Immunology Letters xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

Targeting interferons as a strategy for systemic sclerosis treatment

Marzena Ciechomska*, Urszula Skalska

National Institute of Geriatrics Rheumatology and Rehabilitation, Warsaw, Poland

ARTICLE INFO

Keywords:
Interferon
Systemic sclerosis
Cytokines
Fibrosis
Vasculopathy
Autoimmunity
IFN signaling
Anifrolumab

ABSTRACT

Systemic Sclerosis (SSc) is an autoimmune disease characterised by vasculopathy, uncontrolled inflammation and enhanced fibrosis which can subsequently lead to the loss of organ function or even premature death. Interferons (IFNs) are pleiotropic cytokines that are critical not only in mounting an effective immune response against viral and bacterial infections but also strongly contribute to the pathogenesis of SSc. Furthermore, elevated levels of IFNs are found in SSc patients and correlate with skin thickness and disease activity suggesting potential role of IFNs as biomarkers. In this review, we summarise existing knowledge regarding all types of IFNs and IFN-inducible genes in the pathogenesis of SSc. We then argue why IFN-blocking strategies are promising therapeutic targets in SSc and other autoimmune diseases.

1. Introduction

Systemic sclerosis (SSc) is a rare, incurable autoimmune disease affecting predominately women (men to women ratio: 1:4), with a prevalence of 150–300 per million people. SSc is characterised by an early vascular endothelium damage (vasculopathy), hyperactivation of the immune response (T-cell and monocyte infiltration, B-cell activation) and enhanced collagen synthesis by activated fibroblasts. In consequence, progressive fibrosis of the skin and internal organs develops. The latter leads to organ damage and is the main cause of poor clinical outcomes [1]. The prevalence of SSc varies significantly in different parts of the world and is higher in Southern Europe, North America and Australia than in Northern Europe and Japan [2]. Patients with SSc are classified into diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc). This classification is based on the extent of fibrosis of skin and internal organs. In dcSSc the progress of fibrosis is rapid, whereas lcSSc is mainly associated with vascular manifestations and mild fibrosis [1].

The etiopathogenesis of SSc is unknown, but it is believed that both genetic susceptibility and chronic immune system stimulation with antigens may contribute to the disease development. Disease morbidity and mortality remain high [3,4]. The mean survival after 10 years from disease onset is 66%, whereas the mortality of patients with progressive SSc ranges from 30% to 50%. The cardiopulmonary and renal involvement is the main cause of precocious death [5]. There is no definite cure for SSc and the available treatments have limited efficacy. Currently, development of effective therapy is not fully possible due to the incomplete understanding of disease pathogenesis. The only beneficial treatment compared with classic medical procedures (intravenous cyclophosphamide pulses) is autologous hematopoietic stem cells transplantation (HSCT) which has been shown to prolong patients' survival [6]. Transplantation of other cell types (bone marrow/adipose mesenchymal stem cells, mononuclear blood cells) have been also investigated, but the outcomes were not as beneficial as after HSCT [7].

TGFβ is reported to play a crucial role in skin and organs fibrosis in SSc [8,9], whereas other growth factors including platelets-derived growth factor (PDGF) and connective tissue growth factor (CTGF) are involved in the late stage of fibrotic processes [10]. The vascular damage is mediated by the isoform $_{165}$b of vascular-endothelial growth factor (VEGF$_{165}$b) possessing anti-angiogenic properties [11]. VEGF$_{165}$b isoform is selectively overexpressed by dermal fibroblasts, dermal endothelial cells, dermal perivascular mononuclear inflammatory cells and is stored in platelets [12]. Apart from all these growth factors, the role of interferons (IFNs) in SSc is raised. Especially, type I IFNs and their inducible genes are associated with the SSc pathogenesis and severity, but other IFN types may also contribute to the disease. The presence of an activated IFN system (termed the "IFN signature") in the blood and skin biopsies of SSc patients has been demonstrated, however the mechanism by which IFN signaling contributes to the pathophysiology of fibrosis and to the overall SSc progression is unknown [13]. More details and appropriate references will be presented in the further sections of this manuscript and Table 1.

2. Interferons – structure and activity

IFNs are a heterogeneous family of cytokines possessing many diverse functions. Historically, IFNs have been defined as factors responsible for antiviral defence. Currently, three types of IFNs – type I,

* Corresponding author.

http://dx.doi.org/10.1016/j.imlet.2017.10.011
Received 31 May 2017; Received in revised form 24 October 2017; Accepted 24 October 2017

Table 1
IFNs pathogenic activity in autoimmune connective tissue disorders.

Disease	IFN effects	References
Systemic lupus erythematosus	• circulating IFNα correlates with the disease activity parameters and has anti-angiogenic effects	[43,48]
	• type I IFNs stimulate aberrant expansion of plasmablasts and plasmatic cells	[49,50]
	• type I IFNs contribute to lupus nephritis and cutaneous lupus erythematosus	[44–46]
Sjögren syndrome	• upregulated IRGs expression	[54]
	• IFN signature in PBMCs correlates with anti-Ro(SSA) and anti-La(SSB) Abs titres	[60,61]
	• IFN I signature in monocytes associated with greater disease activity	[62]
Myositis/dermatomyositis	• IRGs expression upregulated in inflamed muscles and PBMCs	[63–65]
	• upregulated serum IFNα activity in juvenile dermatomyositis	[66]
	• higher expression of IRGs in PBMCs associated with anti-Jo1 and anti-Ro(SSA) Abs	[67]
Rheumatoid arthritis	• elevated type I IFN signature and arthralgia are risks factors for developing arthritis	[69,70]
	• high IFN I signature is associated with poor response to rituximab whereas higher IFN score in neutrophils correlates with a good response to anti-TNF treatment	[68,71]
	• increased IFN-regulated transcripts associated with upregulated pathways related to coagulation, complement activation and FA metabolism (in a subset of RA patients)	[39]
Systemic sclerosis	Immune cells	
	• type I IFN signature plays a key role in the activation of monocytes	[72–76]
	• ICs and ATA autoantibodies from SSc serum stimulates IFNα production by pDC	[77,78]
	• increased expression of IRGs in PBMCs and up-regulated production of IFNγ by lymphocytes in SSc patients	[79–81]
	• significantly higher levels of IFNγ in Raynaud's Phenomenon affected patients comparing with HC	[79]
	Endothelial cells	
	• IFNα and IFNγ contribute to the increased vessel permeability	[82]
	• IFNγ treatment of HDMVECs increases expression of profibrotic α-SMA, CTGF, TGFβ and ET-1	[82]
	• IFNγ stimulates migration of immune cells to extravascular tissue (by upregulating endothelial–leukocyte adhesion molecules)	[83]
	Fibroblasts	
	• IFNα (via TLR3 and TLR7) stimulates SSc fibroblasts proliferation, differentiation, production of proinflammatory cytokines, chemokines and collagen	[1,77,84–87]
	• IFN type I signature in SSc fibroblast is present before overt skin fibrosis	[72]
	• in patients treated by BMSC transplantation, the decrease in fibrosis and capillary regeneration correlates with the loss of expression of type I IFN in the skin	[88,89]
	• IFNγ stimulation upregulates CXCL9 and CXCL10 secretion by SSc dermal fibroblasts	[87]
	• IRGs expression in lung tissues correlates with progressive lung fibrosis and IRF5 is implicated in the pulmonary and skin fibrosis	[90,91]

α-SMA: smooth-muscle actin; Abs: antibodies; ATA: anti–topo I autoantibodies; BMSC: bone marrow stem cells; CTGF: connective tissue growth factor; ECM: extracellular matrix; ET-1: endothelin-1; FA: fatty acids; HC: healthy control; HDMVECs: human dermal microvascular endothelial cells; ICs: immune complexes; IRF: IFN-regulated factor; IRGs: IFN-regulated genes; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; SS: Sjögren syndrome; TGF-β: transforming growth factor β; TLR: Toll-like receptor.

type II and type III – can be distinguished. The type I IFNs constitute the biggest family which can be divided into five classes: α, β, ω, ε, and κ. The type II IFNs are represented by only one class, that is IFNγ. This cytokine is a very potent mediator of immune response [14]. Three IFNλ molecules, λ1 (IL-29), λ2 (IL-28A) and λ3 (IL-28B), create the youngest type III IFN family, which has been discovered in 2003 [15]. The fourth type III IFNs member called IFNλ4 has been recently discovered. IFNλ4 is a product of polymorphic IFNλ3 allele IFNL4-ΔG (rs368234815) [16].

2.1. The molecular structure and action of IFNs

All IFNs are class II α-helical cytokines. The signal transduction initiated by the binding of IFNs to their cognate receptors at the cell surface requires activation of the intracellular receptor domains. The activation of intracellular domains relies on tyrosine phosphorylation and is associated with the Janus kinases (JAKs) family. Once phosphorylated, the receptors act as activators of transcription factors (STATs), which are recruited to the receptor and phosphorylated (Fig. 1). After that, the STATs dissociate from the receptor and migrate to the nucleus where they bind to the IFN-stimulated response element (ISRE) at the promoter region of so-called IFN-stimulated genes (ISGs) which are also known as IFN-regulated genes (IRGs) and promote the transcription of more than 300 IRGs including Interferon Induced Protein 44 (IFI44), myxovirus resistance A (MxA), sialic acid binding Ig like lectin 1 (Siglec-1) [17]. ISGs are further named as IRGs for the clarity of this manuscript.

All type I IFNs share the same ability to exert antiviral activity. They are glycosylated proteins containing 160–200 amino acids, sharing 30% to 55% homology and mainly produced by plasmacytoid dendritic cells (pDCs) [18]. In humans, genes encoding type I IFNs are clustered on the short arm of chromosome 9 and are devoid of introns. Type I IFNs transduce intracellular signals through the common receptors IFNAR1/IFNAR2 [19]. Type I IFN receptors are associated with the Janus kinase JAK1 and the tyrosine kinase TYK2. IFNα and IFNβ, which are the most potent and best described members of type I family, are genetically and structurally very similar [20]. Type I IFNs and IFN-inducible genes transcription is regulated by interferon regulatory factors (IRFs) [21]. The IRFs family contains nine members described as: IRF1, IRF2, IRF3, IRF4 (LSIRF/PIP/ICSAT), IRF5, IRF6, IRF7, IRF8 (also known as ICSBP), and IRF9 (ISGF3γ) [22,23]. Several genetic polymorphisms in IRF5, IRF7 and IRF8 have been associated with susceptibility for development of SSc or act as disease modifiers (described in detail further in this manuscript).

IFNγ, the only member of type II IFNs, also exhibits antiviral activity, however it is mainly regarded as a powerful immunomodulatory cytokine. This protein is composed of 140 amino acids and shares no homology with type I IFNs [14]. It is produced by macrophages, NK, NKT and T cells and influences the intracellular environment by recognizing a distinct cell surface receptor named IFNGR1/IFNGR2. These receptors are associated with JAK1 and JAK2 kinases [24].

The youngest IFNs family – type III IFNs – consists of three IFNλ molecules mainly produced by pDCs. They are co-produced with IFNβ but act by binding to a different receptor which is composed of two membrane spanning proteins: IFNLR1 and IL-10R2. Type III IFN receptors are associated with the Janus kinase JAK1 and the tyrosine