Franklin and Wilkins of deoxyribonucleic acid (DNA) structure and function occurred with Crick and Watson concurrently; however, two scientists Isaac and Lindemann described the first IFN in 1957. Technological advancement allows comparison since many pathogens and genetic mutations can be factors in IFN regulation. Cancer cell regulation in research has long been central to host IFN synthesis and/or affected with differential IFN protein subunits defined further acting through 6 protein domains. Type II IFN remains central to immune cell function as it is released by a myriad of immune cells, mainly Natural Killer and T cells and is commonly used as a quantitative measurement of adaptive cellular immunity. Single–stranded and/or double–stranded RNA/DNA viruses as well as bacterial infections (e.g., *Escherichia*) and fungal infections (e.g., Mycobacteria) can affect IFN regulation systems. These utilise intra/extracellular proteins like Toll–like Receptors (TLRs) affected by mutations within the overall IFN transduction pathways. Questions remain over immunological mechanisms contributing to innate and adaptive host immune regulation since type III IFN discovery in 2003 with immune cell phenotypes characterised further. Changes to synthesis of host type I/II/III IFNs may alter homeostatic cellular pathways differentially and beneficially in pathological disorders. We therefore aim to present the rationale of this regulatory protein mechanism of action in context with research developments recently (see Figure 1).

Keywords: interferon; innate; adaptive; genetic; molecular

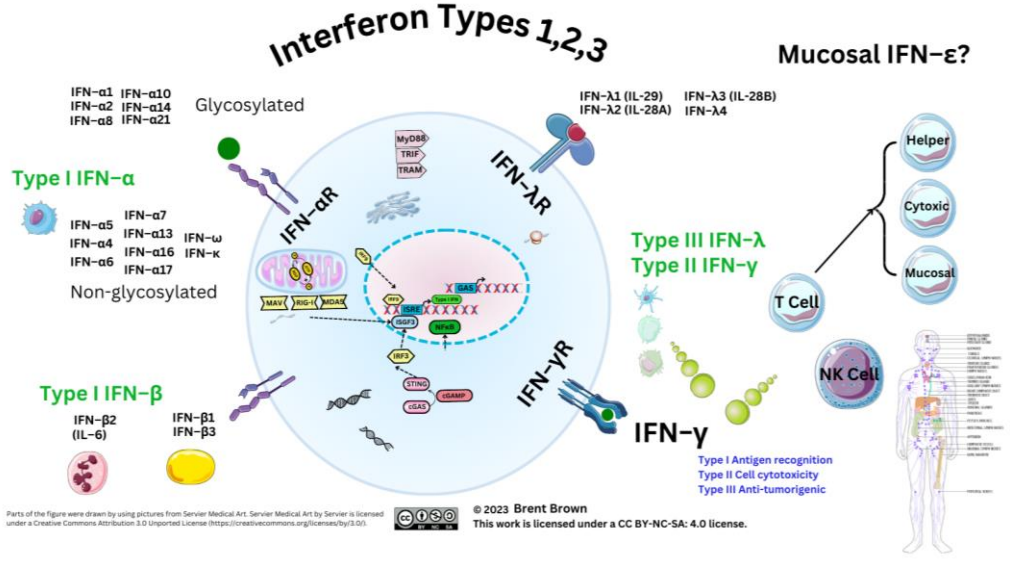

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Figure 1. Interferon Types.

Introduction

Interferons (IFN) are glycoproteins secreted that have historical unique anti–viral activity as well as cellular oncological regulation properties induced through immune cell regulation and secretion for example by dendritic cells (DCs) early in infection. The different types of IFN can stimulate immune system innate/adaptive compartments having pleotropic cellular properties regulated by many immune cells released proteins including cytokines (IL), chemokines (CC, CXC), acting as cellular autocrine/paracrine signals in a hormonal manner [1]. Interferon nomenclature is derived historically as alpha (α, from leukocytes), beta (β, from fibroblasts), and gamma (γ), from mitogen activated lymphocytes stimulated to proliferate. Following the 1957 initial discovery of one IFN, three principal types of IFN are now known divided into type I (α/ β), type II (γ), and recent (2003) discovery of type III (λ), with each having distinct anti–proliferative and anti–viral activities and further sub–types. At least three IFN types have unique variable cell function and are expressed when differentially expressed genes (DEGs), are transcribed and translated during health and/or disease regulated by IFN–stimulated genes (ISGs), as well as IFN–inducible proteins (IFI), with IFI transmembrane (IFIT/M) proteins being additional cellular regulatory factors. Immunisation and therapeutic treatment historically did target IFN therapeutic benefit through pre–clinical development, from phase 1/ 2 to phase 3 and beyond, according to overall safety profile and success rates through regulatory and monitoring authorities like the United States Food and Drug Administration Agency (FDA), European Centre for Disease Control (ECDC), and other organisations. However, literature regarding type I/II/III IFN is required to detail the overall positive and negative controls

Methodology

Currently, indications were more than 100,000 pubmed results showed prior interferon research. Clinical trials (NCT) investigating utility of IFN as a potential therapeutic total number: Furthermore, these are currently divided into other clinical trials that include type I IFN–α (380), type I IFN–β (116), type I IFN–omega (6) and type I (epsilon (1) (5 type II IFN–γ (173), and type III IFN–λ (17) currently (see Supplementary Data S1).

Background

Through either natural IFN or recombinant IFN synthetic compounds, either human type I IFN and/or type II/III IFN concentrations within host populations can train and stimulate both innate/adaptive two immune system branches thereby honing an effective response during disease. One includes T cell synthesis and NK cell synthesis of type II IFN also produced by other antigen presenting cells (APCs), like macrophage phenotypes (M1ϕ/M2ϕ). The immune system senses pathogenic antigens additionally through pattern recognition receptors (PRRs), as well as cellular endosomal expressed Toll–like (TLR) receptors. Cancer pathologies also respond to type II IFN, whilst viral evolution affects type I/II IFN homeostatic immune cell function. This aspect during viral epidemics/pandemics is known over prior decades, evidenced with Dengue Fever virus (DENV), Ebola virus (EBOV), and recently Monkeypox virus (MPXV) [2,3]. It is plausible that regulation of three types of IFN is modulated and can effect early therapeutic and/or clinical disease onset–delaying effects during viral evoked diseases like Influenza A virus (IAV), but also Measles (MeV), as well as Human Immunodeficiency virus (HIV); however other bacterial diseases are similar, such as lower respiratory tract bacterial infection caused by *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus aureus*, as well as oncological diseases, like hepatic melanoma [4]. Other reviews ascertain regulatory IFN proteins can be affected by viral proteins (VP) synthesised by *Coronaviridae* (SARS–CoV–2) as well as *Flaviviridae* (DENV, Yellow Fever) [5]. Individual VP mutations also affect other cytosolic PRRs (e.g., retinoic acid–inducible gene I, RIG–I/ mitochondrial antiviral–signaling protein MAVS) pathways in at least two other virus families (*Filoviridae*/*Nairovidiae*) [2,3,5]. There are unknowns regarding retinoic acid that is a metabolic component of immune cells. Viral mutations occur in both DNA/RNA viruses like the positive–sense single–stranded RNA virus (+ssRNA) Influenza A (*Alphainfluenzavirus).* This has 198 quantified potential antigen subtype combinations of the cellular expressed haemagglutinin/neuraminidase (HA/NA) protein antigens, which also affect

immune cell phenotypes. Different serotypes of Gram negative coccobacilli, *Haemophilus influenzae*, are known to shed intracellular or extracellular membranes during infection (e.g., Hia–Hif or ncHI); whilst others like Avian Influenza virus (IAV, H5N1) have been observed during zoonotic spillover. Therefore, viral antigens co–exist circulating in nature, with increases in antigen circulation necessitate clarification of interferon as a regulatory factor within all host immune responses.

Three or four or more types of IFN may have differential inhibitory or activation mechanisms on the immune system causal in lysing infectious viruses effectively through stimulating immune cellular effector cell activity through a myriad of proteins described here. This is effected though IFN receptors (IFNR) at the cell plasma membrane (PM) surface. This occurs through at least 18 types of IFN binding to 6 IFNR proteins expressed by dendritic cells (DCs) which also have variable phenotypes. Interferon receptors are also expressed by B–lymphocytes, monocytes, and macrophages (M1ϕ/M2ϕ), as well as T–lymphocytes. Receptor expression is also within the cellular PM including glial cells, neurons, and other cells. Interferon receptors (IFNR) therefore initiate downstream/upstream cellular effects as well as T cell secretion of type II IFN–γ upon host cellular viral infection. Plant products can also generate IFN stimulating proteins. Timing of cellular IFN synthesis and cellular secretion affects viral infection, propagation, replication. But also IFN acts through a myriad of cells and protein pathways to effect cellular lysis in organs, tissues and cell systems by regulating other cell cycle proteins, like p38. Immunodeficiency disorders or individual protein mutations may cause errors in IFN/IFNR signaling throughout development.

Therefore, the regulation of type I/II/III IFN response can have resultant detrimental and/or beneficial factors. The subtypes of these proteins directly affect and influence the two branches of the innate and adaptive immune response requiring clarity. Each IFN type fulfils individually unique immunological roles during 5 types of pathology including viral, fungal, bacterial, mycobacterial as well as oncogenic diseases. Immune system modulation and/or evasion may represent evolutionary development within animal hosts varying. Therefore here is the analysis of genetic, molecular, and cellular analysis of type I/II/III IFN mechanisms of action to date that will require further research.

Interferon Types

Overview to Interferon Cellular Types

Type I IFNs are synthesised/secreted after translation from cellular nuclear transcription factors (TFs) resulting in differential anti–viral activity against host pathogens that may vary. Each IFN protein is known as a small molecular weight (MW) molecule in humans; for example type I IFN–α1/13, IFN–α2, IFN– α8 and IFN–α21 are composed of 187–189 amino–acids, while type III IFN–λ are within the MW range 179–200 amino acids. Chemokines in comparison are smaller MW proteins (e.g., CCL2, 99 amino–acids), with pleiotropic effects directing immune cell migration throughout tissues. These small MW proteins are induced through gene synthesis transcription and can be translated earlier in response to pathogenic antigens outside the cell nucleus. Interferon subtypes can be synthesised by myeloid cells like plasmacytoid dendritic cells (pDCs) producing higher concentrations of type I IFN (IFN–α/IFN–β), effecting anti–viral responses in hosts; but also within skin epithelial cell tissues through tumour necrosis factor (TNF) related apoptosis–inducing ligand (TRAIL) and at least ten intra/extracellular PM and vesicular TLRs [6]. On the other hand type II IFN–γ is secreted by at least two effector cells (NK and T cells) together with another two antigen presenting cells (DCs and Mϕ)with different phenotypes. Whilst type III IFN subtypes may also influence host immune responses within epithelial layers. It could generally be considered that through regulating cellular cycle function that each IFN performs different roles with type I IFN–β potentially regulating Mϕ cell cycle (M1ϕ/M2ϕ) and metabolism whilst type I IFN–α could be considered similar in regulation of homeostatic function and observed commonly in inflammation and autoimmune disorders .

Type I IFNs include IFN–β, IFN–δ, IFN–ε, IFN–κ, IFN–τ, IFN–ω, and IFN–ζ amongst others; whilst type III IFNs are composed of IFN–λ (IFN–λ1, IFN–λ2, IFN–λ3, IFN–λ4), known originally as IL29, IL28A, and IL28B with IFN–λ4 discovered in 2014 [7]. Two types of type III IFN (λ2,λ3) are considered to have 96% amino–acid homology [8]. Other classifications of IFN subtype exist and all vary between host animal species encoded by *IFN* genes. To clarify, human IFN consists of at least 18 subtypes, some others of which are type I IFN–α4, IFN–α7, and IFN– α14; whilst in pigs and bats diversity of IFN–ω is worthy of consideration with less type I IFN–α described as discussed further

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[9–11]. Amongst type I IFN–α subtypes, IFN–α2 is O–glycosylated with a recombinant IFN–α2b therapeutic version utilised [12]. However, research studies since 2015 indicate that IFN–α2 is N–glycosylated and can be cleaved during secretion losing 23 amino acids and one aspartic acid (L) at position 44 [13]. Recently it was shown that type I IFN may contain pro–inflammatory glycans known to enhance binding of the predominant antibody (IgG) to immune cell FcγR PM receptors (CD16/CD32/CD64) that could train the immune system response [14,15]. Furthermore, this could influence the T cell response , including both cytotoxic (Tc) and NK cell function, through modulation of sialic acid residues present in other receptors like DC–SIGN or fucose residues.

Therefore in 2019, pharmacokinetic properties of recombinant type I IFN–α2 engineering indicated the production vector could affect pharmacokinetic half–life when glycoengineering indicated Pichia pastoris as a potential option together with purification of recombinant interferon; whilst all subtypes of IFN–β are also N–glycosylated [16–18]. In comparison, other studies show the addition of a glycosyl group on IFN–λ4 may increase anti–inflammatory actions and anti–viral efficacy [19]. It is notable that glycosylated IFNs vary in stability and display antimicrobial effects with research comparatively unknown [20]. Glycosylated IFNs may interact with many carbohydrates and receptors on cell PMs and have higher/lower binding affinities to receptors necessitating clarification.

Respective receptors include type I IFN receptors (IFNAR1/2), type II IFN receptors (IFN–γR1/ IFN–γR2), as well as type III IFN receptors (IFN–λR1 IFN–λR2(IL10R2), each composed of two subunit domains [21,22]. Just prior to 2011, comparisons of type I IFN–α assays allowed type I IFN–α receptor binding studies to show IFN binding to IFNAR1 occurred with higher (μm) affinity whilst binding to IFNAR2 was lower affinity in a smaller (nm) range [23]. However, IFN–β and IFN–λ are produced by various cells, with IFN–α generally synthesised by immune cells, but specifically pDCs during infection with receptors throughout the bodily system [24]. Other reviews establish type I IFN downregulation, while research into type III IFNs is in the early stages; however, we agree with other authors suggesting type III IFNs may have biological mechanisms requiring clarity [25,26]. Much remains unknown with regards to type III IFN–λ signaling proteins. Specific data about therapy and immunisation comes through national clinical trials (NCTs) conducted throughout history before/after the first cloning of IFN receptors in 1990 and the usage of recombinant IFN–α2 (see Supplementary Data S1) [27]. During the recent pandemic, type I IFNs were evidenced to have an effect in reducing SARS–CoV–2 viral genome load requiring further contextual detail [28–32].

The Three Type of Interferon Roles in the Immune System

Cellular effects of IFN are dependant on affinity of 3 types of IFN and subtypes with 6 subunit receptor domains and receptor expression in organs, systems, tissues and cells. In brief, type I IFN–α research to date does indicate unusual variance during host infections with evidential beneficial/detrimental effects, but yet regulates myeloid cell lineages as well as B/T cells and NK cells effects. This training of immune responses occurs through inhibition as well as stimulation of maturation/differentiation of DCs by regulating costimulatory molecules like CD80/CD86 increasing major histocompatibility complex (MHC) antigen presentation as well as stimulation of T cell phenotypes [33]. However, DC maturation is known to occur through pDCs into three types conventional DCs (cDC1, cDC2, cDC3), with the most recent only known since 2017 that can reversibly differentiate into myeloid/monocytic lineages. It is suggested that type I IFN induces the suppressive cytokine IL–10 and mediates pro–inflammatory IFN gene product inhibition through suppressor of cytokine signaling–1 (SOCS–1) and be anti–viral/anti–proliferative as well having anti–tumour activity. This was evidenced from 2002 in more than 40 countries where recombinant type I IFN–α2 was used as a therapeutic to treat various types of leukaemia (B/T cell lymphomas) [34,35]. In comparison, type II IFN–γ is largely produced by only cells of the immune system and primarily T cells that can upregulate MHC class II proteins. It is also produced and regulated by NK cells. Two primary T cell phenotypes produce type II IFN–γ with the majority expressing CD4 and/or CD8 molecule proteins [36]. Historically, type II IFN has been utilised as a measure of T cell activity in research into adaptive immunity. Activity of type III IFN expression can now be measured by expression of the subunit receptors in tissues and cells through cellular mRNA expression. It is currently considered that the mRNA for one receptor subunit domain, IFNLR2 (IL10R2), has been observed in lungs, intestines, liver tissues as well as B cells, neutrophils, macrophages and pDCs but not in NK cells [37]. Additionally, type III IFN is considered to have higher affinity for IFNLR1 with less affinity for IL10R2 possibly explaining some of the differential activity of IL–10 which shares this

receptor. Previously, type III IFN was considered to be predominant on non–hematopoietic cells such as epithelial cells. Type III IFN has lower affinity binding to its respective receptors than type I IFN. Other reviews examine the relevance of single nucleotide point (SNP) mutations of type III IFN pathways during disease [37]. The relevance of type III IFN is only now becoming clearer. Research *in vivo* is indicative that during type III IFN–λ2 (IL28A) deficiency, there is an effect on three crucial immune system branches. Namely, germinal B cell centre formation where antibody forming cells were observed to increase concurrently with increased activity of both T cell branches denoted by T helper ($CD4^+$) cells as well as cytotoxic T ($CD8^+$) cells. Moreover, type III IFN–λ3 has also similarly only just been highlighted as relevant to B cell proliferation and antibody production [37,38].

Immune system modulation and/or evasion may represent evolutionary development within animal host immune systems and vary. Recently, three types of cellular signaling are considered alongside IFN that are cytokines (interleukins , IL) and chemokines (CC/CXC). Individual cellular expression is stimulated by many pathogenic organisms, like Smallpox (VARV), Human Immunodeficiency virus (HIV), but also bacterial pathogens (*Streptococcus),* and others like Respiratory Syncytial virus (RSV) can also cause viral induced pathology., Viral mutations occur in DNA/RNA viruses like the positive–sense single–stranded RNA virus (+ssRNA) Influenza A (*Alphainfluenzavirus),* having 198 potential subtype combinations of haemagglutinin/neuraminidase (HA/NA) protein antigens that can differentially affect immune cell phenotypes. Different serotypes of Gram–negative coccobacilli, *Haemophilus influenzae,* are known to shed intracellular or extracellular membranes during infection (e.g. Hia–Hif or ncHI). Other viruses like Influenza A avian virus (H5N1) can affect variable animal hosts. Severe forms of Influenza A may cause morbidity following secondary bacterial infection.

Therefore, many viral antigens co–exist alongside the novel SARS–CoV–2 antigens in nature. This effective increase in antigen circulation may inhibit or stimulate or sentisite the immune system differentially affecting effective lysis of infectious viruses through host IFN synthesis or unknown metabolic factors. The three shared methods of immune system differential kinetics comprise of pathogenic DNA/RNA 5′ capping, by addition of a methyl (CH3–) group to the 5′ genome with pattern recognition receptors (PRR) including Toll–like receptors (TLRs) affected. Secondly, cellular mitochondrial metabolic changes may change the synthesis rate of reactive oxygen species (ROS), whilst viruses utilise inter–cellular channeling nanotubes [39].The final evolutionary objective considered could be modulation of types of type I/III IFN or indeed the rate of IFN synthesis by either immune cells or infected cells with much remaining unknown.

Supplementary Materials: Welcome to Interferome (monash.edu.au).

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