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MINI-REVIEW

Mitochondria in relation to cancer metastasis: introduction to a mini-review series

Peter L. Pedersen

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Abstract This introductory article and those that follow focus on the roles that mitochondria may have in cancer metastasis (spreading) that all too frequently leads to death of cancer patients. The history of cancer dates back in time to several thousand years BC and continues to this day. Although billions of dollars have been invested, numerous cancer researchers/scientists and oncologist located at universities, hospitals, cancer centers, commercial entities (companies), and government agencies have been unable to discover "magic bullets" to quickly silence most cancers. That is, agents that are effective not only in eradicating the primary tumor at its site of origin, but eradicating also distant tumors that have arisen therefrom via metastatic cells. Fortunately, in recent years some researchers have obtained evidence that the mitochondria of cancer cells are involved not only in providing in part the necessary energy (ATP) to fuel their growth, but hold the secrets to their immortality, and propensity to metastasize (spread) from their original site of origin to other body locations. This introductory article, as well as those that follow, focus on the possible roles of mitochondria in cancer metastasis as well as strategies to arrest cancer metastasis based on this knowledge. Ideally, for a patient to become "cancer free" the anticancer agent/agents used must **1)** eradicate the primary tumor at its site of origin, **2)** eradicate any tumors at other body locations that have arisen via metastasis, and **3)** eradicate any tumor cells that remain in the blood, i.e., circulating tumor cells. One such agent that holds promise for doing all three is the small molecule 3-bromopyruvate (3BP) discovered in the author's laboratory by Dr. Young H. Ko near the turn of the century to be a potent anti-cancer agent [Ko et al.(2001) Can Lett 173:83–91].

Keywords Mitochondria · Cancer · Warburg effect · Metastasis · 3-bromopyruvate · Hexokinase 2

Introduction

This final volume (JOBB 44–6) of the ***Journal of Bioenergetics and Biomembranes*** for the Year 2012 includes in part a brief mini-review series organized by the author. Its focus is on the role(s) mitochondria play in cancer metastasis. Considering that about 1 in 2 men and 1 in 3 women are still predicted to acquire cancer (Hayat et al. 2007), many of whom will die, and that a major reason for their deaths will be its spreading (metastasis) from the site of origin to other sites throughout the body, then the cancer related articles included in this JOBB volume should be of interest to many readers. This is because most of us know someone who has died of cancer, is fighting cancer, or has just discovered they have cancer, and also because we fear that we may become a cancer victim, or already be in the initial stages. Unfortunately for us and fortunately for cancer, it can be asymptomatic for some time. As noted by the World Health Organization Fact Sheet N°297, February 2012, cancer is the leading cause of death worldwide, accounting for 7.6 million deaths (about 13 % of all deaths in 2008).

Most tumors causing these deaths likely exhibit a "Warburg" phenotype, i.e., an elevated conversion of the sugar glucose to lactic acid, even in the presence of oxygen (Warburg 1930). The major contributor to the

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P. L. Pedersen (✉)
Department of Biological Chemistry and Oncology, Sidney Kimmel Cancer Center, and Center for Metabolism and Obesity Research, School of Medicine, Johns Hopkins University,
735 North Wolfe Street,
Baltimore, MD 21205, USA
e-mail: ppederse@jhmi.edu

"Warburg effect" is mitochondrial bound hexokinase as discovered many years ago by a Peruvian scientist, Ernesto Bustamate, then a graduate student in the author's laboratory (Bustamante and Pedersen 1977, 1981). The experiments described in the two papers clearly showed the major role played by mitochondrial bound hexokinase in the "Warburg effect". In the first paper, results were described that showed that the cancer cells (hepatoma cells) under study when grown in the presence of glucose exhibited a strong "Warburg" phenotype but when grown in the presence of galactose exhibited essentially no Warburg effect. The major difference in the two metabolic pathways (i.e., for glucose vs galactose) is that glucose requires mitochondrial bound hexokinase to "kick off" the first step whereas galactose requires galactokinase that is not bound to the mitochondria. This strongly suggested mitochondrial bound hexokinase as a key player in the "Warburg" effect. This was further confirmed via experiments described in the second paper (Bustamante and Pedersen 1981) as it was shown that addition of tumor mitochondria containing bound hexokinase to liver cytosol increased its glycolytic rate to the level of the tumor cytoplasm. In a later study (Nakashima et al. 1988) from the author's laboratory the mitochondrial bound hexokinase was identified as hexokinase 2 (Hk-2).

Significantly, later work in other laboratories would show that Hk-2 wears at least two hats at its mitochondrial bound outer membrane site as it participates also in cell immortalization, i.e., suppression of cell death (Pastorino and Hoek 2003; Robey and Hay 2005). Very significantly, mitochondrial bound Hk-2 is also the underlying biochemical basis of Positron Emission Tomography (PET) used early on at the NIH in human patients (Di Chiro et al. 1982) only 5 years after the above noted Bustamante and Pedersen report. PET is now used throughout the world to detect and monitor cancer progression (growth and metastasis) and its response to therapy including in Lima, Peru, the home of Bustamante and Tulsa, Oklahoma, the original home of the author.

Cancer metastasis: what is it?

There are several definitions all of which are related. Two are noted below.

1. A cancer that has spread to an organ or tissue from a primary cancer located elsewhere in the body.
2. The process by which a cancer spreads from the place it first arose as a primary tumor to distant locations in the body.

Examples: When breast cancer spreads through the blood or lymph systems to other parts of the body, e.g., lungs, bones, or liver, it has metastasized, and when prostate cancer spreads to the lymph nodes or bones it has metastasized.

Synopsis of articles constituting this minireview series

In addition to the editor's Introduction, i.e. this article, this mini-review series commences also with an additional introductory article by Emily Chen (Chen 2012) who points out that more than 90 % of mortality in cancer patients is attributed to metastasis. In addition, Dr. Chen states early on in her article why cancer metastasis is a very difficult disease to treat when she states "Although surgical resection and adjuvant therapy can cure well-confined primary tumors, metastatic disease is largely incurable because disseminated tumor cells spread systemically and they often acquire resistance to existing therapeutic agents". Finally, in describing some studies in which Dr. Chen and others were involved, she states "We showed that metastatic breast cancer cells capable of generating macro-metastases in the brain have a dramatic increase in oxidative metabolism enzymes compared to the bone metastasis and primary breast tumor" (Chen et al. 2007).

In a subsequent article (Bhandary et al. 2012) the authors emphasize that the roles of mitochondria in cancer progression/metastasis include alteration of glycolysis, regulation of ROS (reactive oxygen species) and suppression of intrinsic apoptosis. Later they point out also that ROS can damage nucleic acids resulting in genomic mutations and instability. Finally, they note that "in some cases mitochondrial ROS is enhanced in mtDNA mutation-associated cancer metastasis".

Significantly, the article of Chou and Chan (2012) focuses also on ROS in relation to cancer metastasis. Specifically, the authors introduce mitochondrial proteomic strategies and discuss their recent finding related to cancer metastasis. They emphasize that the mitochondrial respiratory chain is believed to be a major site for ROS production and that elevated ROS is likely a key source to trigger dysfunctional mitochondria and impaired mitochondrial metabolism that subsequently contribute to cancer progression.

In the article by Enns and Ladiges (2012) the authors emphasize that "As a tumor grows, it encounters adverse microenvironments, one of which is low oxygen (hypoxia) which selects tumor cells with characteristics of increased invasiveness". They conclude by stating that "An increase in environmental oxygen in combination with a mitochondrial targeted catalase mimetic and a metabolism booster may be of interest to investigate as a treatment strategy for invasive cancer".

The article of Ishikawa et al. (2012) discusses the controversy as to whether mitochondrial DNA mutations (mtDNA mutations) are responsible for tumorigenesis. To

clarify this issue they report work where they established trans-mitochondrial cybrids with mtDNA exchanged between mouse tumor cells that possess high and low metastatic potential. Significantly, the results revealed that the G13997A mutation in the ND6 gene of mitochondrial DNA from highly metastatic tumor cells reversibly controlled development of metastases by overproduction of (ROS). These investigators also identified other mtDNA mutations that affect metastatic potential but are independent of ROS production.

In the article of Li (2012), the author emphasizes that cellular redox states can regulate cell metabolism, growth, differentiation, motility and apoptosis, and that there is a growing body of literature that suggests the importance of redox status for cancer progression. They go on to summarize data in mouse models of human cancer that indicate a potential link between mitochondrial redox state and tumor metastatic potential.

Finally, as mentioned in the abstract the small molecule 3-bromopyruvate (3BP) has shown promise not only as an agent that can destroy primary cancers but also prevent these cancers from metastasizing. It will be noted in the study reported by Ko et al. (2004) that 19/19 animals (rats), i.e., 100 %, bearing quite large tumors were cured upon treatment with 3BP. The tumors completely disappeared and the animals lived out their lives without the return of cancer. This would suggest that if any metastasis (e.g., liver to lung) had taken place, which likely it had, that 3BP had killed the metastatic cells. Conversely, while killing the parent tumor at its site of origin 3BP may have killed also any metastatic cells that had developed.

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