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Review

Interferon regulatory factors: A key to tumour immunity

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ABSTRACT

Interferon regulatory factors (IRFs), which have 10 members, belong to the transcription factor family and were named because of the regulation of interferon expression. They play important roles in the immune regulation, cell differentiation, cell apoptosis, and cell cycle regulation. This article will review the functional characteristics and immune activity of the family members, especially in the role of cell differentiation and autoimmune diseases. Intensive studies will help uncover the pathogenesis of the disease in a more comprehensive view, and provide novel targets for disease treatment. But the most important problems yet to solve is IRFs function in the development processes of tumour, and whether IRFs can be an important regulator in tumour immune treatment.

Interferons were first discovered as a kind of antiviral proteins in the middle of the last century. Later on, interferon regulatory factors (IRFs) were discovered and named because it could bind to gene promoter sites and upregulated the expression of interferons under infectious conditions, particularly under circumstances of virus infection [1]. IRFs belong to a family of transcription factors, which could regulate the transcription process of interferons through acting at its gene site. All IRFs share a featured structure, which is a domain composed by 115 amino acids at the amino terminus. It is also called the DNA binding domain (DBD). DBD contains five tryptophan repeat sequences and could bind to DNA, and it is similar to the DBD of Myc. The carboxyl terminus of IRFs has a variable domain and endows diverse biological functions to IRFs [2]. Up to now, ten members of IRFs have been discovered in mammals (IRF-1–IRF-9, and v-IRF). They have been reported to be expressed in tissue cells except for immune cells. Emerging evidence has revealed the key function of IRFs is in cell differentiation and apoptosis, cell cycle and immunological regulation. Intensive studies on IRFs are expected to find a novel and effective biological approach for cancer treatment.

1. IRFs in innate immune response

The first line of innate immune defence in the human body is mediated by innate pattern recognition receptors (PRRs), which are consisted of Toll-like receptors (TLR), C-type lectin receptors (CLRs), RIG-like receptors (RLRs) and NOD-like receptors (NLRs) [3]. After recognising different pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), PRRs induced the transcription process of type I interferon, pro-inflammatory cytokines and chemokines through intracellular cascade reaction so as to eliminate pathogen or infectious cells. IRFs are important molecules that transduce PRRs signaling to activate immune cells [4]. IRF-3 and IRF-7 can induce the expression of interferons and then activate the adaptive immune defence through acting on the interferon downstream target gene expression and induce T cell differentiation. Interferons, interleukins and tumour necrosis factor are induced for transcription and expression after the activated PRRs invoked IRF-1/5/7 and NF-κB via specific adaptors and MyD88, thus activating the innate immune responses and adaptive immune defence. The IRFs-associated PRRs pathways are as follows (Table 1).

STING (Stimulator of Interferon Genes), which controls adaptive immune response through a DNA sensing, TLR-independent pathway, and impacts transcriptional factors, such as IRF [5], is identified as an essential factor in controlling host defence countermeasures recently. Studies have also revealed a key role for cyclic-GMP-AMP (cGAMP) synthase (cGAS) in STING activation. Evidence indicates that STING escorts tank binding kinase 1 (TBK1) to endosomal compartments to associate with and activate IRF3 and IRF7, which tanslocate into the nucleus to stimulate innate immune gene transcription [6]. The activated STING signal could be negative regulated by cyclicdinucleotides (CDNs) through phosphorylating STING by UNC-51-like kinase (ULK1/ATG1) to avoid inflammatory disorders [7]. Also, IRF3 participates in cellular antiviral response through RIG-I-Like receptors (RLR) induced IRF3-mediated pathway of apoptosis (RIPA), without enhan-

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Table 1
IRF family-dependent PRR signaling pathway.

Pathway		IRFs	Upstream moleculars	Target protein	References
TLR	IFN-I pathway	IRF-3	TRIF regulatory protein	IFN-I	[54]
	MyD88 signaling pathway	IRF-7	MyD88	IFNβ	[4]
		IRF-5	MyD88, TRAF6	inflammatory cytokines (IL-6, 12; TNF-α)	[55,56]
		IRF-1	MyD88	IFNβ, iNOS, IL-12, p35	[57]
	TLR9	IRF-8	TRAF6	NF-κB, IFN-I	[4]
RLR		IRF-3	TBK1	IFN-I	[58]
		IRF-7	ISGF3	IFNβ, IFNα4	[58,59]
		IRF-5	Unknown	Unknown	[60]
NLR		IRF-3/5	NOD2	IFN	[61,62]

cing the antiviral gene expression. This requires linear polyubiquitination of IRF3 residues by linear polyubiquitinating enzyme complex (LUBAC) [8].

In innate immune response, IRFs can be activated by various PRRs, and one IRF can participate in diverse downstream pathways of PRRs. Different IRFs can be activated by the same molecule (e.g. MyD88), yet multiple activated IRFs can act on the same target gene (e.g. interferon), thus forming a complex regulatory network. This gives us some revelation that there is a degree of relevance between different response modes. Pathways (including transcription factors) participated in the exact regulation of immune responses. The study about IRFs in signaling will provide wide approaches for bio-immunotherapy and cancer treatment.

2. IRFs in immune cell development processes

IRF-1/2/4/6/8 also plays a key role in the development of immune cell (e.g. dendritic cells, NK cells, B lymphocytes and T lymphocytes). Using gene knockout mice, Savitsky D. reported that IRF-1/2/4/8 regulated the differentiation processes of CD4 + DCs, CD8α + DCs and pDC [9]. IRF1 can induce IL-15 to promote NK cell differentiation. IRF-2 facilitates the differentiation of NK cells through intracellular signaling pathways [9]. IRF-8 binds to EBF promoter to induce the expression of EBF, thus activating genes related to B cell differentiation. IRF-4 regulates the apoptosis process of B lymphocytes through targeting Fas apoptosis inhibition molecule [10]. IRF-1 and IRF-2 can initiate activity of T-helper cells. IRF-4 mainly participates in the differentiation process of T-helper2 cells [1]. The functions of IRFs in immune cell maturation are summarised as follows (Table 2).

IRFs participate in anti-tumour process through regulating cancer immune responses. IRF-8 exhibits its anti-tumour effect via inducing the differentiation and maturation of APCs (MΦ, DCs, and B lymphocytes) [11]. Further investigation of IRFs will help demonstrated tumour immune and provide new ways to treat cancer.

3. IRFs in promoting cell cycle and cell differentiation

IRFs play an indispensable role in cell cycle, cell differentiation, and tumour development (Table 3). Among them, IRF-4 is believed to be closely related to haematological malignancies. IRF-2 was found to compete with IRF-1 for binding sites while presenting different functions, but recent studies have shed different views on this molecule.

3.1. IRF-2

IRF-2 is located in chromatin 4q34.1-q35.1 and has no tissue specificity. IRF-2 was reported to have similar binding sites with IRF-1 and the ability to suppress the transcription of IRF-1 through competitively binding to the same target site [12]. IRF-2 can induce carcinogenesis through competitively binding to the PRDI domain of IFN-8 gene and suppressing the function of Blimp1 [13]. Acetylated IRF-2 can lead to the sustained growth of cells via binding to the promoter of histone H4 [14]. IRF-2 was reported to be expressed in oesophagus and pancreatic cancer in high levels [15,16].

Table 2
Roles IRFs play in the immune cell maturation.

IRFs	Immune cells	Target molecules
IRF-1	Induce maturation of NK cells	IL-15
	Induce differentiation of CD8 + T cells	
	Induce differentiation of Th1	IL-12 receptor β1 subunit (T cells); IL-12p35/40 (MΦs/DCs)
	Inhibit differentiation of Th2	Inhibit IL-4
IRF-2	Induce the differentiation of CD4 + DCs	
	Induce maturation of NK cells	
	Induce differentiation of Th1	IL-12p40(MΦs)
	Inhibit differentiation of Th2	Inhibit IL-4
IRF-4	Induce the differentiation of CD4 + DCs	
	Induce maturation of B cells	The light chain of Ig
	Induce differentiation of plasma cells	AID, Blimp-1
	Induce the differentiation of Th2	IL-4
	Induce the differentiation of Th17	IL-17, IL-21
IRF-6	Induce differentiation of keratinocyte	
IRF-8	Promote maturation of CD8α + DCs and pDCs	
	Induce differentiation and maturation of MΦ	Blimp-1, METS
	Induce maturation of B cells	EBF, the light chain of Ig
	Induce differentiation of Th1	BCL, AID

3.2. IRF-4

IRF-4 is highly related to haematological malignancies. IRF-4 was induced for expression after the host is infected with human T lymphocyte leukaemia virus (HTLV-1), which could suppress the expression of G2-M checkpoint cyclin B1 and other DNA repair proteins [17]. IRF-4 was reported to be expressed in a high level in chromosome translocation t (p25; q32) in multiple myeloma (MM) patients [18], and the high expression level of IRF-4 usually indicates a poor prognosis [19]. IRF-4 could activate transcription of MYC, and then high expression level of MYC could further promote the expression of IRF-4. Thus a positive regulation loop was formed [20]. While the positive regulation loop could accelerate disease progression, it needs further investigation about whether breaking the regulation loop could help treat the disease.

4. IRFs in inhibiting cell cycle and differentiation

Most members of IRFs are reported to prevent carcinogenesis through affecting cell cycle and differentiation, yet some IRFs are reported to prevent oncogenesis through immune responses (Table 3).

4.1. IRF-1

IRF was the first IRFs reported to have participation in tumour immunology. IRF-1 knock-out cells were unable to cease cell cycle under DNA damage conditions. IRF-4 can induce transcription of CDK inhibition protein p21 WAF1/CIP1 [21]. Small molecules (e.g. IFN-γ) could facilitate the apoptosis-promoting ability of IRF-1 [22]. IRF-1 gene deletion promoted c-Ha-Ras gene expression and p53 encoded heterozygous gene Trp53 induced carcinogenesis [23]. IRF-1 is located in chromatin 5q31.1, which is a common mutant site in leukaemia and