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Role of Interferon in Cancer Metabolism

Vaishali Chandel and Dhruv Kumar

Abstract

Interferons (IFNs), a pleiotropic cytokine that has long been regarded as an important effector molecule, are increasingly recognized due to their role in cancer and in antitumor immune response regulation. Interferons broadly alter cellular functions in response to viral and other infections. Dysregulation of interferon has been implicated in cancer, autoimmune disorders, and pathogenesis of chronic viral infections. However, the association between interferons and cancer cell metabolism is poorly understood. Emerging evidence suggests the importance of lipid, energy, and amino acid metabolic pathway in regulating interferon response against cancer. Additionally, viruses exploit and modulate the host cell and induce the major metabolic reprogramming causing cancer. In response, interferons upregulate the transcription of large number of interferon stimulating gene (ISG) whose products play a major role in the innate and adaptive immune response against viral infection. Immense research is being done on understanding the role of IFNs in cancer metabolism. Therefore, systematic evaluation of these associations between interferons and cancer metabolism may have important implications for the development of anticancer therapeutics targeting IFN, minimizing toxicity, and limiting off-target effects.

Keywords: interferons, cancer, cancer metabolism

1. Introduction

The interferons (IFNs) are a family of pleiotropic cytokines, which play an important role in anticancer immune response. IFNs broadly modulate cellular functions in response to viral and other infections. These modulations include changes in membrane composition, proliferation, metabolism, protein synthesis, and the nutritional microenvironment [1]. Interferons (IFN) are classified as three major types distinguished by their nature, sequence identity, and distribution of cognate receptors [1]. The type I human IFN encodes a family of 17 distinct proteins (IFN α 13 subtypes, IFN β , IFN ϵ , IFN κ , and IFN ω) consisting of IFN α / β receptor 1 (IFNAR1) and IFN α / β receptor 2 (IFNAR2) subunits that bind to their cognate receptor. The type 1 IFN is located on chromosome 9p. Engagement of receptor activates the receptor-associated protein tyrosine kinases Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2), phosphorylating and activating signal transducer and activator of transcription 1 (STAT1) and STAT2 transcription factors [2]. IFN γ is the only single type II IFN, which binds to IFN γ receptor 1 (IFNGR1) and IFN γ receptor 2 IFNGR2 subunits. The type III IFNs consist of IFN λ 1, IFN λ 2, IFN λ 3, and IFN λ 4, which bind the IFN λ receptor 1 (IFNLR1) [3] (**Figure 1**). Pattern

Figure 1. Interferon signaling and role in cancer. Type I IFN encodes IFN α/β consisting of IFN α/β receptor 1 and 2 subunits that bind to their cognate receptor. Engagement of receptor activates JAK1 and TYK2, phosphorylating and activating STAT1 and STAT2 transcription factors. IFN γ binds to IFN γ receptor 1 and 2 subunits. The type III IFNs consist of IFN λ , which bind the IFN λ receptor 1 and 4. Activation of the three types of interferons mediates downstream signaling pathway in cancer and leads to effector responses such as anti-proliferative, antiviral apoptosis, metabolic regulation, immunoregulation, migration, cellular growth and differentiation, growth inhibitory effects, and cell cycle progression. JAK1: Janus kinase 1; TY2: tyrosine kinase 2; STAT: signal transducer and activator of transcription.

recognition receptor (PRR) pathways activate the expression of type I and type III IFNs. However, cytokines expressed by natural killer (NK) cells and T cells, including IL12 and IL18, or mitogens induce type II IFN [4, 5]. Additionally, mammalian target of rapamycin (mTOR) also activates the expression of IFNs. Integration of mTOR complex 1 (mTORC1) with the major class of energy and nutrient sources [glucose, amino acids, adenosine triphosphate (ATP), and lipids] leads to the cellular activation and translation [6]. mTORC1 activation is important to induce and activate interferon regulatory transcription factor (IRF) such as IRF5 and IRF7, to initiate and maximize the production of type I IFN [7]. The transcription of majority of interferon stimulated genes (ISGs) is mediated by type I IFNs and IFN γ [8]. Three major families of ISGs play a major role in antiviral host immune response; RNA-activated protein kinase (PRK), Mx protein (Myxovirus resistance 1) and ribonuclease L (RNase L) [9]. They are responsible for inhibiting viral replication. PKR is induced by IFN and is a RNA-dependent kinase that phosphorylates eIF2 α , the translation initiation factor 2 α mediating inhibition of viral and cellular translation. Binding of dsRNA activates OAS and stimulates the activity of RNase L causing protein expression inhibition by cellular and viral ssRNA cleavage [10]. In addition, Mx proteins are GTPases, which trap and inhibit viral replication by sensing nucleocapsid-like viral structures [11]. The production of IFNs is important

since they regulate tumorigenesis and mediate metabolic reprogramming by direct or indirect means [1, 12]. IFN plays a major role in cancer metabolism. Cellular metabolism is a complex and fundamental biological process involving catabolism to fuel cellular reactions by the breakdown of macromolecules to generate energy in the form of adenosine triphosphate (ATP) and anabolism that delivers nutrients such as amino acids, carbohydrates, and fatty acids for the synthesis of macromolecules [13]. As compared to the normal cells, the metabolic activities in cancer cells are altered, and these alterations facilitate and support the malignant properties of cancer cells. Therefore, metabolic reprogramming is one of the major hallmarks of cancer [14]. In order to meet biosynthetic and bioenergetic demands to facilitate rapid proliferation, cancer cells perform increased glycolysis even under anaerobic conditions (Warburg phenomenon) [15]. Thus, the conversion of glucose to lactic acid by glucose metabolism fulfills energy demands in cancer cells, as opposed to mitochondrial oxidative phosphorylation in normal cells [16]. Additionally, reliance on glycolysis by cancer cells is a useful adaptation in order to sustain in a hypoxic microenvironment. This glycolytic switch is mediated by various mechanisms [17]. For example, the best described canonical pathway mediating the regulation of tumor cell metabolism is the PI3K-Akt pathway [18]. PI3K-Akt pathway promotes the activity of glucose transporter (GLUT) and stimulates the glycolytic process and production of lactate through activating several glycolytic enzymes such as hexokinase (HK) and phosphofructokinase (PFK). Mechanistically, PI3K-AKT signaling activates mammalian target of rapamycin (mTOR), which activates the transcription factor in turn, hypoxia-inducible factor-1 (HIF-1). HIF-1 cooperation with other transcription factors such as p53, c-Myc, and Oct1 activates transcription of multiple genes involved in glycolytic metabolism, such as HK [19], GLUT-1 and GLUT-3 [20, 21], lactate dehydrogenase (LDH) [22], and phosphoglycerate kinase [23], as well as for pH regulation, such as carbonic anhydrase IX (CAIX) [24] and Na⁺/H⁺ exchanger 1 (NHE1) [25], and suppressors of TCA cycle, such as pyruvate dehydrogenase kinase (PDK) [26]. However, metabolic alteration in cancer cell is not only defined to glucose metabolism, but it is directly interconnected with various other metabolic pathways such as amino acid metabolism through the intermediate 3-phosphoglycerate, pentose phosphate pathway (PPP) by the glucose-6-phosphate intermediate, and metabolism of fatty acids (FA) by pyruvate into Krebs cycle [27].

Therefore, it is important to understand the role of interferons in cancer cell metabolism for the development of novel interventions to treat cancer.

2. Interferons and cancer metabolism

2.1 Type I IFN signaling and cancer metabolism

The correlation between the type I IFN and cancer metabolism in cancer is shown in several studies [1, 7, 12, 28, 29]. However, the mechanism underlying this altered metabolism is poorly understood and not widely studied because of the complexity in regulation by various cellular extrinsic and intrinsic signals [30]. Signaling pathway, including JAK/STAT, ERK/MAP, p38, and PI3/AKT, regulate the metabolic process [28]. Additionally, it has been shown that IRF also plays a major role in regulating metabolism in cancer [31]. The JAK/STAT signaling pathway plays an important role in regulating development, immune function, and apoptosis [32]. It regulates the expression of early response genes [33]. STAT1 and STAT3 alter the gene expression in glucose metabolism, gluconeogenesis, Krebs cycle, and mitochondrial oxidative phosphorylation (OXPHOS). Apart from this metabolic

pathway, STAT 1 and STAT3 play a key role in modulating lipid metabolism in cancer [32, 34, 35]. Also, they have been shown to alter the cellular respiration process and mitochondrial function. The function of mitochondria is decreased due to PPAR γ coactivator-1 α (PGC-1 α) repression, a master regulator in mitochondrial biogenesis [36]. Alternatively, STAT3 localizes in mitochondria and interacts with complex I and II of the electron transport chain (ETC), thereby increasing the oxidation process [37]. Most importantly, while these modifications in metabolic pathways are needed to mount functional immune responses, changes associated with STAT activation may lead to the pathogenic processes during activation of IFN. Specifically, signaling mediated by STAT1 has been shown to mediate tumorigenesis and resistance to chemotherapy and ionizing radiation by upregulating the expression of genes involved in glucose metabolism, Krebs cycle, and OXPHOS [38]. Alternatively, alterations driven by STAT3 in mitochondrial metabolism lead to drug resistance in cancer patients by controlling the mitochondrial transition pore opening [39]. However, further study is needed to understand how these STAT mediated mechanisms facilitate to functional and nonfunctional type I IFN responses. Apart from the STAT signaling pathway, AKT/mTOR signaling has been shown to play an important role in type I IFN effector function regulation. The two complexes of mTOR (mTORC1 and mTORC2) [40, 41] have differential effects on type I IFN responses. mTORC1 plays a key role in ISGs translation [42], whereas mTORC2 performs transcription of IFN-dependent gene via interferon-stimulated response elements [43]. Additionally, mTOR in response to hormonal and environmental signals coordinates metabolism centrally [44]. Also, it has been associated with lipogenesis, adipogenesis, ribosomal biogenesis, and pyrimidine synthesis [45–48]. Previous studies have identified the correlation between mTOR signaling, OXPHOS, fatty acid oxidation (FAO), and glycolysis with type I interferons [49]. A major important regulator of interferon responses is IRFs, which centrally regulate the development of immune cell and effector function [29, 31, 50, 51]. The best described IRFs, IRF4, regulate the expression of the major molecules, which are important for aerobic glycolysis [50] and for suppressing the expression of lipogenic gene involved in lipogenesis and lipolysis activation [52]. In a similar manner, IRF5 upregulates the glycolytic process via activation of AKT and glycolytic gene induction in inflammatory macrophages [29]. Many studies have reported abnormalities in expression of IRF and their role in metabolic diseases such as cancer with poor prognosis, insulin resistance, atherosclerosis, and hepatic steatosis [53–55].

2.2 Type I IFN and altered bioenergetics

Metabolic reprogramming in cancer cells is closely linked to effector function and cellular activation [56]. Bioenergetic pathways include glucose metabolism, tricarboxylic acid cycle (TCA), FAO, OXPHOS, electron transport chain (ETC), and pentose phosphate pathway (PPP) [56]. Since metabolic reprogramming is needed to meet the biosynthetic and bioenergetic demands of the cells, recent studies suggest that metabolites (succinate and citrate) and enzyme pyruvate kinase M2 may play a key role and act as transcription factor and signaling molecule to mediate the immune function and inflammatory processes [27, 57, 58]. An important characteristic of type I IFN in cancer metabolism is upregulated glucose metabolism [59]. The metabolic shift is important to quickly generate ATP to meet energy demands of the cell. In fibroblasts, PI3/AKT signaling is important for type I IFN-associated shift and leads to increased uptake of glucose in the cell [60]. Alternatively, STAT1 mediates aerobic glycolysis in human squamous cell carcinoma [61]. Also, upregulated expression of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) has been shown in variety of tumors [62] (**Table 1**). Furthermore, the

Gene	Role in metabolism	Cancer type	Reference
PFKFB3	Regulator of glycolysis. Associated with many aspects of cancer, including metabolism, carcinogenesis, cancer cell proliferation, vessel aggressiveness, drug resistance, and tumor microenvironment	Liver, breast, head, and neck	[62]
SC4MOL	Protection against virus attack and important contributor in sterol metabolism	Breast, nonsmall cell lung cancer	[63]
SCAP	IFN-driven regulation of lipid metabolism	Brain cancer	[64, 65]
SREBP1/2	IFN-driven regulation of lipid metabolism	Colon, lung, pancreatic	[66]
CH25H	Regulate cellular functions and influence various physiological processes such as cholesterol metabolism, membrane fluidity regulation, and intracellular signaling pathways in cancer	Breast cancer	[67]
CYP27A1	Affects estrogen receptor function by the antagonism of estrogen action and also by the direct modulation of the receptor function modulating metabolism	Breast cancer	[68]
IDO1	Prevents viral proliferation and regulates lipid metabolism and inflammation	Breast, lung, pancreatic, leukemia	[69]
NOS2	Cytostatic and cytotoxic effects against tumor cells	Glioblastoma, melanoma, breast	[70]

Table 1.
Type I IFN immunometabolic gene response in the progression of various cancers.

metabolic shift from OXPHOS to glycolysis contributes to Warburg phenomenon, tumor metastasis, and growth [71]. In cancer cells, decreased rate of mitochondrial OXPHOS is accompanied with the glycolytic shift in immune cells [72]. Consistent with these findings, mouse L929 cell triggered with type I IFN showed signs of reduced OXPHOS and production of ATP [73]. Also, CD4+ T cells isolated from multiple sclerosis patients treated with IFN- β underwent OXPHOS impairment in a dose-dependent manner as compared to healthy individuals [74]. A single nucleotide polymorphism (SNP) in PGC-1 α , a gene involved in the mitochondrial biogenesis, was shown to be associated with reduced intracellular ATP production levels and altered therapeutic response to IFN- β in patients [74]. However, other studies suggest that bioenergetic reprogramming in cancer driven by IFN may be context and cell type dependent [75]. Mouse plasmacytoid DCs (pDCs) stimulated by IFN- α are linked with upregulated glycolytic genes in turn increased glycolysis, OXPHOS, and FAO to meet the energy demand of the cells [76]. mTOR activation mediates upregulation of OXPHOS and FAO and is important in mounting an immune response. In T cell, stimulation of CD8+ memory T cells by IFN- α is associated with upregulated OXPHOS, whereas effector T cell stimulation has not been shown to alter the activity of OXPHOS [77]. Additionally, in the reverse Warburg phenomenon, cancer cells induce aerobic glycolysis in cancer-associated fibroblasts (CAFs), present in the tumor stroma. CAFs generate pyruvate, lactate, and ketone bodies that enter the TCA cycle in cancer cells for mitochondrial OXPHOS. In fact, these tumor-associated stromal cells, for example, tumor-associated macrophages (TAMs), already vary from their original cells and have epigenetic and genetic changes, which result in altered metabolic profiles. Therefore, cancer cells influence

each other not only in terms of growth factor or cytokines, such as IFN, but also on dependency on metabolic pathways. TAMs, for example, derive their ATP from OXPHOS rather than aerobic glycolysis.

2.3 IFN response and lipid metabolism

A wide variety of studies have recognized the role of type I IFNs in modulating lipid metabolism in cancer [7]. Lipids are the major constituent in plasma membrane and various other cellular compartments such as the endoplasmic reticulum, nuclear membrane, Golgi apparatus, lysosomes, and endosomes [7]. Alongside, lipids function as signaling molecules to regulate the majority of cellular processes, including inflammatory, metabolic, and innate immune responses [78]. A number of viruses causing cancer, such as Epstein-Barr Virus (EBV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human Herpesvirus 8 (HHV8), Human Papillomavirus (HPV), Human T-cell Lymphotropic Virus 1 (HTLV), and Merkel Cell Polyomavirus hijack cholesterol and fatty acid (FA) biosynthesis of host to support replication and survival of virus [79]. To counteract this process, *de novo* cholesterol and lipid synthesis is decreased, and cholesterol and FA import is mediated by type I IFNs. After 30 min of exposure to IFN, STAT2-driven reprogramming occurs and is independent of ISG expression [64]. Decreased *de novo* cholesterol and lipid synthesis is a complex mechanism and needs further research to be done upon. Several studies have reported the role of sterol regulatory element-binding protein 2 (SREBP2)/SREBP cleavage-activating protein (SCAP) pathway in IFN-driven regulation of lipid metabolism [64, 65] (**Table 1**). SREBP1 and SREBP2 are recruited by SCAP, a chaperone protein to the nucleus. In the nucleus, SREBP1 and SREBP2 transcription factors regulate cholesterol and lipid metabolism, respectively. Knock out of SREBP2 or SCAP expression in macrophages leads to mice resistant to viral attack supporting the role of IFN response and an interrelationship between lipid metabolism and type I IFN [64, 65]. Additionally, type I IFNs upregulate microRNAs that control cholesterol biosynthesis. Upregulated expression of miR-342-5p in BMM is shown to be associated with IFN- β stimulation. miR-342-5p targets SREBP2, DHCR7, IDI1, and SC4MOL cholesterol biosynthetic genes [80] (**Table 1**). SC4MOL gene catalyzes demethylation of C4-methylsterols and meiosis-activating sterols (MASs) and encodes methyl sterol oxidase (**Table 1**). Accumulation of C4-methylsterols leads to increased proliferation of cancer cells [63]. Oxysterol, a cholesterol derivative participating in cholesterol metabolic regulation, signaling pathways such as Hedgehog, MAPK, and Wnt, and enzymatic activity playing a major role in cancer metabolism, is upregulated by type I IFNs [81]. Of the most important, 25-hydroxycholesterol (25-HC) and 27-HC (CYP27A1) play a key role in sterol biosynthesis regulation, minimizing accumulation of cholesterol and inhibition of viral spread and replication [68]. Cholesterol-25-hydroxylase (CH25H) encodes 25-HC, which is a soluble oxysterol [39]. Type I and II IFN production in response to Toll-like receptor (TLR) activation leads to the expression of CH25H in dendritic cells and macrophages. 25-HC does this by repressing the activation of SREBP2 or by increasing the expression of miR-185 regulating hepatic homeostasis of lipid [7]. Alternatively, 27-HC has been demonstrated to decrease the cholesterol accumulation in lysosomes and decrease inflammation [7] (**Table 1**). However, oxysterol induced by IFN may also have a damaging role in cancer and other inflammatory diseases. 25-HC amplifies proinflammatory mediator production following infection [82]. 22-HC and 27-HC in cancer are detected in high levels in a majority of tumor cells [83, 84]. They mediate the activation of liver X receptors (LXRs) in tumor, upregulating the efflux of cholesterol while promoting an anti-inflammatory state [85]. Additionally, 22-HC and 27-HC

have been reported to enhance the estrogen receptor transcription in breast cancer model, supporting the evidence that it may lead to resistance to hormonal therapy [83] (**Table 1**).

2.4 IFN response and amino acid metabolism

Amino acids serve as a building block for protein synthesis, branched chain fatty acid synthesis, and energy metabolism [27]. Their utilization is associated with metabolic signaling pathway such as nucleotide synthesis and mTOR pathway in tumor cells during immune response. Amino acid metabolism is reprogrammed to meet the biosynthetic and bioenergetic requirements of the cells [27]. However, several other studies have shown the role of amino acid as an important signaling molecule to alter cellular survival and function [27]. For the purpose of the importance of interferons in cancer-associated metabolism, we will focus on arginine and tryptophan metabolism in regulating type I IFN responses.

In response to type I IFN, metabolism of amino acid is tightly regulated against virus causing cancer [86]. A major example of this regulation includes tryptophan metabolism. Tryptophan is one of the nine essential amino acids and is very important in playing a key role in various metabolic pathways. The catabolites of tryptophan play an important role in cancer immunosuppression. Indoleamine-2,3-dioxygenase (IDO), catabolic enzyme converting tryptophan to kynurenine, is the essential rate limiting enzyme expressed in antigen-presenting cells or tumor cells. This metabolic pathway creates an immunosuppressive milieu in tumor-draining lymph nodes and in tumors by inducing apoptosis and T-cell anergy through tryptophan depletion and accumulation of immunosuppressive tryptophan catabolites. Specifically, the synthesis of tryptophan derivatives in kynurenine accounts for more than 80% of tryptophan catabolism. The synthesis of kynurenine is done by the catalytic activity of tryptophan-2,3-dioxygenase (TDO2) and indoleamine-2,3-dioxygenase (IDO1) (**Figure 2**). The expression of ISG (interferon-stimulated gene), IDO1, which is highly effective at controlling and resisting pathogens, is very high across different cell types, whereas TDO2 has a lower affinity for tryptophan and is majorly expressed in hepatocytes [7]. Several studies have shown the development of an immunotolerant state associated with enhanced regulatory response of T cells and suppressed T cell activation and proliferation due to increased tryptophan catabolism [87, 88]. Additionally, metabolites of kynurenine including 3-hydroxyanthranilic acid and quinolinic acid have cytotoxic as well as inflammatory effects [52]. These studies suggest the role of tryptophan catabolism in response to type I IFN in a protective or detrimental manner in cancer. Supporting their protective role, studies have demonstrated that induction of IDO can be important in autoimmune disease prevention and cancer [89]. Consistent with such findings, IDO protein is expressed in varieties of solid tumor and in human malignancies [90] (**Table 1**). These findings and observations highlight the importance of type I IFN in the development of anticancer therapeutics by modulating tryptophan catabolism pathway. In addition to the role of type I IFN in modulating tryptophan metabolism, arginine plays an important role in adaptive and innate immune response [90]. Arginine is catabolized by four different classes of enzyme in various cell types: arginase, arginine: glycine amidinotransferase (AGAT), nitric oxide synthase (NOS), and arginine decarboxylase (ADC) [91]. This catalytic process produces several metabolites, which are biologically important with various functions such as urea, citrulline, glutamate, creatinine, polyamines, and nitric oxide (NO). Arginine is metabolized by arginase and/or NOS pathway [12]. The specific role of arginase or iNOS leads to the functional polarization of these cells into anti-inflammatory M2 phenotypes or M1 inflammatory phenotypes

Figure 2. Tryptophan catabolism in response to type I IFN. The synthesis of kynurenine is done by the catalytic activity TDO2 and IDO1. Increased tryptophan catabolism suppresses T cell activation, and proliferation IDO is an important mediator in metabolism, autoimmune disease prevention, and cancer. TDO2, tryptophan-2,3-dioxygenase (TDO2); IDO1, indoleamine-2,3-dioxygenase.

[12]. The expression of iNOS is increased by type I IFN and is linked to enhanced levels of NO, L-citrulline, and reactive nitrogen species. Furthermore, enhanced glycolysis in tumor cells, TAMs, and other stromal cells, such as CAFs, leads to lactic acid accumulation in the tumor microenvironment. Lactic acid polarizes TAMs to a tumor-promoting phenotype characterized by the expression of arginase1 (ARG1), VEGFA, and several M2 markers via the activation of HIF1 α [12]. This metabolic reprogramming results in accumulation of bioactive metabolites and plays a major role in cytotoxic or cytostatic activities against tumor cells. This suggests that type I IFN signaling may play an important role in tumor immune escape, immunosuppression, and immunopathology [12].

3. IFN- γ and cancer metabolism

In cancer, metabolic reprogramming of macrophages has been widely studied, but its relevance in function of inflammatory cell is a current research interest. Considering the role of Warburg phenomenon (aerobic glycolysis) in M1 macrophages, researchers have been dependent on 2-DG, a competitive inhibitor of glucose in the first reaction step. It was found that induction of 2-DG downregulated both aerobic glycolysis and mitochondrial OXPHOS and had a significant effect in a dose-dependent manner on cell viability and ATP levels. Alternatively, they exploited galactose, which is metabolized to glucose-6-phosphate at a very slow rate, thereby significantly downregulating the glycolytic throughput. Additionally, it was observed that there was downregulation in extracellular acidification rate (ECAR) levels with little effect oxygen consumption rate (OCR), thereby facilitating more exclusive evaluation of the importance of glycolysis in M1 macrophages. Certainly, even under those conditions, macrophages were differentiated by IFN- γ into M1 type phenotype depending on the surface marker expression

and cytokines such as IL-6 and TNF- α . However, levels of IL-1 β and HIF-1 α were profoundly downregulated by galactose, similar to the expression and production of NO. Consistent with these findings, it suggests that aerobic glycolysis in cancer is very particular and plays a significant role for two gene transcription pathways in IFN- γ -stimulated macrophages: HIF-1 α and STAT-1. In a similar manner, IFN- γ activated JAK/STAT-1 pathway in cancer increased phosphorylation of STAT-1 in M1 macrophages, and this response was inhibited by using 2-DG as a competitive inhibitor. Also, TAMs showed an increased glycolysis, and glycolysis inhibition using a competitive inhibitor 2DG revoked the functional phenotype of cancer cells. Galactose showed a significant inhibitory effect on the phosphorylation of STAT-1, supporting the importance of aerobic glycolysis in JAK/STAT-1 pathway. In the absence of IFN- γ , glucose itself could not stimulate JAK/STAT-1 pathway. These findings highlight the importance of IFN- γ triggering signaling pathway in M1 macrophages altering the metabolism in cancer [12].

4. Conclusions

The interrelationship between immune function and cellular metabolism is increasingly recognized. Apart from providing substrates to meet the biosynthetic and bioenergetic demand, metabolites from metabolic pathway and enzymes regulate transcription and translation, epigenetic processes, signaling pathways to control cellular function. Increasing evidence suggests the importance of interferons in modulating cell metabolism in cancer and contributing to effector functions. However, it is unclear if these processes can be harnessed to elicit specific immune functions and/or prevent the development of pathological side effects. In order to target metabolic processes with some level of specificity, we require an in-depth understanding of how these processes are regulated across cell types and tissues. Therefore, it is important for the in depth understanding to develop novel interventions to treat cancer, chronic inflammatory, and infectious diseases.

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Conflict of interest

The authors declare no conflict of interest.

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