Critical Reviews in Oncology/Hematology 117 (2017) 67–72

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

Mitochondrial dysfunctions in bladder cancer: Exploring their role as disease markers and potential therapeutic targets

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Contents

ARTICLE INFO

Article history:
Received 27 March 2017
Accepted 2 July 2017

Keywords:
Bladder cancer
Molecular markers
mtDNA mutations
mtDNA copy number
Lon protease
Mitofusin-2
TFAM

ABSTRACT

Bladder cancer (BC) is a major cause of mortality worldwide as it currently lacks fully reliable markers of disease outcome and effective molecular targets for therapy. Mitochondria play a key role in cell metabolism but the role of mitochondrial dysfunctions in BC has been scarcely investigated. In this review, we explored current evidence for the potential role of mitochondrial DNA (mtDNA) alterations (point mutations and copy number) as disease markers in BC. Some germline mtDNA mutations detectable in blood could represent a non-invasive tool to predict the risk of developing BC. MtDNA copy number and tumor specific mtDNA mutations and RNAs showed encouraging results as novel molecular markers for early detection of BC in body fluids. Moreover, mitochondrial proteins Lon protease, Mitofusin-2, and TFAM may have prognostic/predictive value and may represent potential therapeutic targets. A deeper understanding of mitochondrial dysfunctions in BC could therefore provide novel opportunities for targeted therapeutic strategies.

1. Introduction

Reprogramming of energy metabolism has emerged as a new hallmark of many cancers (Potter et al., 2016). The best characterized metabolic phenotype of tumor cells is the Warburg effect. Otto Warburg observed that cancer cells actively metabolize glucose and produce an excess of lactate even in presence of oxygen; accordingly, he postulated that malignant cells increased glycolytic rate to compensate defects in the mitochondrial respiratory chain (Warburg, 1956). Such increased glycolytic rate, called reverse Pasteur effect or aerobic glycolysis, seems to play an important role in supporting the large-scale biosynthetic programs that are required

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http://dx.doi.org/10.1016/j.critrevonc.2017.07.001
1040-8428/

for active cell proliferation but is not a consistent feature in all cancers. Recent research (Bonuccelli et al., 2010) demonstrates a broad spectrum of bioenergetic phenotypes displayed by cancer both *in vivo* and *in vitro*, with many cancer types displaying a surprising degree of mitochondrial activity.

Mitochondria are essential organelles in all eukaryotic cells. They provide ATP for a multitude of cellular processes by the oxidative phosphorylation system, thus functioning as the fulcrum of metabolic pathways, primary sources of reactive oxygen species (ROS), buffers of intracellular calcium, and regulators of apoptosis as well as of signal transduction (Murphy, 2009; Brookes et al., 2004; Cadenas and Davies, 2000). Mitochondria contain mitochondrial DNA (mtDNA), a small DNA of approximately 16569 bp (Attardi, 1985), which codes for 2 rRNAs (12S and 16S), 22 tRNAs, and 13 proteins subunits of four of the five complexes of the respiratory chain, namely seven subunits of NADH dehydrogenase (complex I), one of cytochrome c reductase (complex III), three of cytochrome c oxidase, (complex IV) and two of ATP synthase (complex V). Therefore, the majority of mitochondrial proteins (about 1500) are coded by nuclear DNA, transcribed and translated in the cytoplasm and then transported in the mitochondria. The non-coding (D-loop) region of mtDNA is about 1.1 kbp long and is the most variable part of the genome; it contains regulatory signals for replication and transcription (Chen and Butow, 2005).

MtDNA is maternally inherited and is present in a large number of copies per cell (about 2–4000, polyploidy) (Lightowlers et al., 1997; Johns, 2003); it may be all of the same type (homoplasmy), wild-type or mutant, or different genotypes may coexist (heteroplasmy) in cells or tissues.

MtDNA it is more susceptible to ROS-induced mutations (point mutations or deletions) than nuclear DNA since it is located close to mitochondrial respiratory chain, the major source of ROS in the cell (DiMauro et al., 2002). Not all mtDNA mutations, however, are deleterious to cells; some may result in dangerous events, others may be simple neutral polymorphisms with no important functional consequences. Moreover, it is important to know the percentage of mutant mtDNA molecules (threshold) that can lead to a dysfunction of the mitochondrial respiratory apparatus (Rossignol et al., 2003; Musicco et al., 2014).

In cancer mitochondrial dysfunctions may involve alterations of mtDNA (deletions, point mutations and copy number variation) (Cruz-Bermúdez et al., 2017) and also mutations in nuclear DNA (Bardella et al., 2011; Picaud et al., 2011; Ward et al., 2010).

Recent research pointed out that in bladder cancer (BC), the most common malignancy of the urinary tract, the main energy source to sustain uncontrolled cells growth and proliferation is an aerobic glycolysis-dependent metabolism; in fact, BC cells display increased expression of genes coding for glicolysis, for the pentose phosphate pathway, and for fatty-acid synthesis (Massari et al., 2016) suggesting a deficit of mitochondrial activity in this cancer. In spite of increasing evidence for such metabolic abnormalities in BC development and progression, little attention has been paid to the potential role of mitochondrial dysfunctions in this cancer.

This review therefore aimed to explore current evidence for the potential role of mitochondrial dysfunctions, including alterations of mtDNA (point mutations and copy number) and altered expression of some mitochondrial proteins, as diagnostic, prognostic, predictive markers as well as potential therapeutic targets in BC.

2. MtDNA mutations in BC

MtDNA mutations may be induced by several mechanisms, including (1) increased ROS and oxidative damage, (2) defects in nuclear genes, like polγ and P53, involved in mtDNA replication and stability, (3) altered nucleotide biosynthesis or transport, (4) exogenous sources (UV, ionizing radiation, ozone, pesticides, metal, tobacco smoking, *etc.*) (DeBalsi et al., 2017).

MtDNA mutations could play different roles in cancer (Brandon et al., 2006); they could arise either in the female germ line (germline mutations), thus predispose to cancer, or in the affected tissues, thus represent tumor-specific somatic mutations.

2.1. Germline mutations

Recent studies attempted to identify germline mtDNA mutations that could predispose to BC since they have the potential to represent markers for predicting the risk of developing BC. The analysis of mtDNA from blood, neoplastic tissue, and non-neoplastic tissue adjacent to cancer of 26 patients with BC, and DNA from blood of 504 healthy controls of different ethnicities, demonstrated that the C16069T mtDNA variation was associated with BC (Shakhssalim et al., 2013). Moreover, the analysis of 926 BC patients and 926 healthy-controls matched on age, gender, and ethnicity revealed two mtDNA polymorphisms associated with BC, namely T10464C and A4918G variations. Analysis of the joint effect of low mtDNA content and polymorphisms A4918G revealed a 2.5 fold increase in the risk of harboring BC (Williams et al., 2015). These few studies however reported mere associations and lacked functional proof that certain mitochondrial variants, many of which are common polymorphisms, may actually predispose to BC.

Functional studies with cybrid cells, *i.e.* cells in which different mtDNA mutations may be investigated independently from the nuclear background, will help to clarify the role of these variants. Moreover, since these polymorphisms are maternally linearly inherited, it would be very important to monitor the daughters of patients to verify whether such risk is increased in the generations to which the mutation is passed on.

2.2. Tumor-specific somatic mutations

Tumor-specific somatic mtDNA mutations may participate in the tumor development or/and progression process and may be classified as tumorigenic or adaptive. Tumorigenic mutations may be pathogenic mutations that alter the mitochondrial respiratory chain and increase mitochondrial ROS production. ROS may diffuse in the nucleus and induce mutations in genes which regulate cell replication, in proto-oncogenes and in tumor-suppressor genes. Adaptive mutations are instead mild mtDNA mutations that may allow an adaptation of cancer to the adverse environment condition, like hypoxia, conferring cancer the ability to metastasize (Brandon et al., 2006). It is worth mentioning that some mtDNA mutations may be only innocent passengers in cancer, thus not contributing to the tumorigenic or metastatic potential, whereas others may contribute as drivers or as complementary gene mutations according to the multiple-hit model (van Gisbergen et al., 2015).

As for BC, mtDNA mutations have been described in neoplastic tissue (Fliss et al., 2000) in the form of point mutations, single-base deletions, and insertions in the non-coding D-loop region or in the coding regions for protein components of oxidative phosphorylation. The most frequent mutations in D-loop region were seen in the poly(C) mononucleotide repeat located at positions 303–309 (Parrella et al., 2003; Wada et al., 2006). Moreover, the analysis of mitochondrial genes ATPase6, cytochrome B, ND1, and D310 region in 38 BCs and 21 microdissected normal bladder tissue samples indicated that G8697A, G14905A, C15452A, and A15607G polymorphisms were significantly more frequent in BC patients than in controls. Also the set of mtDNA polymorphisms A3480G, T4216C, T14798C, and G9055A was significantly more frequent in patients than in controls, suggesting its relevance in detecting BC. However,