Chapter

Role of Interferon in Cancer Metabolism

Vaishali Chandel and Dhruv Kumar

Abstract

Interferons (IFNs), a pleotropic 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 pleotropic 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 (IFNα 13 subtypes, IFNβ, IFNε, IFNκ, and IFNω) consisting of IFNα/β receptor 1 (IFNAR1) and IFNα/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]. IFNγ is the only single type II IFN, which binds to IFNγ receptor 1 (IFNGR1) and IFNγ receptor 2 IFNGR2 subunits. The type III IFNs consist of IFNλ1, IFNλ2, IFNλ3, and IFNλ4, which bind the IFNλ receptor 1 (IFNLR1) [3] (Figure 1). Pattern
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\(\gamma\) \([8]\).

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\(\alpha\), the translation initiation factor 2\(\alpha\) 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

---

**Figure 1.** Interferon signaling and role in cancer. Type I IFN encodes IFN\(\alpha/\beta\) consisting of IFN\(\alpha/\beta\) 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\(\gamma\) binds to IFN\(\gamma\) receptor 1 and 2 subunits. The type III IFNs consist of IFN\(\lambda\), which bind the IFN\(\lambda\) 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.
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, 29, 51]. 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 [28]. Signaling pathway, including JAK/STAT, ERK/MAP, p38, and PI3/AKT, regulate the metabolic process [29]. Additionally, it has been shown that IRF also plays a major role in regulating metabolism in cancer [30]. The JAK/STAT signaling pathway plays an important role in regulating development, immune function, and apoptosis [34]. It regulates the expression of early response genes [31]. 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]. Also, they have been shown to alter the cellular respiration process and mitochondrial function. The function of mitochondria is decreased due to PPARG coactivator-1 α (PGC-1 α) repression, a master regulator in mitochondrial biogenesis [35]. Alternatively, STAT3 localizes in mitochondria and interacts with complex I and II of the electron transport chain (ETC), thereby increasing the oxidation process [36]. 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 [37]. Alternatively, alterations driven by STAT3 in mitochondrial metabolism lead to drug resistance in cancer patients by controlling the mitochondrial transition pore opening [38]. 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) [39, 40] have differential effects on type I IFN responses. mTORC1 plays a key role in ISGs translation [41], whereas mTORC2 performs transcription of IFN-dependent gene via interferon-stimulated response elements [42]. Additionally, mTOR in response to hormonal and environmental signals coordinates metabolism centrally [43]. Also, it has been associated with lipogenesis, adipogenesis, ribosomal biogenesis, and pyrimidine synthesis [44–47]. Previous studies have identified the correlation between mTOR signaling, OXPHOS, fatty acid oxidation (FAO), and glycolysis with type I interferons [48]. A major important regulator of interferon responses is IRFs, which centrally regulate the development of immune cell and effector function [30, 49–51]. The best described IRFs, IRF4, regulate the expression of the major molecules, which are important for aerobic glycolysis [49] and for suppressing the expression of lipogenic gene involved in lipogenesis and lipolysis activation [84]. In a similar manner, IRF5 upregulates the glycolytic process via activation of AKT and glycolytic gene induction in inflammatory macrophages [51]. 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 [52–54].

2.2 Type I IFN and altered bioenergetics

Metabolic reprogramming in cancer cells is closely linked to effector function and cellular activation [55]. Bioenergetic pathways include glucose metabolism, tricarboxylic acid cycle (TCA), FAO, OXPHOS, electron transport chain (ETC), and pentose phosphate pathway (PPP) [55]. 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, 56, 57]. An important characteristic of type I IFN in cancer metabolism is upregulated glucose metabolism [58]. 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 [59]. Alternatively, STAT1 mediates aerobic glycolysis in human squamous cell carcinoma [60]. Also, upregulated expression of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) has been shown in variety of tumors [61] (Table 1). Furthermore, the
Role of Interferon in Cancer Metabolism
DOI: http://dx.doi.org/10.5772/intechopen.92020

metabolic shift from OXPHOS to glycolysis contributes to Warburg phenomenon, tumor metastasis, and growth [62]. In cancer cells, decreased rate of mitochondrial OXPHOS is accompanied with the glycolytic shift in immune cells [63]. Consistent with these findings, mouse L929 cell triggered with type I IFN showed signs of reduced OXPHOS and production of ATP [64]. 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 [65]. A single nucleotide polymorphism (SNP) in PGC-1α, 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 [65]. However, other studies suggest that bioenergetic reprogramming in cancer driven by IFN may be context and cell type dependent [66]. 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 [67]. 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 [68]. 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

| 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 | [61] |
| SC4MOL | Protection against virus attack and important contributor in sterol metabolism | Breast, nonsmall cell lung cancer | [74] |
| SCAP | IFN-driven regulation of lipid metabolism | Brain cancer | [71, 72] |
| SREBP1/2 | IFN-driven regulation of lipid metabolism | Colon, lung, pancreatic | [88] |
| CH25H | Regulate cellular functions and influence various physiological processes such as cholesterol metabolism, membrane fluidity regulation, and intracellular signaling pathways in cancer | Breast cancer | [89] |
| 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 | [76] |
| IDO1 | Prevents viral proliferation and regulates lipid metabolism and inflammation | Breast, lung, pancreatic, leukemia | [90] |
| NOS2 | Cytostatic and cytotoxic effects against tumor cells | Glioblastoma, melanoma, breast | [91] |

Table 1.
Type I IFN immunometabolic gene response in the progression of various cancers.
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 [69]. 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 [70]. 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 [71]. 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 [71, 72] (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 interrelation-ship between lipid metabolism and type I IFN [71, 72]. 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 [73] (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 [74]. 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 [75]. 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 [76]. Cholesterol-25-hydroxylase (CH25H) encodes 25-HC, which is a soluble oxysterol [38]. 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 [77]. 22-HC and 27-HC in cancer are detected in high levels in a majority of tumor cells [78, 79]. They mediate the activation of liver X receptors (LXRs) in tumor, upregulating the efflux of cholesterol while promoting an anti-inflammatory state [80]. 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 [78] (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 [81]. 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 [82, 83]. Additionally, metabolites of kynurenine including 3-hydroxyanthranilic acid and quinolinic acid have cytotoxic as well as inflammatory effects [84]. 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 [85]. Consistent with such findings, IDO protein is expressed in varieties of solid tumor and in human malignancies [86] (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 [86]. 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) [87]. 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.
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 HIF1α [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-1β and HIF-1α 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-1α 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.

Acknowledgements

We sincerely thank all authors for their valuable inputs and carefully reading the chapter.

Conflict of interest

The authors declare no conflict of interest.
Author details

Vaishali Chandel and Dhruv Kumar*
Amity Institute of Molecular Medicine and Stem Cell Research (AIMMSCR), Amity University, Noida, Uttar Pradesh, India

*Address all correspondence to: dhruvbhu@gmail.com; dkumar13@amity.edu
References

[1] Parker BS, Rautela J, Hertzog PJ. Antitumour actions of interferons: Implications for cancer therapy. Nature Reviews. Cancer. 2016;16(3):131-144. DOI: 10.1038/nrc.2016.14

[2] Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. Nature Reviews. Immunology. 2014;14(1):36-49. DOI: 10.1038/nri3581

[3] Kotenko SV, Gallagher G, Baurin VV, Lewis-Antes A, Shen M, Shah NK, et al. IFN-λs mediate antiviral protection through a distinct class II cytokine receptor complex. Nature Immunology. 2003;4(1):69-77. DOI: 10.1038/ni875

[4] Seder RA, Gazzinelli R, Sher A, Paul WE. Interleukin 12 acts directly on CD4+ T cells to enhance priming for interferon gamma production and diminishes interleukin 4 inhibition of such priming. Proceedings of the National Academy of Sciences of the United States of America. 1993;90(21):10188-10192. DOI: 10.1073/pnas.90.21.10188

[5] Freund-Brown J, Chirino L, Kambayashi T. Strategies to enhance NK cell function for the treatment of tumors and infections. Critical Reviews in Immunology. 2018;38(2):105-130. DOI: 10.1615/CritRevImmunol.2018025248

[6] Weichhart T, Hengstschläger M, Linke M. Regulation of innate immune cell function by mTOR. Nature Reviews. Immunology. 2015;15(10):599-614. DOI: 10.1038/nri3901

[7] Fritsch SD, Weichhart T. Effects of Interferons and viruses on metabolism. Frontiers in Immunology. 2016;7(630):1-13. DOI: 10.3389/fimmu.2016.00630

[8] Samuel CE. Antiviral actions of Interferons. Clinical Microbiology Reviews. 2001;14(4):778-809. DOI: 10.1128/CMR.14.4.778

[9] Levy DE, García A. The virus battles: IFN induction of the antiviral state and mechanisms of viral evasion. Cytokine & Growth Factor Reviews. 2001;12(2-3):143-156. DOI: 10.1016/s1359-6101(00)00027-7

[10] Sadler AJ, Williams BR. Interferon-inducible antiviral effectors. Nature Reviews. Immunology. 2008;8(7):559-568. DOI: 10.1038/nri2314

[11] Haller O, Staeheli P, Schwemmle M, Kochs G. Mx GTPases: Dynamin-like antiviral machines of innate immunity. Trends in Microbiology. 2015;23(3):154-163. DOI: 10.1016/j.tim.2014.12.003

[12] Ahmed D, Cassol E. Role of cellular metabolism in regulating type I interferon responses: Implications for tumour immunology and treatment. Cancer Letters. 2017;409:20-29. DOI: 10.1016/j.canlet.2017.08.037

[13] DeBerardinis RJ, Thompson CB. Cellular metabolism and disease: What do metabolic outliers teach us? Cell. 2012;148(6):1132-1144. DOI: 10.1016/j.cell.2012.02.032

[14] Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57-70. DOI: 10.1016/s0092-8674(00)81683-9

[15] Zheng J. Energy metabolism of cancer: Glycolysis versus oxidative phosphorylation (review). Oncology Letters. 2012;4(6):1151-1157. DOI: 10.3892/ol.2012.928

[16] Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. The Journal of General Physiology. 1927;8(6):519-530. DOI: 10.1085/jgp.8.6.519
Innate Immunity in Health and Disease

[17] Eales KL, Hollinshead KE, Tennant DA. Hypoxia and metabolic adaptation of cancer cells. Oncogene. 2016;5:e190. DOI: 10.1038/oncsis.2015.50

[18] Sandulache VC, Myers JN. Altered metabolism in head and neck squamous cell carcinoma: An opportunity for identification of novel biomarkers and drug targets. Head & Neck. 2012;34(2):282-290. DOI: 10.1002/hed.21664

[19] Mathupala SP, Rempel A, Pedersen PL. Glucose catabolism in cancer cells: Identification and characterization of a marked activation response of the type II hexokinase gene to hypoxic conditions. The Journal of Biological Chemistry. 2001;276(46):43407-43412. DOI: 10.1074/jbc.M108181200

[20] Maxwell PH, Dachs GU, Gleadle JM, Nicholls LG, Harris AL, Stratford IJ, et al. Hypoxia-inducible factor-1 modulates gene expression in solid tumors and influences both angiogenesis and tumor growth. Proceedings of the National Academy of Sciences of the United States of America. 1997;94(15):8104-8109. DOI: 10.1073/pnas.94.15.8104

[21] Ebert BL, Firth JD, Ratcliffe PJ. Hypoxia and mitochondrial inhibitors regulate expression of glucose transporter-1 via distinct cis-acting sequences. The Journal of Biological Chemistry. 1995;270(49):29083-29089. DOI: 10.1074/jbc.270.49.29083

[22] Firth JD, Ebert BL, Ratcliffe PJ. Hypoxia regulation of lactate dehydrogenase A. interaction between hypoxia-inducible factor 1 and cAMP response elements. The Journal of Biological Chemistry. 1995;270(36):21021-21027. DOI: 10.1074/jbc.270.36.21021

[23] Kim JW, Gao P, Liu YC, Semenza GL, Dang CV. Hypoxia-inducible factor 1 and dysregulated c-Myc cooperatively induce vascular endothelial growth factor and metabolic switches hexokinase 2 and pyruvate dehydrogenase kinase 1. Molecular and Cellular Biology. 2007;27(21):7381-7393. DOI: 10.1128/MCB.00440-07

[24] Kumar D. Regulation of glycolysis in head and neck squamous cell carcinoma. Postdoc Journal. 2017;5(1):14-28. DOI: 10.14304/surya.jprv5n1.4

[25] Meijer TW, Kaanders JH, Span PN, Bussink J. Targeting hypoxia, HIF-1, and tumor glucose metabolism to improve radiotherapy efficacy. Clinical Cancer Research. 2012;18(20):5585-5594. DOI: 10.1158/1078-0432

[26] Ward PS, Thompson CB. Metabolic reprogramming: A cancer Hallmark even Warburg did not anticipate. Cancer Cell. 2012;21(3):297-308. DOI: 10.1016/j.ccr.2012.02.014

[27] O’Neill LA, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. Nature Reviews. Immunology. 2016;16(9):553-565. DOI: 10.1038/nri.2016.70.A

[28] Robey RB, Weisz J, Kuehmerle NB, Salzberg AC, Berg A, Brown DG, et al. Metabolic reprogramming and dysregulated metabolism: Cause, consequence and/or enabler of environmental carcinogenesis? Carcinogenesis. 2015;(Suppl 1):S203-S231. DOI: 10.1093/carcin/bgv037

[29] Platanias LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. Nature Reviews. Immunology. 2005;5(5):375-386. DOI: 10.1038/nri1604

[30] Zhao GN, Jiang DS, Li H. Interferon regulatory factors: At the crossroads of immunity, metabolism, and disease. Biochimica et Biophysica Acta. 2015;1852(2):365-378. DOI: 10.1016/j.bbadis.2014.04.030
[31] Stark GR, Darnell JE Jr. The JAK-STAT pathway at twenty. Immunity. 2012;36(4):503-514. DOI: 10.1016/j.immuni.2012.03.013

[32] Camporeale A, Demaria M, Monteleone E, Giorgi C, Wieckowski MR, Pinton P, et al. STAT3 activities and energy metabolism: Dangerous liaisons. Cancers (Basel). 2014;6(3):1579-1596. DOI: 10.3390/cancers6031579

[33] Pitroda SP, Khodarev NN, Beckett MA, Kufe DW, Weichselbaum RR. MUC1-induced alterations in a lipid metabolic gene network predict response of human breast cancers to tamoxifen treatment. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(14):5837-5841. DOI: 10.1073/pnas.0812029106

[34] Dinasarapu AR, Gupta S, Ram Maurya M, Fahy E, Min J, Sud M, et al. A combined omics study on activated macrophages—Enhanced role of STATs in apoptosis, immunity and lipid metabolism. Bioinformatics. 2013;29(21):2735-2743. DOI: 10.1093/bioinformatics/btt469

[35] Sisler JD, Morgan M, Raje V, Grande RC, Derecka M, Meier J, et al. The signal transducer and activator of transcription 1 (STAT1) inhibits mitochondrial biogenesis in liver and fatty acid oxidation in adipocytes. PLoS One. 2015;10(12):e0144444. DOI: 10.1371/journal.pone.0144444

[36] Wegrzyn J, Potla R, Chwae YJ, Sepuri NB, Zhang Q, Koeck T, et al. Function of mitochondrial Stat3 in cellular respiration. Science. 2009;323(5915):793-797. DOI: 10.1126/science

[37] Pitroda SP, Wakim BT, Sood RF, Beveridge MG, Beckett MA, MacDermed DM, et al. STAT1-dependent expression of energy metabolic pathways links tumour growth and radioresistance to the Warburg effect. BMC Medicine. 2009;7:68. DOI: 10.1186/1741-7015-7-68

[38] Poli V, Camporeale A. STAT3-mediated metabolic reprogramming in cellular transformation and implications. Frontiers in Oncology. 2015;5:121. DOI: 10.3389/fonc.2015.00121

[39] Oh WJ, Jacinto E. mTOR complex 2 signaling and functions. Cell Cycle. 2011;10(14):2305-2316. DOI: 10.4161/cc.10.14.16586

[40] Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science. 2005;307(5712):1098-1101. DOI: 10.1126/science.1106148

[41] Kaur S, Lal L, Sassano A, Majchrzak-Kita B, Srikanth M, Baker DP, et al. Regulatory effects of mammalian target of rapamycin-activated pathways in type I and II interferon signaling. The Journal of Biological Chemistry. 2007;282(3):1757-1768. DOI: 10.1074/jbc.M607365200

[42] Kaur S, Sassano A, Majchrzak-Kita B, Baker DP, Su B, Fish EN, et al. Regulatory effects of mTORC2 complexes in type I IFN signaling and in the generation of IFN responses. Proceedings of the National Academy of Sciences of the United States of America. 2012;109(20):7723-7728. DOI: 10.1073/pnas.1118122109

[43] Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. 2017;168(6):960-976. DOI: 10.1016/j.cell.2017.02.004

[44] Laplante M, Sabatini DM. mTORC1 activates SREBP-1c and uncouples lipogenesis from gluconeogenesis. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(47):18970-18975. DOI: 10.1073/pnas.1113291108
[45] Buel GR, Kim SG, Blenis J. mTORC1 signaling aids in CADalyzing pyrimidine biosynthesis. Cell Metabolism. 2013;17(5):633-635. DOI: 10.1016/j.cmet.2013.04.018

[46] Iadevaia V, Liu R, Proud CG. mTORC1 signaling controls multiple steps in ribosome biogenesis. Seminars in Cell & Developmental Biology. 2014;36:113-120. DOI: 10.1016/j.semcdb.2014.08.004

[47] Zhang L, Tschumi BO, Corgnac S, Ruegg MA, Hall MN, Mach JP, et al. Mammalian target of rapamycin complex 1 orchestrates invariant NKT cell differentiation and effector function. Journal of Immunology. 2014;193(4):1759-1765. DOI: 10.4049/jimmunol.1400769

[48] Pantel A, Teixeira A, Haddad E, Wood EG, Steinman RM, Longhi MP. Direct type I IFN but not MDA5/TLR3 activation of dendritic cells is required for maturation and metabolic shift to glycolysis after poly IC stimulation. PLoS Biology. 2014;12(1):e1001759. DOI: 10.1371/journal.pbio.1001759

[49] Man K, Miasari M, Shi W, Xin A, Henstridge DC, Preston S, et al. The transcription factor IRF4 is essential for TCR affinity-mediated metabolic programming and clonal expansion of T cells. Nature Immunology. 2013;14(11):1155-1165. DOI: 10.1038/ni.2710

[50] Zhao B, Takami M, Yamada A, Wang X, Koga T, Hu X, et al. Interferon regulatory factor–8 regulates bone metabolism by suppressing osteoclastogenesis. Nature Medicine. 2009;15(9):1066-1071. DOI: 10.1038/nm.2007

[51] Hedl M, Yan J, Abraham C. IRF5 and IRF5 disease-risk variants increase glycolysis and human M1 macrophage polarization by regulating proximal signaling and Akt2 activation. Cell Reports. 2016;16(9):2442-2455. DOI: 10.1016/j.celrep.2016.07.060

[52] Bi X, Hameed M, Mirani N, Pimenta EM, Anari J, Barnes BJ. Loss of interferon regulatory factor 5 (IRF5) expression in human ductal carcinoma correlates with disease stage and contributes to metastasis. Breast Cancer Research. 2011;13(6):R111. DOI: 10.1186/bcr3053

[53] Mei Z, Wang G, Liang Z, Cui A, Xu A, Liu Y. Prognostic value of IRF-2 expression in colorectal cancer. Oncotarget. 2017;8(24):38969-38977. DOI: 10.18632/oncotarget.17163

[54] Alsamman K, El-Masry OS. Interferon regulatory factor 1 inactivation in human cancer. Bioscience Reports. 2018;38(3): pii: BSR20171672. DOI: 10.1042/BSR20171672

[55] Sugiura A, Rathmell JC. Metabolic barriers to T cell function in tumors. Journal of Immunology. 2018;200(2):400-407. DOI: 10.4049/jimmunol.1701041

[56] Shirai T, Nazarewicz RR, Wallis BB, Yanes RE, Watanabe R, Hilhorst M, et al. The glycolytic enzyme PKM2 bridges metabolic and inflammatory dysfunction in coronary artery disease. The Journal of Experimental Medicine. 2016;213(3):337-354. DOI: 10.1084/jem.20150900

[57] Tannahill GM, Curtis AM, Adamik J, Palsson-McDermott EM, McGettrick AF, Goel G, et al. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. Nature. 2013;496(7444):238-242. DOI: 10.1038/nature11986

[58] Boussiotis VA. Targeting T cell metabolism for improvement of cancer immunotherapy. Frontiers in
Role of Interferon in Cancer Metabolism
DOI: http://dx.doi.org/10.5772/intechopen.92020

Onecology. 2018;8:237. DOI: 10.3389/fonc.2018.00237

[59] Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K pathway in human disease. Cell. 2017;170(4):605-635. DOI: 10.1016/j.cell.2017.07.029

[60] Avalle L, Pensà S, Regis G, Novelli F, Poli V. STAT1 and STAT3 in tumorigenesis: A matter of balance. JAKSTAT. 2012;1(2):65-72. DOI: 10.4161/jkst.20045

[61] Yi M, Ban Y, Tan Y, Xiong W, Li G, Xiang B. 6-Biphosphatase 3 and 4: A pair of valves for fine-tuning of glucose metabolism in human cancer. Molecular Metabolism. 2019;20:1-13. DOI: 10.1016/j.molmet.2018.11.013

[62] Lu J, Tan M, Cai Q. The Warburg effect in tumor progression: Mitochondrial oxidative metabolism as an anti-metastasis mechanism. Cancer Letters. 2015;356(2 Pt A):156-164. DOI: 10.1016/j.canlet.2014.04.001

[63] Liberti MV, Locasale JW. The Warburg effect: How does it benefit cancer cells? Trends in Biochemical Sciences. 2016;41(3):609-634. DOI: 10.1146/annurev-mbio-032713-120236

[64] Lewis JA, Huq A, Najarro P. Inhibition of mitochondrial function by interferon. The Journal of Biological Chemistry. 1996;271(22):13184-13190. DOI: 10.1074/jbc.271.22.13184

[65] Haghiakia A, Faissner S, Pappas D, Pula B, Akkad DA, Arning L, et al. Interferon-beta affects mitochondrial activity in CD4+ lymphocytes: Implications for mechanism of action in multiple sclerosis. Multiple Sclerosis. 2015;21(10):1262-1270. DOI: 10.1074/jbmc.271.22.13184

[66] Porporato PE, Filigheddu N, Pedro JMB, Kroemer G, Galluzzi L. Mitochondrial metabolism and cancer. Cell Research; 28(3):265-280. DOI: 10.1047/jbrc.271.22.13814

[67] Bajwa G, DeBearderini RJ, Shao B, Hall B, Farrar JD, Gill MA. Cutting edge: Critical role of glycolysis in human plasmacytoid dendritic cell antiviral responses. Journal of Immunology. 2016;196(5):2004-2009. DOI: 10.4049/jimmunol.1501557

[68] Ganeshan K, Chawla A. Metabolic regulation of immune responses. Annual Review of Immunology. 2014;32:609-634. DOI: 10.1146/annurev-immunol-032713-120236

[69] Hubler MJ, Kennedy AJ. Role of lipids in the metabolism and activation of immune cells. The Journal of Nutritional Biochemistry. 2016;34:1-7. DOI: 10.1016/j.jnutbio.2015.11.002

[70] Thaker SK, Ch'ng J, Christofk HR. Viral hijacking of cellular metabolism. BMC Biology. 2019;17(1):59. DOI: 10.1186/s12915-019-0678-9

[71] York AG, Williams KJ, Argus JP, Zhou QD, Brar G, Vergnes L, et al. Limiting cholesterol biosynthetic flux spontaneously engages type I IFN signaling. Cell. 2015;163(7):1716-1729. DOI: 10.1016/j.cell.2015.11.045

[72] Blanc M, Hsieh WY, Robertson KA, Watterson S, Shui G, Lacaze P, et al. Host defense against viral infection involves interferon mediated down-regulation of sterol biosynthesis. PLoS Biology. 2011;9(3):e1000598. DOI: 10.1371/journal.pbio.1000598

[73] Robertson KA, Hsieh WY, Forster T, Blanc M, Lu H, Crick PJ, et al. An interferon regulated microRNA provides broad cell-intrinsic antiviral immunity through multi-hit host-directed targeting of the sterol pathway. PLoS Biology. 2016;14(3):e1002364. DOI: 10.1371/journal.pbio.1002364

[74] Sukhanova A, Gorin A, Serebriiskii IG, Gabitova L,
Zheng H, Restifo D, et al. Targeting C4-demethylating genes in the cholesterol pathway sensitizes cancer cells to EGF receptor inhibitors via increased EGF receptor degradation. Cancer Discovery. 2013;3(1):96-111. DOI: 10.1158/2159-8290

[75] Gorin A, Gabitova L, Astsaturov I. Regulation of cholesterol biosynthesis and cancer signaling. Current Opinion in Pharmacology. 2012;12(6):710-716. DOI: 10.1016/j.coph.2012.06.011

[76] Civra A, Francese R, Gamba P, Testa G, Cagno V, Poli G, et al. 25-Hydroxycholesterol and 27-hydroxycholesterol inhibit human rotavirus infection by sequestering viral particles into late endosomes. Redox Biology. 2018;19:318-330. DOI: 10.1016/j.redox.2018.09.003

[77] Gold ES, Diercks AH, Podolsky I, Podymogin R, Askovich PS, Treuting PM, et al. 25-Hydroxycholesterol acts as an amplifier of inflammatory signaling. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(29):10666-10671. DOI: 10.1073/pnas.1404271111

[78] Kloudova A, Guengerich FP, Soucek P. The role of oxysterols in human cancer. Trends in Endocrinology and Metabolism. 2017;28(7):485-496. DOI: 10.1016/j.tem.2017.03.002

[79] Baek AE, Yu YA, He S, Wardell SE, Chang CY, Kwon S, et al. The cholesterol metabolite 27 hydroxycholesterol facilitates breast cancer metastasis through its actions on immune cells. Nature Communications. 2017;8(1):864. DOI: 10.1038/s41467-017-00910-z

[80] Raccosta L, Fontana R, Maggioni D, Lanterna C, Villablanca EJ, Paniccia A, et al. The oxysterol-CXCR2 axis plays a key role in the recruitment of tumor-promoting neutrophils. The Journal of Experimental Medicine. 2013;210(9):1711-1728. DOI: 10.1084/jem.20130440

[81] Musella M, Manic G, De Maria R, Vitale I, Sistigu A. Type-I-interferons in infection and cancer: Unanticipated dynamics with therapeutic implications. Oncoimmunology. 2017;6(5):e1314424. DOI: 10.1080/2162402X

[82] Mellor AL, Munn DH. IDO expression by dendritic cells: Tolerance and tryptophan catabolism. Nature Reviews. Immunology. 2004;4(10):762-774. DOI: 10.1038/nri1457

[83] Taylor MW, Feng GS. Relationship between interferon-gamma, indoleamine 2,3-dioxygenase, and tryptophan catabolism. The FASEB Journal. 1991;5(11):2516-2522

[84] Routy JP, Routy B, Graziani GM, Mehraj V. The kynurenine pathway is a double-edged sword in immune-privileged sites and in cancer: Implications for immunotherapy. International Journal of Tryptophan Research. 2016;9:67-77. DOI: 10.4137/IJTR.S38355

[85] Brown RR, Ozaki Y, Datta SP, Borden EC, Sondel PM, Malone DG. Implications of interferon-induced tryptophan catabolism in cancer, autoimmune diseases and AIDS. Advances in Experimental Medicine and Biology. 1991;294:425-435. DOI: 10.1007/978-1-4684-5952-4_39

[86] Hornyák L, Dobos N, Koncz G, Karánya Z, Páll D, Szabó Z, et al. The role of indoleamine-2,3-dioxygenase in cancer development, diagnostics, and therapy. Frontiers in Immunology. 2018;9:151. DOI: 10.3389/fimmu.2018.00151

[87] Rath M, Müller I, Kropf P, Closs EI, Munder M. Metabolism via arginine or nitric oxide synthase: Two competing arginine pathways in macrophages.
[88] Cheng X, Li J, Guo D. SCAP/SREBPs are central players in lipid metabolism and novel metabolic targets in cancer therapy. Current Topics in Medicinal Chemistry. 2018;18(6):484-493. DOI: 10.2174/1568026618666180523104541

[89] Eibinger G, Fauler G, Bernhart E, Frank S, Hammer A, Wintersperger A, et al. On the role of 25-hydroxycholesterol synthesis by glioblastoma cell lines. Implications for chemotactic monocyte recruitment. Experimental Cell Research. 2013;319(12):1828-1838. DOI: 10.1016/j.yexcr.2013.03.025

[90] DeBerardinis RJ, Cheng T. Q’s next: The diverse functions of glutamine in metabolism, cell biology and cancer. Oncogene. 2010;29(3):313-324. DOI: 10.1038/onc.2009.358

[91] Chang CF, Diers AR, Hogg N. Cancer cell metabolism and the modulating effects of nitric oxide. Free Radical Biology & Medicine. 2015;79:324-336. DOI: 10.1016/j.freeradbiomed.2014.11.012