International Immunopharmacology 40 (2016) 542–549

Contents lists available at ScienceDirect

International Immunopharmacology

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

Review

The important roles of type I interferon and interferon-inducible genes in systemic lupus erythematosus

Shuaihantian Luo [a], Yunuo Wang [b], Ming Zhao [a], Qianjin Lu [a,*]

[a] Department of Dermatology, Second Xiangya Hospital of Central South University, Hunan Key Laboratory of Medical Epigenetics, Changsha, Hunan, China
[b] Department of Endocrinology, Second Xiangya Hospital of Central South University, Changsha, Hunan, China

ARTICLE INFO

Article history:
Received 21 July 2016
Received in revised form 30 September 2016
Accepted 14 October 2016
Available online xxxx

Keywords:
Systemic lupus erythematosus
Type I IFN
IFN-inducible genes

ABSTRACT

Systemic lupus erythematosus (SLE) is a severe autoimmune disease that causes multiple-organ dysfunction mainly affecting women in their childbearing years. Type I IFN synthesis is usually triggered by viruses, and its production is tightly regulated and limited in time in health individuals. However, many patients with systemic autoimmune diseases including SLE have signs of aberrant production of type I interferon (IFN) and display an increased expression of IFN-inducible genes. Continuous type I IFNs derived from activated plasmacytoid dendritic cells (pDCs) by interferogenic immune complexes (ICs) and migration of these cells to tissues both break immune tolerance and promote an on-going autoimmune reaction in human body. By the means of detecting type I IFNs and IFN-inducible genes, it can help with diagnosis and evaluation of SLE in early stage and more efficiently. Anti-IFN-α monoclonal antibodies in SLE patients were recently reported and is now being investigated in phase II clinical trails. In this review, we focus on recent research progress in type I IFN and IFN-inducible genes. Possible mechanisms behind the dysregulated type I IFN system in SLE and how they contribute to the development of an autoimmune process, and act as a biomarker and therapeutic target will be reviewed.

Contents

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease resulting in multi-organ and multi-system dysfunction and is associated with significant morbidity and mortality. Although genetic factors, endocrine, infections and environmental factors were reported to contribute to pathogenesis of SLE, the clear etiology has not been well elucidated [1]. This disease is characterized by hyperactive autoreactive immune cells with abnormal production of autoantibodies forming immune complexes resulting in tissue inflammation and organ damage. The current treatment regimen of SLE involves systemic corticosteroids and immunosuppressants, which are associated with significant adverse effects such as osteoporosis and Cushing's syndrome. Since interferon (IFN) was discovered in 1950s by Alick Isaacs in year of 1957

* Corresponding author at: Second Xiangya Hospital, Central South University, No.139 Renmin Middle Road, Changsha, Hunan 410011, China.
E-mail address: qianlu5860@gmail.com (Q. Lu).

http://dx.doi.org/10.1016/j.intimp.2016.10.012
1567-5769/

[2], it was no longer regarded as an independent cytokine, or rather, it was a multifunctional immune factor which comprised a great number of immunocompetence and built bridge between innate and adaptive immunity [3,4]. Type I IFNs are mainly secreted by innate immune cells and have important roles in the protection of cells from viral and bacterial infections [5–8]. However, many studies have reported that type I IFN system over-expressed in the serum of patients with autoimmune disease and its level also correlated with abnormal expression of downstream inducible genes, including SLE [9–12]. Pre-existing autoantibodies were not necessary for development of autoimmunity, although presence of autoantibodies before IFN-α therapy considerably increased the risk for autoimmune diseases [13,14]. The conclusions are pro-inflammatory functions of IFNs can both break tolerance and promote an on-going autoimmune reaction in human body. In this review, we summarized the up-to-date research progress of type I IFN and IFN-inducible genes in SLE, which will be helpful not only for better understanding of the pathogenesis, but also for disease management.

2. Type I IFN and IFN-inducible gene

Interferon was a widely studied cytokines which had a long research history (Table 1). Based on the difference in the primary protein structure, there are over 20 kinds of IFN genes that have been identified by now. These IFN genes can be divided into three families: type I, type II and type III (Table 2). Type I IFN includes 13 IFN-α subtypes. IFN-β, IFN-ω, IFN-κ, and IFN-ε are secreted by innate immune cells, which are the main immune cells to display anti-infection functions. Type II IFN, called IFN-γ (gamma), is mainly derived from activated T cells. Type III IFN consists of some IFN-λ, distribution and functions of which was limited [15,16]. Among these, type I IFN is discovered with the functions of anti-virus, anti-tumor, anti-proliferation, and also have immunomodulatory functions which can best be described as a general activation of immune cells [2].

Table 1
Milestone of IFN research.

Year	Research progress	Ref.
1957	IFN was first discovered in study of chicken embryos infected with influenza virus.	[2]
1962	IFN inhibited cell proliferation and intracellular bacterial growth.	[98,99]
1964	Infection of bacteria and endotoxin could induce production of IFN.	[100]
1965	IFN-γ was first discovered and classified as type II IFN.	[101]
1967	Double-stranded RNA (dsRNA) could induce production of IFN.	[102]
1969	IFN inhibited proliferation of tumor cells.	[103]
1970s	IFN played an important role in the regulation of the immune cells and induced the antivirus response in cell.	[104–106]
1975	Type I IFN have subtype of IFN-α and IFN-β. High-level IFN was detected in some autoimmune diseases and it could induce adverse reactions in animal model.	[107]
1980s	Separation and sequencing of IFN-α, IFN-β and IFN-γ	[108,109]
1985	IFN was proved to interact with upstream IFN Stimulated Response Element (ISRE) of IFN-inducible genes.	[110,111]
1988	Transcription factor family of IFN Regulatory Factor (IRF) was first discovered.	[112]
1990	Function identification of IFN-stimulated gene factor 3 (ISGF-3)	[113]
1994	Functions and features of type I IFN receptor was identified and JAK-STAT pathway was proved to be the main signal pathway of it.	[114]
1998	IRF3 and IRF7 played critical roles in induction of IFN.	[115]
1999	Plasmacytoid dendritic cells significantly induced production of type I IFN.	[116]
2001	TLR3 recognized dsRNA and mediated IFN pathway.	[117]
2005	Virus immune response of dsRNA and ssRNA in cytoplasm triggered IFN by helicase of RIG-I or MDA5.	[118]
2010	First anti-IFN biologics, Sifalimumab, began clinical trial.	[119]
2015	Mitochondrial DNA stress primes the antiviral innate immune response and upregulation of type I IFN and inducible genes.	[120]

Table 2
Classification and main source of IFN.

Type	Members	Receptor	Main source
Type I	IFN-α, IFN-β, IFN-δ, IFN-ε, IFN-κ, IFN-τ, IFN-ω	IFN-αR1/IFN-αR2	Innate immune cells: macrophage, dendritic cell
Type II	IFN-γ	IFN-γR1/IFN-γR2	Activated T cells
Type III	IFN-λ1, IFN-λ2, IFN-λ3	IL-28R1/IL-10R2	Unknown

Typically, all nucleated cell types can produce type I IFN upon pathogenic infection, but the principal type I IFN producer is the plasmacytoid dendritic cell (pDC). When sensed by pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs) such as certain Toll-like receptors (TLRs) or cytoplasmic nucleic acid sensors, activation of downstream transcription factors such as interferon regulatory factor (IRF) induce type I IFN expression [3,5,14]. pDCs are specialized IFN-producing cells that can release up to 1000 times more type I IFNs than any other cell type. pDCs express TLR7 and TLR9 in their endosomal membranes and can therefore become activated by pathogens that invade pDC through receptor-mediated endocytosis [4]. Besides, the activation and signal transduction of some downstream molecular such as MAVS, STING, TBK, IKK results in activation of IRF3/7, which are also the direct initiator of type I IFN secretion [16].

There is a family of receptors on cell membrane to respond to interferon (Table 2). Binding of different IFNs to receptors results in the activation and repression of over 2000 genes with a multitude of biological functions. Type I and II interferon can induce hundreds of the same genes (about a 70% overlap) [21]. Type I IFN responses are mediated via the IFN-α receptor (IFNAR), comprising the subunits IFNAR1 and IFNAR2, which appear to be expressed by all cell types [17–19]. IFNAR-2 is the primary binding protein and binds IFN molecules with high affinity, while IFNAR-1 binds the molecule with low affinity. The human type I IFN system comprises 17 different ligands binding to two receptor subunits which following initiates signaling cascades leading to expression of IFN-inducible genes (Fig. 1) [20]. Type I IFN-inducible genes have many families which comprise of over 350 genes (Table 3). The most thoroughly characterized type I IFN signaling pathway is the Janus activating kinase (JAK)-signal transducer and activator of transcription (STAT) pathway involving phosphorylation of cytoplasmic JAK1 and tyrosine kinase (TYK) 2, and subsequently STAT 1 and 2 [21]. Phosphorylation and activation of STAT results in their homo- or hetero dimerization, translocation to the nucleus where it binds to IFN regulatory elements and triggers transcription of several hundreds of type I IFN-inducible genes (Fig. 1) [22–25]. Activation of STAT4 and STAT6 by type I IFNs has also been reported in certain cell types such as endothelial and lymphoid cells [26,27].

3. Type I IFN and IFN-inducible genes in pathogenesis of SLE

3.1. Abnormal type I IFN and IFN-inducible genes production in SLE

Normally, type I IFN genes are strictly regulated, and normally almost no constitutive IFN-α production can be detected in healthy individuals. However, in serum of SLE patients, IFN-α was upregulated accompanied with upregulation of associated IFN-inducible genes such as MX1, ISG54, and ISG56. In some gene microarray studies, a lot of overexpressed type I IFN-inducible genes were screened out in SLE patients [28,29,33,34]. The similar results were also found by Genome Wide Association Studies (GWAS) in SLE [35–38]. In partial transcription factors of IFN pathway such as IRF5, IRF7, IRAK1, TREX1, STAT4, PTPN22, genetic alterations of these genes associated with SLE were detected in a lot of studies which suggesting that these genes may be involved in the pathogenesis of SLE [39,40]. Additionally, uncontrolled activation of downstream pathways and IFN-inducible genes have also been detected to be upregulated and associated with many autoimmune