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Unveiling the Pathophysiology of Cancer through Mitochondria Mediated Mechanisms

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Abstract

Over the years, glycolysis has been known as the crucial metabolic machinery for both energy production and growth in cancer cells. Cancer is ubiquitously considered as mitochondrial metabolic disease. Mitochondria have been investigated as excellent key player for cellular energy metabolism, free radical generation and apoptosis. Defects in mitochondria have long been contributed for oncogenesis episodes. Likewise, employing central bioenergetic functions, mitochondria have been proven for building blocks in tumor microenvironment, regulated redox and calcium homeostasis, and thereby cause cell death. Therefore, mitochondria have been established as promising targets for the development of novel chemotherapeutic agents. The findings are reviewed for cancer mechanisms through which mitochondria regulate all episodes of cancer development, with a focal point on the therapeutic action of targeting mitochondrial metabolism for chemotherapy.

Keywords: Mitochondria; Cancer; Chemotherapy; Metabolism; Apoptosis

Introduction

A paradigm shift in recent years has given rise to a new classification of cancer and has eradicated two major misconceptions that cancer is entirely cell intrinsic disorder originating due to epigenetic or genetic modifications and the version that aerobic glycolysis is the source of energy for malignant cells [1]. The new definition highlights the importance of the host immune system and its interaction with the growing tumor along with the fundamental influence of mitochondrial metabolism on all steps of oncogenesis [2]. The role of mitochondria in cancer was revisited in the mid-1990s with the revelation that successful apoptosis/programmed cell death is triggered by mitochondrial outer membrane permeabilization (MOMP) and eventually leads to caspase activation and protein substrate cleavage [3]. This discovery further aided the research and culminated with the recognition that most cancer cells display an increased resistance to regulated cell death mostly due to alterations in the mitochondrial control of the process [4]. It is well documented that apoptosis controls differentiation and development, has a vital role in tissue homeostasis, and is deregulated in cancer [5]. Therefore, major efforts were focused on the evolution of new molecules that would eventually target mitochondria as a strategy for chemo- or radio-sensitization.

The mitochondria offer the promise of more efficient discovery and development of novel therapies as well as improved and more individualized disease prevention and treatment [6]. At the moment, the need of the hour is to adapt approaches that investigate multiple components of regulatory networks, which may provide better insights into disease diagnosis, prognosis, and treatment. Thus, it also becomes obligate to study and focus on the mitochondria from a metabolic perspective as some of the metabolites may solely drive oncogenesis and a few may adapt to serve bioenergetic or anabolic functions, hence bestowing malignant cells with substantial metabolic plasticity [7]. Thus, mitochondrial metabolism currently stands out as an optimistic target for the development of novel antineoplastic agents, here; we critically review the cancer mechanisms whereby mitochondria effect malignant transformation, tumor progression and response to treatment, and discuss the potential of targeting mitochondrial metabolism for cancer therapy in future.

Cancer Origin

Hypoxia may potentiate free radical mediated oxidative cell/tissue injury, which could exert both short and long term consequences for health and performance (Zhang and Zhang, 2018). Oxidative

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stress can impair the normal physiologic transmission through multiple pathways converging into mitochondria [8]. Generally, the first line of defense against ROS is taken care by superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and NADPH oxidase by catalyzing their conversion to less reactive species [8]. SOD catalyses the dismutation of superoxide into oxygen and hydrogen peroxide. The H_2O_2 is further taken care by catalase and converted into water and oxygen [9]. On the other hand, the nitric oxide synthase catalyzes L-arginine to citrulline generating NO, which is a potent vasodilator and thus is an integral member of vascular homeostasis [10]. NOS_3 is a homodimer that generates NO and L-citrulline from L-arginine. When exposed to oxidant stress, including peroxynitrite ($ONOO^-$), or deprived of its reducing cofactor or substrate, NOS_3 uncouples to the monomeric form that generates O_2^- rather than [11]. Thus, Uncoupled NOS3 is thought to be a prominent source of ROS. It is also well established that coenzyme Q couple is responsible for producing reactive oxygen species (ROS) in defective mitochondria. ROS can lead to genetic instability due to mutations in the genetic makeup, also a characteristic of the tumor cells [12]. A recent study conducted by Bartesaghi et al., 2013, showed tumorigenic transformation and p53 inactivation in neural progenitor cells following damage to their oxidative phosphorylation unit [13]. Researchers also believe in the notion that almost all kinds of tumor somatic mutations may arise due to insufficient respiration which is backed by fermentation. This gradual transformation in cellular energy production not only leads to genomic instability and somatic mutations but may also account for all of the disease hallmarks described [14]. Additionally, even the hallmark of metastasis is damaged respiration of myeloid cells or their hybrids having the capability of surviving and spreading in the system naturally. Taking into consideration all the hallmarks, the origin of cancer as a mitochondrial metabolic disease is widely accepted by the cancer biologist. Oncogenic paradox is the mechanism by which a broad range of incongruent environmental carcinogens and rare germline mutations might fabricate tumors with telomere activity [15]. It is now central to understand how this mechanism leads to damaged cellular respiration thus, shifting the energy production from oxidative to substrate level phosphorylation. This might also result in several alterations in the tissue morphogenetic fields due to prolonged shift from respiration to fermentation. Major repercussions are observed due to acidification via fermentation leading to destabilization of the tissue internal environment. One of the repercussions is enhanced angiogenesis and then the progression of tumor at a later stage [16]. This tumor will remain as an unhealed wound inside the body and is subjected to some epigenetic modifications [17]. These epigenetic disturbances may lead to genome instability and further contribute to respiratory impairment and tumor progression. Over the time, the nuclear genomic instability in the tumor cells would upset the physiological homeostasis of the body leading to an augmented proliferation in tissue stem cells and their progenitors [18]. In an environment of uncertainty and unpredictability, there may be increased biological chaos which initially originated from chronic injury to cellular inhalation with alteration in immunosuppressive cells activity.

Malignant Transformation: The Role of Mitochondria

Otto H. Warburg in his pioneer work gave the concept of metabolic reprogramming, where cancer cells convert glucose into lactate even in the presence of high oxygen tension. This “Warburg effect” is a recognized hallmark of cancer [19]. Mitochondria carry out many functions beyond energy generation, including the production of reactive oxygen species (ROS), regulation of cell signaling and death, and biosynthetic metabolism. Moreover, mitochondrial dysfunction, ranging from very low activity to hyperactivation of this organelle, has been illustrated in quite a few cancer types. Thus, it is clear so far that the biology of mitochondria in cancer is fundamental to our understanding of cancer physiology and patho-physiology, as several conventional cancer hallmarks result in an altered mitochondrial function. Malignant transformation of a cell requires the accretion of several genetic changes during the process of tumor initiation and progression [20]. Precisely, it is the change from a pre-neoplastic cell into one that expresses malignant phenotype: in this environment, the proliferation is uncontrolled and the apoptosis control has failed. It involves genetic modification of the parent cells. Several studies have demonstrated that mutations in mitochondrial DNA might also affect various electron transport chain components via increased ROS generation. In order to understand the underlying biology of cancer, it is vital to identify and study these genetic and correlated alterations during cancer development. Mitochondria may lead to malignant transformation by at least three key mechanisms: (I) mitochondrial ROS support the accretion of potentially oncogenic DNA defects and the commencement of oncogenic signaling pathways; (II) the abnormal accumulation of specific mitochondrial metabolites, including fumarate, succinate, and 2-hydroxyglutarate (2-HG), has significant transforming effects; (III) functional deficits in mitochondrial permeability transition (MPT) are generally required for the endurance of neo-formed malignant precursors.

In order to curb these lethal consequences, mitochondrial fitness must be maintained internally and this is generally done by mitophagy, which removes damaged mitochondria from the system and also quenches the production of ROS [21]. Different groups have shown that the knockout of genes that are essential for autophagy such as Atg5 or Atg7 might promote oncogenesis [22]. Another parallel study supported the concept that silencing of Fanconi anemia (FA) genes in tumors may orchestrate proper mitophagy which result in onco-supression due to proper elimination of damaged mitochondria from the system [23]. Failure of this sequence results in overproduction of ROS and proliferation of tumor. It is now evident that an expression of gene may greatly influence by its own structure and among various structural aspects, the mutations in a gene may play major role. Hence, it is obvious for these processes that they are governed by various molecules i.e. initiating from genes to ending at its products. The gene regulation by way of its expression is an important integral phenomenon in the maintenance of normal physiology under a sustained/ continuous exposure to a given or a new environment.

In addition to supporting mutagenesis, ROS may also upset many signalling cascades, like mitogen-activated protein kinase (MAPK) [24], hypoxia inducible factor 1-α (HIF-1α) [25], and epidermal growth factor receptor (EGFR) signaling [26]. In addition to the above mentioned pathways, Ras and Erk signaling are also activated following severe defects of the mitochondrial respiratory function due to mtDNA depletion and ROS overproduction [27]. It was also recently shown that ROS produced from mitochondria may lead to lung cancer growth via MAPK/ERK cascade activation. Cancer cells proliferation was enhanced to due activation of transcription specific factors like the nuclear factor kappa B (NF-κB) and associated factors.

Alternatively, ROS levels can be augmented to a cytotoxic level in breast cancer models by using inhibitors of GSH and Trx pathways.

Inhibiting the antioxidant enzyme, glutathione peroxidase, through inhibition of fumarate in the Krebs cycle, elevated ROS and tumour cell growth [28]. As a result of the paradoxical role of ROS in cancer cells, both pro- and antioxidant approaches have shown tumor enhancing and tumor regressing effects.

Selective Targeting of Mitochondria

As an endosymbiotic organelle, the mitochondrion has retained a remnant of its bacterial ancestor genome, the mitochondrial DNA (mtDNA) [29]. The majority of proteins are encoded in the nuclear genome, synthesized by cytoplasmic ribosomes and transported into mitochondria. The past decade has discovered new roles for the mitochondrial translation machinery and in apoptotic signaling and the regulation of cell division. As a result, therapeutic advancements targeting mitochondrial protein synthesis have come into sight as new interventions to combat many types of malignancies.

The anatomy of budding tumors has been exploited by inducible gene therapy strategy. As a consequence of reasonably poor vascularization, the center of most tumors is usually a nutrient-starved and hypoxic environment. Promoters stimulated by hypoxia or nutrient deficiency have been utilized to drive expression of tumoricidal genes. Over the years, different groups have also shown that modifications in the mtDNA might change the course of treatment and may give rise to chemotherapy resistance [30]. In a parallel study it was reported that mutations in the NADH dehydrogenase-subunit-4 (MT-ND4) lead to acquired chemo-resistance during paclitaxel carboplatin treatment [31]. In the era of development many pioneering technologies have been developed and successfully implemented on humans. The technology for using genes to provide a desired treatment has become an effective strategy due to advances in research. In a similar approach, spindle transfer, a promising strategy aimed at promoting clinical germline gene therapy against inherited mitochondrial disorders [32]. It is also possible to restore the abnormal mitochondrial functions by editing the altered mtDNA sequence and likely cure the tumor. Also, stimulating a programmed mitophagy may also help in quashing the deleterious mtDNA variants [33]. Regulatory systems have been developed to control or specifically block the replication of the mutant mtDNA by synthetic peptides, thereby allowing the selective breeding of the wild-type DNA [34].

Somatic mutations in mitochondrial genome are frequent and regularly reported in diverse types of cancer. Functional consequences of these mutations are not completely understood. Generally, these mutations are point mutations, insertion–deletions, or large scale deletions dispersed in protein coding genes. These are reflection of poor DNA repair mechanism and direct exposure to ROS. In a recent attempt to correct mtDNA mutations, researchers are taking help of DNA repair enzymes and by targeting this machinery to mitochondria are bestowing favourable results. In a related study, an expression vector containing the gene for the DNA repair enzyme, human 8-oxoguanine DNA glycosylase/apurinic lyase (hOGG1) was transfected *in vitro* which resulted in reduced mtDNA damage commenced by free fatty acids [35]. Furthermore, overexpression of hOGG1 gene in mitochondria may also attenuate breast cancer progression *in vivo* studies performed recently [36]. These techniques and strategies might also provide protection against deleterious effects of ROS and protect normal cells during cancer chemotherapy or preventing deleterious phenotypes associated with the physiological process of aging [37]. At present, hOGG1 has been the most commonly selected enzyme to boost tDNA repair, alternative approaches may also target various other proteins to mitochondria, such as endonuclease III (EndoIII) and endonuclease VIII (EndoVIII). Researchers are also targeting other restriction endonucleases like SmaI and PstI, which have been used as a powerful tool for correcting mitochondrial dysfunction [38,39], resulting in the eradication of the mutant mtDNA and restitution of usual mitochondrial functionality. Finally, the targeting of ROS generation system might represent an efficient therapeutic approach for the treatment of subjects with intestinal cancer.

Conclusion

Mitochondria are vital organelles for energy generation but also play central roles in carcinogenesis, cancer progression, and metastasis aiding altered energy metabolism in cancer cells. Mitochondrial metabolism is also associated with other mitochondrial cascades such as redox signalling, mitophagy, and mitochondrial biogenesis. These pathways cross-talk and seem to play synergistic roles in cancer. Targeting mitochondrial pathways and signalling cascades individually or epistatically might be considered as future cancer therapy. In recent times, cancer experts are focusing on the metabolic reprogramming of cancer cells to use altered metabolites for therapeutic approach. Moreover, mutations of mitochondrial DNA have been considered as promising tumor biomarkers, while the well regulated interplay between nuclear and mitochondrial genomes sheds new light on the molecular and functional mechanisms underlying the onset and progression of complex diseases, such as cancer.

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