p53 and *c-Myc* in Reprogramming Energy Metabolism in Metastasis

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Abstract

Cancer, a highly morbid and mortal disease, which shows properties of metastasis thereby tumours formation at a distant site has been in the last decade been probed and overwhelmingly researched and has been shown to have two significant emerging hallmarks in the pathogenesis of metastasis which are (a) Reprogramming Energy Metabolism (REM) and (b) Evading Immune Destruction (EID). REM has the ability to reprogram and modify the cellular status whilst EID has the ability to evade the natural killer (NK) cells and the macrophages. Cancer cells get benefited by these features in terms of acquisition of nutrition, uptake of glucose, metabolic interactions with the micro environment, thereby resulting in increased nitrogen demand. In this paper, we have discussed the benefits of these emerging hallmarks for cancer cells to sustain and proliferate inside the body and the role of p53 a tumours suppressor gene and c-Myc an oncogene in the regulation of metastasis. Recognition of the broad applicability of these abstractions will progressively aid in the development of new means to treat human cancer.

Keywords: Cancer cells • Oncogene • p53 • c-Myc • Reprogramming energy metabolism • Evading immune destruction

Introduction

An elevated frame of research suggests that two candid hallmarks which are involved in the pathogenesis of cancer metastasis, are reprogramming energy metabolism (REM) which has the ability to reprogram and modify the cellular status and the other hallmark, in pathogenesis evading immune destruction (EID) which allows the cancer cells to evade the T and B lymphocytes, natural killer cells and macrophages. Because of its capability, these processes are considered as emerging hallmarks [1]. The other characteristics of neoplasia` like acquisition of nutrition, genome instability, leading to the progression of tumours spread including metastasis is also benefitted from REM and EID. The inflammation caused by the innate immune cells which are framed to fight against infections and wounds can accidentally support the ability of metastasis of cancer cells thus establishing the broadly appreciated dual characteristic of inflammation which includes tumours promotion and inflammatory response [2]. Also by defective antigen presentation, immune-inflammatory cells benefit the cancer cells in evading the immune destruction. In this paper, we discuss the role of tumours suppressor gene p53 and oncogene c-Myc and their role in the regulation of cancer metastasis.

Description

Reprogramming Energy Metabolism (REM)

In the progression of cancer the metabolic reprogramming plays a decisive role. When there is altered metabolism, the cells are inhibited by tumours cells, at the expense of elevated glucose uptake thereby causing an increased rate of glycolysis [3-6]. This anomalous character of cancer cells was first observed by Otto Warburg and he stated that cancer cells have the ability to reprogram

their cells even in the presence of oxygen and they limit the energy production by the energy metabolism thus leading to aerobic glycolysis [7]. REM is broadly accepted as a hallmark of cancer mainly by the expression of key regulation pattern in the pathway of glycolysis but, aerobic glycolysis helps help in production of ATP alternative to oxidation of mitochondrial phosphorylation[8].

Signaling network of reprogramming energy metabolism in cancer cells

The network shows the metabolic aspect of cell proliferation which includes the production of lactate, glycolysis and TCA cycle which activate a precursor of the macromolecule, protein or lipids. The activation of p13k by binding to the surface receptor with a growth factor activates the serine/threonine kinases Akt and mTOR pathway and this continuous activation due to mutation occurs in tumours. HIF-1a is a transcription factor which utilizes the glucose carbon. During growth factor stimulation of PI3K/Akt/mTOR pathway the HIF-1a is up regulated as shown in Figure 1 [9]. It gets modified and targets
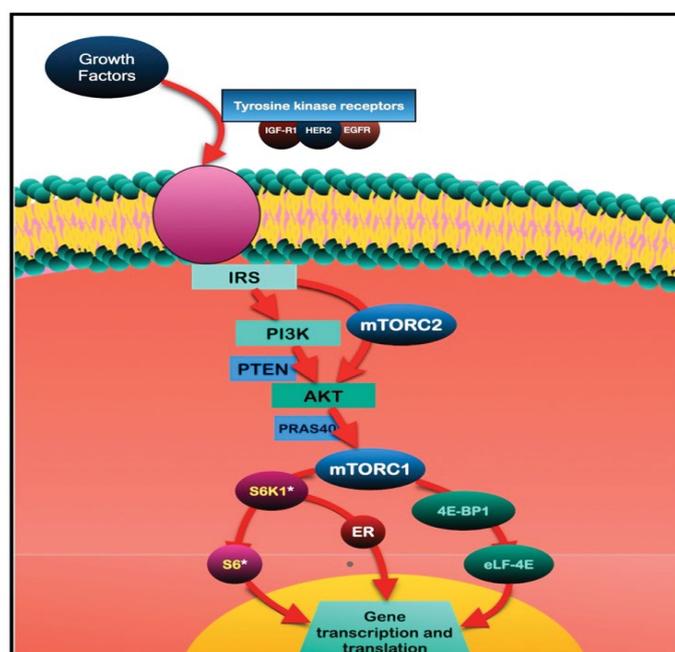
Figure 1. Signaling network of reprogramming energy metabolism in cancer cells.

the complex ligase which includes the tumours suppressor VHL (von Hippel-Lindau). Intermediation of the TCA cycle, ROS, VHL results in impairment of HIF-1a degradation which regulates the activity of transcription by targeting the Glucose Transporter 1[10]. Combined with the metabolism of glucose, it raises the utilization of glucose and production of lactate, inhibiting the pyruvate to acetyl-CoA conversion by pyruvate dehydrogenase. Myc is a transcription factor which increases the metabolic enzymes required for biosynthesis of nucleotide [11].

Benefits by REM

Glucose and amino acids uptake: The biosynthetic demands of the cancer cells combined with the proliferative demands, leaves them in need of the nutrition from the environment. The two main nutrients are glutamine and glucose for their survival and biosynthesis [12,13]. The glucose and glutamine catabolize to manage the carbon intermediate diversities which are utilized for many macromolecule build-ups. Added, glucose and glutamine controlled oxidation allow the cells to seize their nutritive need in the form of NADH and FADH2, which transfers to the electron chain with electrons to boost the generation of ATP [14]. The PI3K/Akt signaling molecules also play a vital role in uptake of glucose other than oncogenic stimulus. Signaling protein such as RAS unregulated the GLUT1 mRNA expression and elevated consumption of glucose (Figure 2) [15]. Thus signaling nodes are activated in the cancer cells aberrantly.

Use of opportunistic modes of nutrient acquisition: After the uptake of glucose, there is a scarcity of nutrition resulting in increased uptake of nutrition from the environment to benefit the cancer cells. Lacking in the delivery of vascular nutrient in emerging tumours is an emergency for hypoxic areas which depresses the biosynthetic reactions [16]. Thus in order to meet the nutritive demand, cancer cells use the opportunity of macro-autophagy to proliferate and survive in unfavorable conditions [17]. This helps the cancer cells to access the accessible areas to utilize their metabolic pathways to sustain. Thus with the process of macro-autophagy, a self-metabolic process it makes the cancer cells withstand the nutrient deprivation [18].

Benefits of mitochondria in cancer metabolism

Dysfunction of mitochondria is one of the most important pathogenetic mechanisms of cancer metabolism which relies on glycolysis. The cancer cells are benefited by the role of mitochondria in the modulation for the progression of cancer acting as energetic centers [19,20]. Many studies proved that a rise in mitochondrial activity and OXPHOS is associated with the aggressiveness of cancer. For the maintenance and function of mitochondria mt-DNA transcription factor a (mtTFA/TFAM) is necessary. Metabolism of mitochondria is related to the behavior of malignancy in oral cancer. The tumours usually prefer the pathway of glycolysis in the presence of oxygen, thus OXPHOS plays a crucial role in the progression of cancer [21].

Use of glycolysis/TCA cycle: Intermediates for biosynthesis and NADPH production, for the generation of acetyl-CoA glucose is preferentially used for the TCA cycle oxidation. The electrons are transferred to the transport chain of electrons *via* NAD+/NADH and FAD/FADH2 for fuelling the production of ATP [22].

Increased demand for nitrogen: For the biosynthesis of the nucleotide in the cancer cell, the Glutamate derived from glutamine serves as a nitrogen donor for the essential amino acid production *via* transamination [23]. Asparagine which is biosynthesized to aspartate similar to glutamate also plays a crucial role in the deprivation of glutamine which utilizes the amine nitrogen to glutamine which results in tumours progression and thereby increase the disease severity [24].

Metabolic interactions with the microenvironment: Cancer cells benefit from the microenvironment for the tumours growth which consists of various strategies including extracellular matrix alterations and interactions of cells. The raised extracellular glucose and glutamine utilization by cancer cells lead to the extracellular lactate accumulation which affects the tumours environment cell types. Elevated lactate level stimulates the acid production of hyaluronic acid and contributes to the tumours invasiveness [25]. With the increase in the VEGF, P13K, HIF alpha.
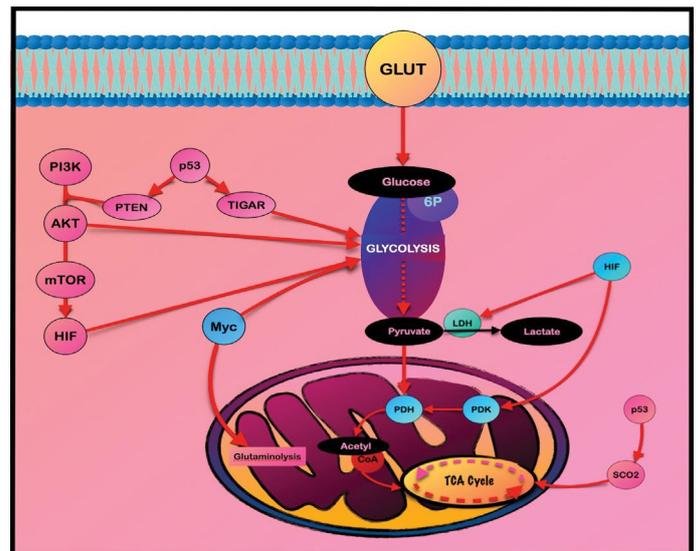

Figure 2. Glucose and amino acids uptake.

Evading immune destruction: The ability of the tumours to manage the detection of arms of the immune system in order to avoid the extent of immunological killing by evading immune destruction. The formation of tumours involved in the role of the immune system for the progression of incipient neoplasia and micro metastases. Tumours striking increases in certain cancers in immunocompromised patients by the role of defective immunological monitoring [26]. The incidence of tumours increases with the deficiency in the CD8+ cytotoxic T lymphocytes (CTLs), CD4+ Th1 helper T cells function [27,28].

Mechanisms of immune suppression in the tumours microenvironment

Tumours uses various mechanisms for evading immune destruction. Tumours down regulates the MHC-1 expression for killing CTL. tumours-associated macrophages and myeloid-derived suppressor cells inhibit the CTL by the PD-1 receptor. CTL is inhibited by other soluble factors in a tumours. HIF-1 induced by hypoxia in tumours produces SDF-1 is a chemokine attracts TAMS and MDSCS to the environment of tumours *via* CXCR4 receptor. Cytokines such as IL-10 along with DCs, inhibits CTLS directly. The myeloid-derived factors that inhibit the activity of CTL which includes TGF-b, ROS and reactive nitrogen intermediates and arginine and nitric oxide synthase are the enzymes for the metabolite function of CTL [29].

Defective antigen presentation

TAA presentation to lymphocytes is dependent critical on the various components of the processing antigen machinery. It mainly has four massive steps are processing of peptide, transportation of peptide, presentation of antigen and assembly of MHC class I [30]. The cancer immunoediting fundamental mechanism allows tumours cells to evade immune surveillance with the down-modulation of machinery antigen processing. MHC class I loss is the usual way to evade immune recognition [31,32].

Immune inflammatory cells

Myeloid cells of tumours normally suppresses the NK and CTL cell activity have been easily identified as MDSCs. Myeloid cells recruitment is beneficial for the developing of tumours by promoting angiogenesis and progression of tumours affording to evade immune destruction [33,34].

p53

p53 is the most often targeted gene for tumours prevention. p53 mutation occur in almost 50% of all tumours. The dysfunctional signaling of p53 *via* various mechanisms added to the mutation of p53. The dysfunction of p53 by the negative regulators such as Pirh2, Cop1, MDM2 and MDM4are generally overexpressed leads to the initiation and progression of tumours [35].

Reprogramming metabolic pathways and regulation by p53

The unusual high glycolysis rate seen in all types of cancers under aerobic conditions is due to the glycolysis in the cytosol which leads to the breakdown of glucose to pyruvate which is a source of energy in the cell process. Oxidative phosphorylation is the alternative for the production ATP is the consequence of oxidizing NADH and FADH2 (Figure 3) [36]. Glycolysis acts faster by the oxidative phosphorylation which produces the ATP production for the bioenergetics maintenance in the demand of energy. It act as a major energy generator [37]. The activity of the cancer cell to divide and grow which needs a lot of energy gains from the glycolysis in the ATP production leads to the proliferation of cells. Hypoxia induces the ROS *via* p53. HIF1 stabilizes the activity of p53 which is associated with the negative regulation of p53 [38].

The p53 mutations in Hemopoietic malignancies are associated with the dysfunction on immune host regulation. In studies proved that inactivation of p53 induces the inflammatory cytokine production IL-1,-6 by macrophages [39]. The inflammatory molecules (IL-6, cyclooxygenase 2) were produced by p53 inactivation. The nitric oxide synthase produced through NF-_B and STAT pathways [40]. p53 inactivation also enhances the production of macrophage migration. The pro-inflammatory cytokine that promotes inflammation through the NF-_B pathway (Figure 4) [41]. The up regulation of programmed death ligand 1 was due to the effects of p53 dysfunction/mutation-induced inflammatory [42]. p53 also monitors vital functions of the immune system, related to cancer [43]. The oncogene induced senescence leads to the promote PDH and improves oxidation of pyruvate as stated in TCA cycle [44]. The function of cytotoxic T-cells by tumours clearance by the immune system and it leads to substantial metabolic reprogramming [45]. By metabolic competition, both cancer and immune cells can compete for ideal nutrients within the microenvironment. This has been shown for cancers in which high glucose uptake was induced by overexpression of hexokinase 2 [46].

c-Myc oncogene

c-Myc controls various aspects of the reprogrammed cells it acts as a master regulator which supports the proteins, nucleic acid and lipids for the proliferation of the cell. Overexpression of c-Myc causes a coordinated alteration in the gene families which leads to the cellular proliferation.

c-Myc regulates reprogramming energy metabolism

- c-Myc regulates the energy metabolism *via* glutamine which supplies the energy for the proliferation and growth of mammalian cells [47].

- Overexpression of cMyc cells to is associated with the catabolism of glutamine during the process of gene expression.

- Mitochondrial metabolism reprogramming is the consequence of c-Myc-dependent glutaminolysis which depends on glutamine
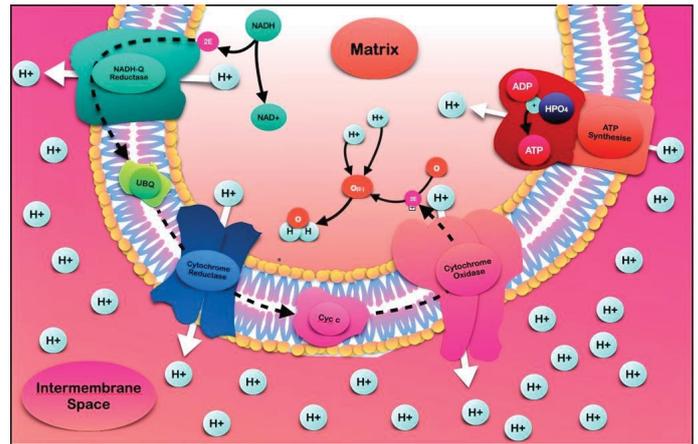
Figure 3. Reprogramming metabolic pathways and regulation by p53.

Figure 4. Immune regulatory molecules and pathways.

catabolism to retain the viability of cells and TCA cycle anaplerosis [48].

- The main mitochondrial function of cancer cells is glutamine catalyzing in order to generate ATP and lactate. Overexpression of c-Myc in transformed cells leads to the glucose to lactate conversion and glutamine oxidation *via* TCA cycle [49].

- In conditions of hypoxia with elevated c-Myc with excess glucose consumption was observed in order to generate glutamine and thereby excrete lactate by utilizing TCA cycle which is used for cell survival.

Thus these are some of the mechanisms that help in the regulation of gene *via* Myc regulation of miRNAs, metabolism of glutamine and ROS homeostasis in the mitochondria [50].

c- myc regulation in evading immune destruction

Myc regulation has a straight role in the maintenance of Myc- driven tumorigenic. Myc is regulated by the expression of CD47 and PD-L1 which is up regulated in the immune surveillance checkpoint [51]. A transcriptional regulatory mechanism of Myc is an amplifier that regulates the expression of genes in multiple mechanisms [52]. Elevated expression of Myc is associated with the proliferation and tumours genesis which induces the expression of CD47 and PD-L1. These promoters involved in the cell growth cause the activation of Myc thereby influencing the cancer immunoediting *via* evading the immune system causing tumours proliferation. This suppresses both the innate and adaptive immune response and favor the growth of tumours [53]. CD47 and PD-L1 thus respond to the tumours environment *via* T cell activation and angiogenesis [54]. The overexpression of Myc in human cancers may be especially ill-protected to an immune checkpoint blockade.

Future

EID and REM have the greatest impact on clinical research. Results have so far been achieved promisingly by first and second line settings and thus further development should be focused on combination therapy in clinical trials with various immunogenic and radiation therapy together with predictive markers which will improve the results further [55]. By targeting the specific oncogene in future it will inhibit the specific pathway which would further allow stratification of patients in clinical trials and thereby yield promising results from novel therapeutic strategies.

Conclusion

Cancer cells undergo various alterations in metabolic pathways for progression of disease *via* deregulation of oncogene and tumours suppression gene. These paper overviews the unity of mitochondria, genes and metabolic enzymes which are involved in cancer cells including p53, c-myc in its
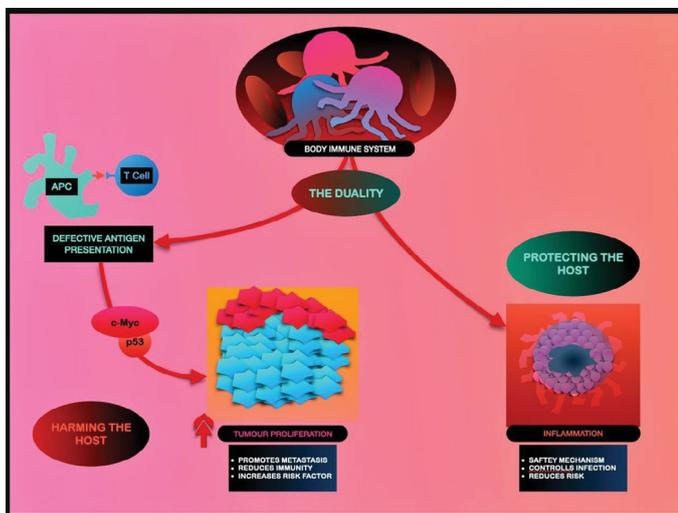
regulation of emerging hallmarks. By targeting the REM and EID of tumours, cancer therapeutic strategies would give us promising results and evolve as novel therapeutic agents to minimize morbidity and mortality in cancer patients.

Acknowledgement

Conflict of Interest

None.

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