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Review Article

Looking to the metabolic landscapes for prostate health monitoring

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ABSTRACT

Abnormal metabolism is a widely accepted biological signature of prostatic diseases, including prostate cancer and benign prostate hyperplasia. Recently accumulated epidemiological and experimental evidence illustrate that the metabolic syndrome, impaired mitochondrial function, and prostatic pathological conditions intersect. The perturbed metabolism and metabolic mediates influence key signaling pathways in various prostatic pathological conditions. This short review article aids to highlight recent findings on metabolism, metabolic mechanisms, and mitochondrial metabolism as a possible route to finding a cure for prostate diseases, including prostate cancer. The effort to better understand the role that mitochondria plays in cancer metabolism and the biological meaning of defective and/or deleted mitochondrial DNA in cancer will also be discussed.

1. Metabolism, metabolic syndrome, and prostate health

The definition of metabolism is the set of life-sustaining chemical transformations within the cells of living organisms.[1] Metabolic syndrome (MetS) is a common and complex cluster of clinical conditions. It includes abdominal obesity, hypertension, hypertriglyceridemia, hyperglycemia, and low high-density lipoprotein cholesterol. MetS is a risk factor of cardiovascular and metabolic complications; which is associated with several medical conditions such as type 2 diabetes, cardiovascular diseases, and nonalcoholic fatty liver disease.[1–3]

A series of epidemiological evidence suggests that MetS is also associated with various prostatic diseases; which include hypogonadism, erectile dysfunction, infertility, and bladder and prostate dysfunctions, such as benign prostate hyperplasia (BPH) and lower urinary tract symptoms (LUTS). Recent studies demonstrated that MetS is associated with an enlarged prostate size, suggesting metabolic reprogramming in prostatic diseases.[4] Moreover, MetS is associated with prostatic inflammation.[5] Epidemiological studies showed that LUTS and BPH are associated with obesity and prostatic inflammation. Recently, a series of urinary chemokines associated with obesity and prostatic inflammation were measured in BPH/LUTS patients and healthy controls. The levels of these cytokines (e.g., CXCL-8, CXCL-10, and sIL-1ra) were increased in BPH/LUTS patients, suggesting a significant association between obesity, inflammation, and BPH/LUTS.[6]

MetS has also been proposed to be associated with prostate cancer (PC), which is the sixth leading cause of cancer death among the male population. Consistent with accumulating epidemiological evidence, MetS plays a role in PC. Abnormal metabolism in MetS is linked with the alteration of signaling networks (e.g., insulin and insulin-like growth factor-I), and the modification of sex steroid pathways (e.g., testosterone and estradiol).[7,8] Consistent with findings from BPH/LUTS, MetS-related cytokines, growth factors, leptin, and adiponectin are increased significantly in patients with PC.[9,10]

2. Cancer metabolism

Altered metabolism has been widely accepted as a cancer hallmark.[11] The Nobel Laureate, Otto H. Warburg, who demonstrated that cancer cells have an altered energy metabolism, first postulated the Warburg effect. He found a fundamental difference in the metabolism between normal and cancer cells is the ratio of glycolysis to respiration.[12,13] Instead of using an oxidative breakdown of pyruvate in mitochondria, cancer cells convert glucose into

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lactate and primarily use glycolysis to synthesize ATP, even in the presence of high oxygen tension. Thus, aerobic glycolysis can produce ATP at a high rate, which is an aggressive metabolic phenotype and is the dominant metabolism in cancer cells. The Warburg effect has been found in a series of cancer cells that exhibit a much higher rate of glucose uptake, consumption, and lactate production; leading to a higher volume of amino acid and fatty-acid synthesis that is needed for rapid cell proliferation.

More recently, the Warburg effect has been more defined in the context of metabolic reprogramming, which is specifically observed in cancer cells, not normal cells. Oncogenic signals can be triggered by activation of oncogenes (e.g., BRAF mutant V600E and c-Myc), loss of tumor suppressors (e.g., p53), and/or activation of metabolic signaling pathways (e.g., mTORC1).[6,8,14–18] These can all contribute to metabolic rewiring or reprogramming. BRAF V600E increases 3-hydroxy-3-methylglutaryl-CoA lyase, intracellular levels of acetoacetate, and MEK1 phosphorylation, suggesting that there is crosstalk between metabolic pathways and cell-signaling networks.[14,19]

In glioma and acute myeloid leukemia, cancer associated mutants of isocitrate dehydrogenases 1 and 2 produce an oncometabolite, 2-hydroxyglutamate, and inhibit DNA repair process.[20–22] As MYC is a key driver of cell-cycle entry and progression, the MYC-dependent cell growth is linked to impairment of mitochondrial function through the mitochondrial serine hydroxymethyltransferase. A previous comprehensive profile of mitochondrial targets of MYC revealed approximately 400 mitochondrial genes,[23] the functions of which are associated with mitochondrial transcription, translation, protein import, and complex assembly. It has become evident that the impairment of mitochondrial biogenesis by MYC overexpression leads to the Warburg effect in cancer through the stimulation of oxidative metabolism, fatty acid metabolism, and production of acetyl-CoA as a source of energy and chemical intermediates for biosynthesis.[24] MYC overexpression also increases the expression of glucose transporter 1, pyruvate kinase muscle isozyme M2 (PKM2) and lactate dehydrogenase, and cell division cycle 25A (CDC25A), which are all important glycolytic genes. In addition, mutant of p53, a well-known tumor suppressor, also stimulates the Warburg effect through the RhoA/ROCK/ glucose transporter 1 signaling pathway that controls cell metabolism.[25]

Lastly, in the epidermal growth factor receptor-promoted tumorigenesis we can observe another example suggesting that altered metabolism influences cell signaling networks. epidermal growth factor receptor activates the c-Src-mediated CDC25A phosphorylation, which allows the interaction of CDC25A with PKM2. Upon binding, CDC25A can dephosphorylate PKM2, leading to β-catenin activation.[26]

Being a double-edged regulator of cancer cell metabolism, 5′ AMP-activated protein kinase (AMPK) plays a role in tumor initiation, progression, metastasis, etc. Although AMPK is a well-known tumor suppressor and negative modulator of cancer formation and growth, recent findings demonstrate that AMPK activation enhances tumor growth in a specific cell environment.[27] However, the underlying mechanism that decides the fate of AMPK still remains unclear.

3. Mitochondria and mitochondrial DNA in cancer metabolism

Mitochondria, as a main source of energy and biosynthesis, play a decisive role in cancer metabolism.[28] Mitochondria is the location of ATP production and its intermediates; contributing to the reprogramming of bioenergetics metabolism by regulating the biosynthesis of amino acids, lipids, nucleic acids, etc.[29,30] Mitochondria have a well-recognized role in the activation of signaling pathways and in the mediation of cell apoptosis, proliferation, differentiation, stemness, tumorigenesis, etc.[31,32] Given that the mitochondria senses stimuli and makes cells respond accordingly to microenvironment changes, mitochondrial metabolism has been considered as a potential cancer therapeutic strategy.

Mitochondria have their own genome containing approximately 16,000+ base pairs of double-stranded and circular DNA molecules, mitochondrial DNA (mtDNA). MtDNA encodes for polypeptides of the mitochondrial respiratory chain, transfer RNAs, and ribosomal RNAs. In cancer cells, modification, reduction, or depletion of mtDNA has been identified; which is often linked to those in the nuclear genome and biological outcomes, such as chemo-resistance and tumorigenesis.[33] The relevance of metabolic reprogramming in conferring drug resistance could be explained through the biological effects of mtDNA defects.[34]

MtDNA depletion or defects have been observed in various key cancer types, such as lung, gastric, colorectal, prostate, and breast cancer. At the molecular level, defected mtDNA in cancer cells results in increased cell invasion, metastasis, epithelial-to-mesenchymal transition, and stemness.[35,36] Furthermore, several studies in different cancer cell types showed that mtDNA depletion leads to the activation of key antiapoptotic signaling pathways, which allow cancer cells to be more resistant to therapies.[25,37,38]

The role of mitochondrial dysfunction in promoting chemoresistance has been suggested in previous literature.[37] MtDNA depletion made human myelogenous leukemia cells to be resistant to TNF-induced cell apoptosis.[37,39] The mtDNA-defected hepatocarcinoma cells became resistant to the reactive oxygen species-inducing cell apoptosis by increasing expression of antioxidant enzymes, such as glutathione peroxidase and manganese superoxide dismutase.[40] Transfer of mtDNA from aggressive breast cancer phenotypes was able to provide metastatic characteristics in NIH3T3 cells. Cisplatin-sensitive ovarian cancer cells showed an increased mitochondrial membrane potential and higher basal oxygen consumption compared to its cisplatin-resistant derivative. Depletion of mtDNA in cisplatin-sensitive ovarian cancer cells resulted in resistance to cisplatin.[41,42] When mtDNA was depleted, androgen-dependent LNCaP prostate cancer cells became resistant to paclitaxel, a chemotherapy agent.[43,44] The mtDNA depleted PC-3 prostate cancer cells became more invasive, cancer-stem like, and resistant to chemotherapy as well as radiotherapy.

Recently, mitochondrial RNA has been shown to play a role in cancer progression and chemo-resistance through the horizontal mitochondrial transfer mechanism; which is the cell-to-cell transfer of mitochondria through intercellular bridges of tube-like structures, called tunneling nanotubes.[45–50] This horizontal mitochondrial transfer was observed not only between cancer cells but also between endothelial cells and cancer cells, contributing to chemoresistance to doxorubicin treatment.[41,51]

There are several reports on the alternative delivery mechanisms of the horizontal transfer of mtDNA, one of which is proposed to be through exosomes, a type of membrane vesicle that originates from the endosomal and plasma membrane. Glioblastoma and astrocytes cells released exosomes containing mtDNA.[52,53] MtDNA-containing exosomes were found in the serum and tumors obtained from prostate cancer patients. These recent findings collectively suggest that targeting mitochondria in cancer cells may offer a novel strategy for cancer treatment.

4. Concluding remarks and perspectives

Collectively, accumulating evidence based on research in the laboratory and clinical settings implicates that metabolic rewiring through mitochondrial bioenergetics, biosynthesis and crosstalk with activated signaling pathways are critical for cancer initiation, progression, metastasis, and chemo-resistance. However, there is

still a missing piece of the puzzle in the field. We still have to continue emerging studies to assess how to reverse the reprogrammed metabolism in cancer, how to deal with the perturbed heterogeneous metabolism in patients, and when the best timing is to add antimetabolic approaches to get maximized and synergistic benefits during chemotherapy for patients.

Conflicts of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Authors' contributions

WK and JK designed the study, led obtaining funding, and overviewed the literature analysis and drafting the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All the data supporting the findings here are contained within the manuscript.

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