Interference by interferons: Janus faces in vascular proliferative diseases

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Received 10 January 2005; received in revised form 5 March 2005; accepted 21 March 2005
Available online 27 April 2005
Time for primary review 23 days

Abstract

Interferons (IFNs) display pleiotropic properties; not only do they protect cells from viral infections but they may also modulate cell growth and differentiation as well as innate and adaptive immune responses. Therapeutic applications of IFNs have proven efficacy in a variety of illnesses, including hepatitis, multiple sclerosis, and some forms of cancer. Emerging evidence has been obtained during recent years that interferons impact on molecular and cellular mechanisms implicated in the development of vascular proliferative diseases such as atherosclerosis, restenosis, and cardiac allograft vasculopathy. Further appreciation and delineation of the precise mechanisms on how interferons influence vascular proliferative disease processes could potentially facilitate the development of novel treatment options attenuating these common causes of cardiovascular morbidity and mortality.

Keywords: Interferon; Vascular proliferative diseases; Atherosclerosis; Restenosis; Cardiac allograft vasculopathy; Proliferation; Cell cycle; Immunity; IRF-1

Now, by two-headed Janus, nature hath framed strange fellows in her time. William Shakespeare, in: “The Merchant of Venice”.

1. Introduction

More than half a century ago, interferons (IFNs) were discovered as molecules that confer an anti-viral state in virus-susceptible cells [1]. This landmark discovery led to the establishment of a new field of research involving virology, cell biology, immunology, and oncology among other disciplines. Interferons are in fact pleiotropic cytokines since they not only protect cells from viral infections but also modulate cell growth and differentiation [2,3] as well as innate and adaptive immune responses [4]. IFNs were among the first cytokines used in clinical trials to treat infectious diseases, malignancies, and neural disorders.

Presently, interferons have proven efficacy and constitute first-line drug therapy for several clinically important diseases including hepatitis B and C [5], malignant melanoma [6], and multiple sclerosis (MS) [7].

In the cardiovascular field, interferons were early recognized to play an important role in the anti-viral defense against coxsackievirus B3 in viral heart disease [8,9] and currently, a randomized multi-center trial is ongoing to prospectively evaluate the impact of chronic interferon-β therapy for 6 months in patients with biopsy-proven viral cardiomyopathy. This trial was initiated based on encouraging results of a small pilot trial [10]. Yet, the majority of cardiovascular morbidity and mortality is captured by clinical complications of vascular proliferative diseases, which include forms of atherosclerosis, in-stent restenosis, vein bypass graft atherosclerosis and cardiac allograft vasculopathy [11,12]. As implicated in the term, proliferation and migration of vascular smooth muscle cells (SMC) due to vascular injury of multifactorial origin play a crucial pathophysiological role for disease development [12] and also hold the key for novel therapeutic
approaches to prevent or limit the progression of these diseases [13,14]. This review will focus on the emerging delineation of the involvement of distinct members of the interferon family on the molecular and cellular control of vascular proliferative mechanisms and their potential therapeutic implications.

2. The interferon system

According to their receptor binding capability, interferons are categorized in two distinct classes (Table 1). Type I interferons comprise α-interferons, β-interferon as well as IFN-α, IFN-κ and IFN-τ. These interferons, encoded by several genes located on chromosome 9, are functionally active as monomers and activate a specific receptor complex which is composed of two major receptor subunits, IFNAR1 and IFNAR2 [15]. In contrast, type II IFN includes exclusively IFN-γ, which is encoded by a single gene on chromosome 12 and mainly secreted by Th-1 lymphocytes, natural killer (NK) [16] and NKT cells [17]. Similar to the type I IFN receptor, the type II IFN receptor is composed of two receptor subunits, IFNGR1 and IFNGR2 [18]. However, type I IFNs cannot bind to the type II IFN receptor and vice versa. IFN receptors are expressed on nearly all cell types and display strict species specificity in their binding to IFN [19].

3. Interferon signaling

Upon binding to their appropriate receptor, IFNs induce complex intracellular signaling processes involving Jak (janus kinases) and STAT (signal transducers and activators of transcription) proteins [20], thus ultimately leading to transcriptional activation of IFN-sensitive genes (ISG).

Common interferon signaling involves several steps: (a) IFN-evoked dimerization of the appropriate receptor on the cellular surface, causing (b) initiation of intracellular tyrosine phosphorylation, subsequently followed by (c) dimerization of phosphorylated STATs, d) activating them for nuclear transport where they (e) bind to specific DNA sequences and stimulate transcription. Type I interferons additionally require the IRF family transcription factor p48 (IRF-9) [21]. In a human cell line, it could be demonstrated that IFNs induce the expression of 250–300 genes and downregulate ten others [22], an estimation based on the analysis of only one third of the transcriptome. ISGs code for proteins that regulate membrane composition, transcription, translation, RNA and protein stability, secretion, membrane trafficking, nuclear pore opening, stress signaling, apoptosis, cell cycle and antigen presentation [16,23–26]. Promoter analysis of a number of type I IFN but also some type II IFN regulated genes revealed that a conserved interferon-stimulated response element (ISRE) is critical for IFN response [27]. The consensus sequence for ISRE is AGGTTCNNTTCTT [28]. IFN-γ response genes contain a variety of response elements [29]. Most known early type II IFN stimulated genes possess an element known as GAS (gamma-interferon-activated site) [30]. Phosphorylated STAT1 undergoes homodimerization and is converted into its transcriptionally active form, termed IFN-γ activated factor/IFN-α activated factor (GAF/AAF), which binds to GAS [31]. A related element is known as pRE (palindromic IFN response element) [32]. The detection of ISRE led to identification of ISRE interacting proteins, known as ISGFs (interferon-stimulated gene factors). These comprise members of the IRF (interferon regulatory factor) family as well as STATs. Whereas ISGF2 and ISGF3 are positive regulators, ISGF1 appears to be a repressor [33]. ISGF2 was later identified as IRF-1 [34]. IRFs are a family of genetically distinct but structurally related cellular proteins. Their DNA binding domain recognizes a similar DNA sequence, IRF-E, found within the promoters of IFN-α/β and many IFN-inducible genes [35]. To date, nine individual members of this family have been identified, termed IRF-1 to IRF-9 [36,37]. In addition, virally encoded IRFs that interfere with cellular IRFs have been described [38,39]. An overview of IFN signaling is provided in Fig. 1.

Interferon signaling does additionally interfere with other signaling pathways. It has been shown that the p38 mitogen-activated kinase (MAPK) pathway is required for full IFN-induced ISRE and GAS element dependent transcription [40]. It was found that MAPK, specifically, the 42-kDa MAPK or extracellular signal-regulated kinase 2 (ERK2), interacts with the alpha subunit of IFN-α/β receptor in vitro and in vivo. Treatment of cells with IFN-β induces tyrosine phosphorylation and activation of MAPK and leads to MAPK and STAT1 communoprecipitation. Furthermore, expression of dominant negative MAPK inhibits IFN-β

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<th>Table 1</th>
<th>Overview of the human interferon families</th>
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<td>IFN</td>
<td>Gene locus (chromosome)</td>
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<td><strong>Type I interferons</strong></td>
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<td>α</td>
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So far, IFNs α, β and γ have been investigated in the context of vascular diseases.
induced transcription [41]. Therefore, MAPK appears to regulate IFN-α and IFN-β activation of early response genes by modifying the Jak–STAT signaling cascade. Studies in primary human cell lines have convincingly underscored the critical role of p38 MAPK in IFN-induced growth inhibitory activity [42].

4. Type I interferons: negative regulators of cell growth, proliferation, migration and apoptosis

4.1. Impact of type I IFNs on cell growth and proliferation

Type I interferon signaling has been shown to lead to cellular growth arrest and eventually apoptosis. From a biological perspective this makes perfectly sense since it may be deleterious for the organism if virally infected cells would undergo further growth and/or division. IFN can regulate a variety of genes involved in cell cycle control (Table 2), the ultimate common trail of proliferative signaling pathways. Insights into IFN induced cell cycle regulation have been mostly identified to date in non-vascular cell lines. The cell cycle is regulated by the oscillatory activity of complexes comprised of cyclins and corresponding cyclin-dependent kinases (CDK) [43]. These complexes can be kept inactive by cyclin-dependent kinase inhibitors (CKI). There are two major groups of CKI in eukaryotic cell cycle regulation: the ink4 protein family (p15ink4b, p16ink4a, p18ink4c, p19ink4d) and the cip/kip family, consisting of p21cip1, p27kip1 and p57kip2. Ink family CKIs oppose the various activities of different cyclin D-dependent kinases whereas cip/kip CKIs mainly keep cyclin A-CDK2 and cyclin E-CDK2 complexes inactive [44]. Type I IFN induced cell cycle arrest in G0/G1 phase has been shown in lymphoid cells and is preceded by a rapid transcriptional induction of p21cip1 and p15kip2 [45]. Additionally, p27kip1 levels are upregulated, typically on a post-transcriptional level [45,46]. In this context, it is important to acknowledge that particularly cyclin-dependent kinase inhibitors of the cip/kip family are known to play a key role in vascular proliferative diseases and are crucial targets for antiproliferative cardiovascular therapies [13]. Sirolimus (rapamycin), which has been shown to effectively limit the onset [47] as well as the progression of cardiac allograft vasculopathy [48], imposes its cell cycle inhibitory effect.
predominantly via an increase of p27kip1 levels [49]. Stents eluting rapamycin have greatly alleviated the clinical problem of in-stent restenosis [50], another proliferative vascular disease. Further cell cycle inhibitory effects of type I IFN has been demonstrated in HeLa cells and include the suppression of retinoblastoma protein (Rb) phosphorylation [45,51] and the inhibition of E2F mediated transcription by the interferon inducible protein p202 [52] in transformed cells, thus negatively interfering with G1/S cell cycle progression. c-myc is a proto-oncogene actively involved in cell cycle progression [53] and control of initiation of translation [54]. Type I IFNs inhibit c-myc expression on the transcriptional level [55] in lymphoma cells.

Other IFN target genes regu1atively involved in cellular proliferation include CrkL, PKR (double-stranded RNA-activated protein kinase), 5′ OAS (oligoadenylate synthetase) as well as members of the IRF family which will be addressed later. CrkL is an adaptor for the C3G/Rap1 pathway linking tyrosine phosphorylated receptors to downstream signaling components. At least in transformed cell lines, the formation of STAT5-CrkL complexes induced by type I IFN is associated with transcriptional activation of other genes implicated in growth arrest [56], for example PML [57]. Antiproliferative activities have been identified for RNAse L and 5′ OAS [58] as well as PKR [59]. Germline mutations have been found for RNAse L and constitute a major risk factor for the development of prostate cancer [60], thus underscoring the importance of this gene as a tumor suppressor. PKR has recently been shown to directly inhibit vascular smooth muscle cell proliferation [61]. An overview of effector proteins regulated by IFNs is provided in Table 2.

4.2. Regulation of apoptosis

The role of apoptosis for the initiation and maintenance of atherosclerotic processes still remains to be exactly defined, however, there is evidence that apoptotic processes have pathophysiological impact for both atherosclerosis [62] and other vascular proliferative diseases such as restenosis [63]. IFNs have either pro- or anti-apoptotic effects, depending on several factors such as the state of cell differentiation. For instance, IFN-γ promotes either proliferation or apoptosis in malignant human T cells, depending on the presence or absence of serum and expression levels of the type II IFN receptor [64]. Several pro-apoptotic genes are induced by IFNs, for example CD95L [65], TRAIL [66] and members of the caspase family such as caspase-8 [67]. Additionally, IFNs may repress gene expression of anti-apoptotic proteins such as Bcl-2 and Bcl-xL [68]. Further information about interferons and apoptosis is provided elsewhere [69].

4.3. Type I interferons and cellular migration

Cellular migration constitutes an important mechanism for the formation of vascular lesions [70]. Data regarding the impact of interferons on cellular migratory mechanisms is limited. IFN-β mediated inhibition of leukocyte migration through the human brain microvascular endothelial cell monolayer is thought to be a major mechanism for the therapeutic effect of IFN-β in MS [71]. In the cardiovascular field, it could be shown that IRF-1, a gene typically induced by IFNs, inhibits mitogen-mediated smooth muscle cell migration [72]. It has been speculated that the mechanism by which this occurs might be due to the induction of members of the cip/kip CKI protein family, which are recognized to inhibit SMC migration [73].

4.4. Type I interferons and their role in vascular proliferative diseases

Type I interferons comprise potent antiproliferative properties that are also prevalent in human vascular smooth muscle cells. Upon appropriate stimulation, SMC produce an IFN-β response [74] and administration of recombinant IFN-β leads to potent arrest of SMC growth without induction of toxicity, as measured by LDH release [75]. Interestingly, IFN-α2 or IFN-α8 did not impose an appreciable growth inhibitory effect in this cell culture model [75]. The fact that in this study IFN-β did not interfere with endothelial cell proliferation in the presence of intact type I IFN signaling when given in similar dosages is remarkable and might be beneficial for treatment strategies
targeting vascular proliferative diseases since protection of the endothelium is considered to be an important aspect [76] in this context. This observation is in agreement with previous findings that type I IFN may impose no effect on endothelial proliferation [77], or increase tube formation [78], depending on the origin of the endothelial cell lineage. Recombinant overexpression of IFN-β in a porcine coronary vascular injury model was sufficient to suppress smooth muscle cell proliferation in vivo and consecutively neointima formation. Toxicity could not be observed and endothelial surface regrowth was completed at the end of the investigational period [79].

4.5. Impact of interferon regulatory factor-1 (IRF-1) on vascular proliferative diseases

Neointimal proliferation is a paradigm for vascular proliferative diseases and its magnitude determines clinical outcome. The development of neointima formation is dependent on several risk factors reviewed elsewhere [80], but may also be dependent on the expression of endogenous factors limiting SMC proliferation and migration. IRF-1 has been shown to be endogenously expressed both in humans and animals following vascular injury and leads to suppression of growth related genes like the S-phase marker MIB-1 [72].

IRF-1 was the first identified member of the family of interferon regulatory factors and characterized by its ability to bind to the IFN-β gene [81]. There has been growing evidence that the transcription factor IRF-1 is a tumor suppressor and encompasses a broad biological spectrum. Pleiotropic effects of IRF-1 include an inhibitory role in the regulation of smooth muscle cell proliferation: the protein is downregulated in proliferating and upregulated in quiescent SMCs [82]. IRF-1 can directly bind to and activate the iNOS (NOS2) promoter [83], thus upregulating NO release. Additionally, IRF-1 may directly induce antiproliferative genes like PKR [84] and lysyl oxidase [85]. Importantly, IRF-1 induces cell cycle arrest in G1 by induction of the CKI p21cip1 [86], a mechanism which can be observed both in coronary artery SMCs as well as in human and experimental vascular lesions [72]. Mitogen-mediated SMC migration is abrogated by IRF-1 [72]. Recombinant overexpression of IRF-1 in an established animal model of vascular injury attenuates neointima formation [72,87]. These observations may have clinical relevance. Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear transcription factors. Thiazolidinediones (TZD) are PPARγ ligands and comprise a drug class recently introduced in clinical medicine, also known as "insulin-sensitizers" [88,89]. Recent studies suggest that PPARγ ligands may inhibit atherosclerotic processes [90] as well as vascular smooth muscle cell growth and neointima formation [91]. Evidence exists that oral treatment with PPARγ ligands may limit in-stent restenosis in human diabetics [92]. Interestingly, novel data suggest that TZDs impose their effect on SMCs via upregulation of IRF-1 and consecutive activation of p21cip1 [93]. This particular pathway may also be responsible for the antimigratory effects of TZDs in human SMCs [94].

5. Impact of interferons on the innate and acquired immune system

Inflammatory processes may activate, maintain or augment the formation of vascular lesions [95]. In particular, there is evidence that T cells may be involved in atherosclerotic processes [96]. Both type I and type II IFNs are known to impact the immune system, however, within the IFN family, IFN-γ plays the predominant immune modulatory role. Specifically, all members of the IFN families regulate the development and activities of several immune cell lines. In this context, it is well established that IFNs upregulate MHC class I expression, thereby promoting the development CD8+ T lymphocytes [97]. Type I IFNs may also regulate components for MHC class I antigen presentation [98] as well as the expression of cytokines that influence T cell responses such as IL-12, IL-15 and IFN-γ [99]. Chemokines may be chemoattractive for T cells and play a role in atherosclerotic lesion formation [100]. IFN-α/β influence the expression of CC chemokines that are attracting T cells. IFN-induced STAT1 binding to an ISRE-like element within the promoter region of RANTES upregulates gene expression [101]. Paradoxically, IFN-β inhibits mRNA expression of RANTES, MIP-1α and their associated receptor CCR5 in T cells derived from MS patients [102]. IFN-α/β also regulate functions of other immune cells. NK cell cytotoxicity is upregulated [103] and maturation as well as terminal differentiation of dendritic cells is promoted [104]. Both cell types have been involved in atherosclerotic processes [105,106]. IL-7 mediated B and T cell development might be selectively inhibited by type I IFN [107]. However, survival of B cells can be promoted by IFNs through the PI3K/Akt signaling pathway [108]. Clearly, our understanding of the contributions of different IFNs for the regulation of complex immune responses, in particular with the interference of other regulators, is limited and the challenge continues to assign particular responses to distinct interferons under consideration of the micro- and macroenvironment, receptor expression and interplay with other immune modulatory mechanisms.

6. Impact of type II interferon (IFN-γ) on vascular proliferative diseases

Similar to IFN-α/β, type II IFN exhibits direct antiproliferative effects, e.g. in SMCs [109], as well as immune modulatory properties. The latter can be considered to be more pronounced for the cytokine IFN-γ, compared to type
IFNs [79]. IFN-γ elicits a dose-dependent growth inhibitory effect in vascular SMC [110,111], e.g. by induction of NO [112] or by modulation of the E2F/Rb pathway [109]. It is also reported that IFN-γ inhibits extracellular matrix synthesis [113]. Switching to in vivo studies, evidence has been fostered that parenteral administration of IFN-γ inhibits neointimal formation following experimental vascular injury [114,115].

Controversially, there is a growing body of evidence that protracted expression of IFN-γ elicits atherosclerotic processes. Responsible pathophysiological mechanisms include IFN-γ mediated induction of VCAM-1 in endothelial cells [116], MHC II expression on macrophages and SMC [116] and lipoprotein receptors on SMCs [117]. Furthermore, T cells accumulate early in atherosclerotic lesions, in particular CD4+ T cells [118] as well as macrophages. Studies on how T cells and macrophages interact indicate that IFN-γ plays a pivotal role in the mediation of this immune response [119,120]. IFN-γ potentiates atherosclerosis in apoE deficient mice compared to mice deficient of both apoE and type II IFN receptor [121]. Amongst others, the authors found that the presence of IFN-γ altered lipidprotein metabolism as well, e.g. resulting in an increase of free cholesterol. In a very elegant study, Tellides and colleagues have shown that IFN-γ facilitates atherosclerotic processes even in the absence of leukocytes [122]. This study indicated that endothelial expression of MHC class I and II antigens is not constitutive and is sustained by IFN-γ, thus leading to enhanced atherosclerosis. Additionally, it was found that IFN-γ treatment leads to upregulation of PDGF β-receptors without altering ligand binding affinity. PDGF is regarded as a “competence factor” for SMC mitogenesis and plays a prominent role in the initiation of SMC proliferation [123]. This finding is in accordance with a previous study reporting IFN-γ mediated upregulation of PDGF β-receptors [124] which was among the first to report pro-mitogenic effects of IFN-γ in culture, followed by others [125]. IFN-γ is also implicated in cardiac allograft vasculopathy [126,127], which belongs to the family of vascular proliferative disease. Vascular remodeling (change in vessel diameter) is considered an important determinant in immune-mediated arterial injury. There is evidence that outward vascular remodeling and intimal thickening, two manifestations of arteriosclerosis with opposing effects on luminal size, may result from immune effector mechanisms that are T-cell dependent and interferon (IFN)-γ mediated [128].

The observation of the dichotomous effects of IFN-γ on major mechanisms of arteriosclerosis has led to the proposal that IFN-γ may be involved in the determination of atherosclerotic plaque vulnerability [121] and eventually promotes plaque rupture by thinning and destabilizing the fibrous cap [129]. Consistent with this hypothesis, T cells predominantly localize at the shoulder region of an atherosclerotic plaque and additionally, IFN-γ has been shown to stimulate secretion of cathepsin-S, a cysteine protease, from macrophages [130].

7. Conclusions: good and bad interferons in vascular proliferative diseases?

Within recent years, a variety of studies implied emerging evidence that interferons of both classes, type I and II, play a prominent role in the course of vascular proliferative diseases. Based on current knowledge, type I interferons are likely to predominantly play a protective role by inhibiting mitogen mediated smooth muscle cell migration and proliferation while simultaneously may protecting (re-)endothelialization processes [75]. The family of type I IFNs is quite heterogeneous, and the different biological functions between members of the IFN-α/β group may be dependent on receptor density and expression, cell type, downstream signaling events, the micro- and macroenvironment and other cytokines [15]. IFN-β is known to preferentially induce a variety of genes particularly involved in regulation of proliferation as compared to IFN-α [22]. Accordingly, in particular in the smooth muscle cell context, current data suggest that IFN-β may display a more prominent antiproliferative effect than members of the IFN-α group [75]. This may have therapeutic consequences since at least local application of IFN-β is able to inhibit vascular proliferative processes [79]. In this context, it is important to acknowledge that patients receiving chronic IFN-β therapy for the treatment of MS [131] or viral cardiomyopathy [10] do not appear to have an increased cardiovascular event rate [132]. However, since patients in these studies were not at increased risk for adverse vascular events, no final judgment about the safety of systemically applied IFN-β therapy in patients with advanced vascular diseases can be drawn. Yet, a recent study demonstrated that administration of IFN-β decreases rather than accelerates recruitment of infiltratory cells to infarcted tissue [133], thus objecting theories that recombinant type I IFN may enhance the chances for acute vascular syndromes in selected patients.

The role of type I IFNs, in particular IFN-β, for the pathophysiology of vascular proliferative diseases remains yet largely undefined. However, studies are currently conducted to elucidate potential roles and mechanisms. Based on current data, it is tempting to speculate that type I IFNs are predominantly atheroprotective.

However, this seems not to be the case for type II IFN, namely IFN-γ. Presence of IFN-γ appears to be required for the onset and the progression of atherosclerotic lesion formation [121,122] and cardiac allograft vasculopathy [126,127]. How does this relate to the direct antiproliferative effects of locally administered IFN-γ in SMCs? While type I IFNs mainly function on the cellular level, IFN-γ is primarily a cytokine, essentially exclusively secreted by NK, NKT and CD4+ T cells. These particular cells play an important role in the development of atherosclerosis [134,135], as discussed earlier. Further, in the context of atherosclerosis, proliferative mechanisms are prevalent subsequent to the onset of endothelial injury and immune...
modulatory processes [12], where IFN-γ mediated effects are thought to play a pivotal role [134]. However, some groups still try to take advantage of the direct antiproliferative effects of IFN-γ on SMCs, e.g. by loading it on a drug-eluting stent platform [136], thus circumventing systemic administration. Clearly, type I and II interferons do not display redundancy regarding their biological impact on vascular proliferative mechanisms, a phenomenon well known and characterized in the context of their antiviral properties [137]. This is exemplified by the regulation of ICAM-1, a gene involved in atherosclerotic lesion formation [138], which is upregulated by IFN-γ but not type I IFNs [22].

Not only IFNs themselves but genes which are subsequently induced such as IRF-1 may interfere with vascular proliferative mechanisms. In this perspective it is important to point out that IRF-1 may also be induced even in the absence of interferon [3]. The observation that IRF-1 is regulated in the human neointima, characterized as an endogenous inhibitor of vascular proliferative processes and, at least in part, responsible for the beneficial effect of PPARγ ligands on SMC proliferation and migration, clearly confirms the clinical relevance of interferons and their regulatory factors.

7.1. Future perspectives for interferon research in vascular diseases

Future research should further elucidate the mechanisms by which type I IFNs, in particular IFN-β and subsequently induced genes may induce an atheroprotective effect. In particular, deleterious, pro-atherogenic actions of IFN-γ might be counteracted by type I IFNs, an effect which is recognized in multiple sclerosis where IFN-γ mediated cellular effects might be counteracted by the administration of recombinant IFN-β in humans [139]. Novel treatment therapeutic strategies might be developed to target the deleterious role of systemically active IFN-γ in plaque formation and instability, thus helping to alleviate these important problems of modern cardiovascular medicine.

Therefore, it is highly desirable that further scientific efforts will elucidate the precise mechanisms on how interferons and subsequently induced genes may interfere with vascular proliferative disease processes, which could ultimately lead to the development of novel therapeutic concepts. Hence, one could agree with the quotation “The medical story of interferons has only begun” [140].

Acknowledgements

The author gratefully acknowledges the continuous support from the Deutsche Forschungsgemeinschaft (We 1811/1-1, 2-1 and 3-1/3-2). This article is dedicated to my children Aliena Francisca, Jonas Samuel and Jonathan Lucas for their grace and absolution for spending many hours on clinical and experimental medicine.

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