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Original Article

Role of cellular metabolism in regulating type I interferon responses: Implications for tumour immunology and treatment

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ABSTRACT

Type I interferons (IFN) are increasingly recognized for their role in regulating anti-tumour immune responses. However, chronic activation of these pathways can result in immunosuppression and has been linked to poor responses to genotoxic and radiotoxic therapies. Emerging evidence suggests energy, lipid and amino acid metabolism play an important role in regulating and fine tuning type I IFN responses. Further, dysregulation of these processes has been implicated in the pathogenesis of chronic viral infections and autoimmune disorders. Systematic evaluation of these interrelationships in cancer models and patients may have important implications for the development of targeted IFN based anti-cancer therapeutics with minimal toxicity and limited off target effects.

Introduction

It is increasingly recognized that type I interferons (IFNs) play an important role in anti-cancer immune responses [1,2]. Recent studies have shown that tumour expression of type I IFNs and interferon stimulated genes (ISGs) correlate with favourable disease outcomes [2,3]. Conventional chemotherapeutics, radiotherapeutics and immunotherapeutics also require intact type I IFN signaling in infiltrating immune cells to mediate immunological control [4]. However, these pleiotropic cytokines appear to play a dichotomous role in cancer immunology and treatment [5]. Sustained IFN signaling is associated with immunosuppression and has been linked to poor responses to genotoxic and radiotoxic therapies [6,7]. Further, type I IFNs increase program death-ligand 1 (PD-L1) expression, which may contribute to the development of resistance to checkpoint inhibitors [8]. To date, type I IFNs have been approved for use in a number of hematological and solid tumours [9,10]. Initially developed for their anti-proliferative, anti-angiogenic and pro-apoptotic properties, these recombinant proteins showed limited clinical benefit and were often associated with autoimmune, inflammatory and metabolic symptoms as well as hematological and neurological side effects [2,11]. New anti-cancer immunotherapies targeting type I IFN pathways (i.e., type I IFN-encoding vectors and type I IFN-expressive cells) have been designed to exploit the immunomodulatory properties of these cytokines and are typically delivered to the tumour microenvironment [2]. While local delivery will help limit the off target effects, a comprehensive understanding of the mechanism that drive protective vs. pathogenic responses in long and short term type I IFN administration are required to ensure the success of these new therapeutics.

abbreviations: IFN, interferon; ISG, interferon stimulated genes; PD-L1, program death-ligand 1; TLR, Toll-like receptor; RIG, retinoic acid-inducible gene-like helicases; RLR, RIG-I-like receptor; PAMP, pathogen-associated molecular pattern molecule; DAMP, damage-associated molecular pattern molecule; IFNAR, IFN-α receptor; IRF, IFN regulatory factor; ISGF3, IFN-stimulated gene factor; ISRE, IFN-stimulated response elements; PI3K, phosphatidylinositol 3-kinase; NF-κB, nuclear factor-κB; mTOR, mammalian target of rapamycin; PIKK, PI3K-related kinase; PGC-1α, PPARG coactivator-1α; ETC, electron transport chain; mTORC, mTOR complex; FAO, fatty acid oxidation; OXPHOS, oxidative phosphorylation; TCA, tricarboxylic acid; BMM, mouse bone marrow-derived macrophages; PFKFB3, 6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase; RSV, respiratory syncytial virus; DC, dendritic cell; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus; RRMS, relapsing-remitting multiple sclerosis; HCMV, human cytomegalovirus; FA, fatty acid; SREBP, sterol regulatory element-binding protein; SCAP, SREBP cleavage-activating protein; MAS, meiosis-activating sterols; 25-HC, 25-hydroxycholesterol; LXR, liver X receptor; SOCS, Suppressor of cytokine signaling; IDO1, Indoleamine 2,3-dioxygenase 1; NOS, nitric oxide synthase; ADC, arginine decarboxylase; AGAT, arginine:glycine amidinotransferase; NO, nitric oxide.

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Type I IFNs are classically identified as anti-viral cytokines which inhibit viral replication and protect against infection [12,13]. However, more recent studies have shown that these pleiotropic proteins play a broader role in regulating immune function and in driving anti-bacterial, anti-fungal, anti-parasitic and anti-tumour immune responses [1,14–16]. They modulate innate and adaptive immune responses by promoting MHC expression, NK cytotoxicity, and high-affinity antigen specific T cell and B cells responses and by restricting activation of pro-inflammatory pathways and cytokine production [1,16,17]. To maintain a balanced response, these processes must be fine-tuned at the level of signaling, transcription and translation [18]. Loss of this fine-tuning can result in sustained IFN signaling, immunosuppression and tissue damage, which has been implicated in pathogenesis of chronic viral infections, autoimmune diseases and cancer [17]. The identification of novel regulators including epigenetics, non-coding RNA and cellular metabolism, may provide important new insights into mechanisms that enhance type I IFN immunomodulatory properties while limiting their detrimental effects.

Emerging evidence suggests that immune function is not only supported by, but is dependent on, metabolic reprogramming [19–21]. This reprogramming is required to meet the bioenergetic and biosynthetic demands of the cells and to activate and regulate gene expression, signal transduction and epigenetic profiles [20]. Alterations in cellular bioenergetics, amino acid metabolism and lipid metabolism have been shown to affect cytokine production, signaling protein activity and cell differentiation processes [22–24]. Further, by altering cellular metabolism, it may be possible to shape and fine tune innate and adaptive immune responses. In this review, we provide an overview of recent evidence suggesting that cellular metabolism plays a critical role in regulating type I IFN responses. We also discuss how dysregulation of these processes contributes to the pathogenesis of chronic viral infections and autoimmune disease. Based on these findings, we also suggest that immunometabolism may represent a mechanism by which we can fine tune type I IFN responses to limit tissue damage and immunosuppression. Careful examination of these interrelationships may have far-reaching implications for tumour immunology, drug development and clinical oncology.

Activation of type I IFN responses

The type I IFNs consist of 20 subtypes including IFN-α (14 isoforms) and IFN-β as well as IFN-ε, -κ, -τ, -δ, and -ζ. These cytokines are produced by a number of different cells following engagement of three families of transmembrane and cytosolic receptors; toll like receptors (TLRs), the retinoic acid-inducible gene like helicases (RIG-I-like receptors [RLR]), and cytoplasmic DNA sensors [14,25–28]. These receptors recognize a wide range of pathogen-associated molecular pattern molecules (PAMPs) and damage-associated molecular pattern molecules (DAMPs) and play an important role in initiating innate immune responses during infection and following cell death and tissue damage. Type I IFNs signal through a ubiquitously expressed transmembrane IFN-α receptor (IFNAR), composed of IFNAR1 and IFNAR2 subunits. Engagement of the IFNAR is associated with a ligand-dependent rearrangement and dimerization of the receptor subunits and autophosphorylation of associated Janus family kinases [29,30]. In canonical signaling, Tyk2 and Jak1 activation recruits and results in the dimerization of STAT1 and STAT2 [31–33]. This heterodimer then migrates to the nucleus and associates with IFN regulatory factor (IRF) 9 to form the IFN-stimulated gene factor 3 (ISGF3) complex, which binds to the IFN-stimulated response elements (ISREs) on the promotor of ISGs. In some cells, other STAT homo- (e.g., STAT1-STAT1, STAT3-STAT3, STAT4-STAT4, STAT5-STAT5, STAT6-STAT6) and heterodimers (STAT1-STAT3, STAT1-STAT4, STAT1-STAT5, STAT2-STAT3 and STAT5-STAT6) are also formed, which bind to IFN-γ-activated site (GAS) elements in the ISG promoter [34–37]. Recent studies have also shown that STAT2 is an important regulator of type I IFN signaling. It is an essential adaptor in USP18-mediated suppression of type I IFN responses [38]. Further, phosphorylation of STAT2 at threonine-387 and serine-738 has been shown to negatively regulate IFN-α and IFN-β signaling [39,40].

In addition to activation of the JAK-STAT pathway, a number of ancillary pathways including p38 MAP kinase pathway, MAP kinase kinase/ERK/MAPK signal-interacting kinase cascade and phosphatidylinositol 3-kinase (PI3K) pathways also play an important role in IFN signaling [41,42]. Both p38 and ERK/MAPK signaling regulates anti-viral and anti-proliferative responses [43,44]. Alternatively, PI3K-AKT-signaling increases protein synthesis and cell proliferation, mediates pro- or anti-apoptotic signals in a cell dependent manner [45–47] and regulates transcriptional activation of STAT1 and nuclear factor-κB (NF-κB) [18]. PI3K-AKT signaling also regulates IFN-inducible activation of the mammalian target of rapamycin (mTOR) [42]. mTOR is a serine/threonine protein kinase in the PI3K-related kinase (PIKK) family that plays a critical role in coordinating cell growth and metabolism (see discussion below).

Cellular responses to type I IFN are cell type and context-dependent and vary during the course of an immune response [17,38,48,49]. The variability in these responses are due, in part, to the cumulative effects of signaling processes on resultant ISG expression profiles [17]. To date, transcriptional profiling has identified over 1000 ISG associated with type I IFN responses, which span a variety of functional categories including antiviral proteins, inflammatory mediators, transcriptional activators and repressors, signaling molecules, apoptosis mediators, and proteins associated with DNA replication and repair [48,50,51]. A subset of ISG products are associated with cellular metabolic processes including amino acid, lipid and nucleotide metabolism [52–56]. While the role of these metabolic ISGs in antiviral immune responses have been well characterized, their more fundamental role in regulating cell function and survival remain largely uncharacterized.

Interrelationships between cellular metabolism and type I IFN responses

Type I IFN signaling and cellular metabolism

Several studies have shown that metabolic reprogramming is required to mount functional type I IFN responses [57,58]. However, the mechanisms underlying this reprogramming remain poorly characterized. This reprogramming is likely complex and may be regulated by a combination of cell intrinsic and extrinsic signals [17]. Consistent with this finding, a number of studies have shown that JAK/STAT, p38, ERK/MAPK and PI3K/AKT signaling can regulate metabolic processes (reviewed in Ref. [18]). Further, increasing evidence suggests the IRF family of transcription factors plays an important role in regulating cellular metabolism [59]. For the purposes of this mini review, we will focus on the potential contribution of JAK/STAT and mTOR signaling as well as IRF mediated transcription on metabolic reprogramming.

The JAK/STAT pathway controls cellular responses to cytokines by regulating the expression of nuclear-encoded early response genes [60]. This complex network of homo- and heterodimers play a central role in regulating immune function, development, and apoptosis [34]. STAT1 and STAT3 have also emerged as key