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MINI-REVIEW

Mitochondrial dysfunction and cancer metastasis

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Abstract Mitochondria have an essential role in powering cells by generating ATP following the metabolism of pyruvate derived from glycolysis. They are also the major source of generating reactive oxygen species (ROS), which have regulatory roles in cell death and proliferation. Mutations in mitochondrial DNA (mtDNA) and dysregulation of mitochondrial metabolism have been frequently described in human tumors. Although the role of oxidative stress as the consequence of mtDNA mutations and/or altered mitochondrial functions has been demonstrated in carciongenesis, a causative role of mitochondria in tumor progression has only been demonstrated recently. Specifically, the subject of this mini-review focuses on the role of mitochondria in promoting cancer metastasis. Cancer relapse and the subsequent spreading of cancer cells to distal sites are leading causes of morbidity and mortality in cancer patients. Despite its clinical importance, the underlying mechanisms of metastasis remain to be elucidated. Recently, it was demonstrated that mitochondrial oxidative stress could actively promote tumor progression and increase the metastatic potential of cancer cells. The purpose of this mini-review is to summarize current investigations of the roles of mitochondria in cancer metastasis. Future development of diagnostic and therapeutic strategies for patients with advanced cancer will benefit from the new knowledge of mitochondrial metabolism in epithelial cancer cells and the tumor stroma.

Keywords Cancer metastasis · Mitochondria · Mitochondrial DNA mutations · Mitochondrial Oxidative Stress · Breast Cancer Metastasis

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Introduction

More than 90 % of mortality in cancer patients is attributed to metastases, not the primary tumors that produce disseminated tumor cells (Gupta and Massague 2006; Mehlen and Puisieux 2006; Steeg 2006). For example, the 5-year survival rate for patients diagnosed with stage 1 breast cancer is 98–100 % whereas the 5-year survival rate for patients diagnosed with metastatic breast cancer is down to 16–20 %. 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. Therefore, our ability to treat cancer effectively largely depends on our ability to predict the formation of macrometastases and to eradicate metastatic tumors at the secondary sites.

The most important feature of metastasis is that different tumor types can formation metastases in the same or different organs (Fidler 2003; Paget 1989). The propensity for certain tumors to seed in a particular organ was first conversed by Stephen Paget a century ago as the of "seed and soil" theory. For example, the major site of prostate cancer metastasis is the bone (Edlund et al. 2004). Breast and lung cancer can colonize similar tissues, including bone, lung, liver, and brain (Hess et al. 2006; Patanaphan et al. 1988), but the kinetics of metastatic progression between these two types of cancers are different. Breast cancer metastases are often detected following years or decades of remission (Karrison et al. 1999; Schmidt-Kittler et al. 2003), whereas lung cancers establish distant macrometastases within months of diagnosis (Feld et al. 1984; Hoffman et al. 2000). Furthermore, there is often a time gap (metastatic latency) between organ infiltration and colonization before the detection of clinically overt metastasis. Many questions pertaining to the organ-specific metastasis such as the origin of disseminated tumor cells and the molecular basis of metastatic latency are largely unknown, but recent discoveries have

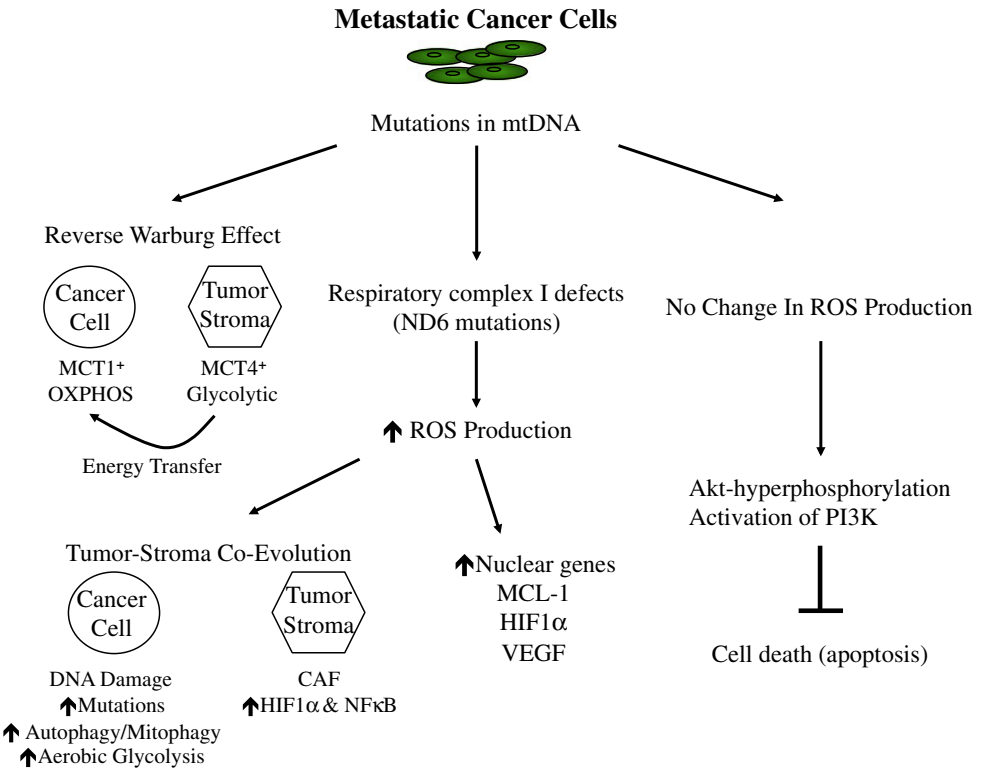

Fig. 1 Mechanisms of promoting cancer metastasis through mitochondrial DNA mutation or dysregulation of mitochondrial metabolism

established new paradigms that will guide future research on metastasis.

The role of mitochondria in cancer metastasis

Mitochondria are the primary energy producers of the cell that regulate intracellular energy metabolism, cell death, and free radical (ROS) production (Karbowski 2010; Lambert and Brand 2009; Martinou and Youle 2011; Murphy 2009; Scatena 2012). Human mitochondria contain a small amount of their own DNA (mtDNA) that encodes 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes encode enzymes involved in oxidative phosphorylation, and the remaining genes encode transfer RNAs (tRNAs) and ribosomal RNAs (Chen et al. 2010; Falkenberg et al. 2007; Taanman 1999; Tarassov et al. 2007). Because mtDNA is not associated with histones and is in close proximity of ROS production, mtDNA is directly exposed to the damaging effect during oxidative phosphorylation. Numerous studies have reported the association of mtDNA mutations in human tumors, including somatic mutations (Brandon et al. 2006; Modica-Napolitano et al. 2007), tumor-specific changes in the mtDNA copy number (Desouki et al. 2005; Lee et al. 2005; Mambo et al. 2005; Mizumachi et al. 2008; Selvanayagam and Rajaraman 1996; Tseng et al. 2006; Yin et al. 2004; Yu et al. 2007), and alteration of mitochondrial gene expression (Eng et al. 2003; Espineda et al. 2004; Isidoro et al. 2004; Weber et al. 2002). However, the causality of mtDNA mutations in tumor progression is not well understood. By replacing the endogenous mtDNA of a poorly metastatic mouse tumor cell line with mtDNA of a highly metastatic mouse tumor cell line (trans-mitochondrial cybrids), Ishikawa et al. showed that mtDNA mutations can enhance the metastatic potential of tumor cells by inducing complex I defects and resulting in increased ROS production as well as up-regulation of nuclear genes essential for cell survival and angiogenesis (Ishikawa et al. 2008). Additional evidence implicating the role of mitochondrial oxidative stress in cancer metastasis comes from Goh and colleagues (Goh et al. 2011). They demonstrated that targeted increase of catalase (an anti-oxidant enzyme) in mitochondria of a breast cancer mouse model alleviated mitochondrial oxidative stress and dramatically reduced metastatic burden in tumor-bearing mice (Goh et al. 2011).

As opposed to increased ROS production, mtDNA mutations can also enhance cancer metastasis by promoting apoptotic resistance in cancer cells. By creating cybrids in breast cancer cell lines, Kulawiec et al. reported that cybrids carrying mtDNA mutations showed a higher frequency of lung metastasis compared to cybrids carrying wild type mtDNA without mutations (Kulawiec et al. 2009). These mtDNA mutations constitutively activate the PI3/Akt pathway and protect cancer cells from stress-induced cell death. More recently, a new cancer paradigm, the "reverse Warburg effect," was proposed to elucidate the involvement of mitochondrial metabolism and cancer metastasis. In this model, metastatic cancer cells secrete hydrogen peroxide (H_2O_2) to induce oxidative stress and aerobic glycolysis in the stroma cells, which then generate L-lactate and ketone bodies to fuel

the oxidative mitochondrial metabolism in epithelial cancer cells. Sotgia et al. demonstrated this two-compartment model by analyzing the bioenergetic status of breast cancer lymph node metastasis (Sotgia et al. 2012). Using a selected panel of metabolism markers, they showed that mitochondrial mass and activity are increased in metastatic breast cancer cells, whereas lymph-node associated stroma showed no sign of altered mitochondrial mass and activity. Interestingly, we had a similar observation in metastatic breast cancer cells in the brain. We showed that metastatic breast cancer cells capable of generating macrometastases in the brain have a dramatic increase in oxidative metabolism enzymes compared to the bone metastasis and primary breast tumor (Chen et al. 2007). To assess the prognostic value of the reverse Warburg effect in patients, Witkiewicz et al. stained human breast cancer tissue microarrays containing tissues from triple-negative breast cancer patients (prone to metastasis and poor clinical outcome) with a glycolytic marker MCT4 and found a specific correlation between high stromal MCT4 expression and decreased patient survival whereas tumor MCT4 staining had no prognostic value of clinical outcome (Witkiewicz et al. 2012). Together, these results provide new insights on how mitochondrial metabolism contributes to metastatic growth at the secondary sites and demonstrate the clinical utility of metabolic enzymes as biomarkers for identifying high-risk cancer patients and as new targets for anti-cancer therapy.

In summary, the articles that comprise this minireview volume of the Journal of Bioenergetics and Biomembranes should provide the interested reader with an up to date view of ongoing research in the role of mitochondria in cancer metastasis (Fig. 1), which is attributed to greater than 90 % of mortality in cancer patients. Clearly, dysregulation of mitochondrial functions in epithelial cancer cells and cancer-associated stroma can promote the formation of clinically overt metastasis and therefore merit continued consideration as a therapeutic target in future research on cancer metastasis. Also, it might be beneficial to consider developing new antioxidant-based anti-cancer therapy to alleviate mitochondrial stress and prevent or reverse metastatic growth.

References

Brandon, M., Baldi, P. and Wallace, D.C. (2006). Mitochondrial mutations in cancer. Oncogene 25, 4647-62

Chen, E.I. et al. (2007). Adaptation of energy metabolism in breast cancer brain metastases. Cancer Res 67, 1472-86

Chen, X., Li, J., Hou, J., Xie, Z. and Yang, F. (2010). Mammalian mitochondrial proteomics: insights into mitochondrial functions and mitochondria-related diseases. Expert Rev Proteomics 7, 333-45

Desouki, M.M., Kulawiec, M., Bansal, S., Das, G.M. and Singh, K.K. (2005). Cross talk between mitochondria and superoxide generating NADPH oxidase in breast and ovarian tumors. Cancer Biol Ther 4, 1367-73

Edlund, M., Sung, S.Y. and Chung, L.W. (2004). Modulation of prostate cancer growth in bone microenvironments. J Cell Biochem 91, 686-705.

Eng, C., Kiuru, M., Fernandez, M.J. and Aaltonen, L.A. (2003). A role for mitochondrial enzymes in inherited neoplasia and beyond. Nat Rev Cancer 3, 193-202

Espineda, C.E., Chang, J.H., Twiss, J., Rajasekaran, S.A. and Rajasekaran, A.K. (2004). Repression of Na,K-ATPase beta1-subunit by the transcription factor snail in carcinoma. Mol Biol Cell 15, 1364-73

Falkenberg, M., Larsson, N.G. and Gustafsson, C.M. (2007). DNA replication and transcription in mammalian mitochondria. Annu Rev Biochem 76, 679-99

Feld, R., Rubinstein, L.V. and Weisenberger, T.H. (1984). Sites of recurrence in resected stage I non-small-cell lung cancer: a guide for future studies. J Clin Oncol 2, 1352-8

Fidler, I.J. (2003). The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 3, 453-8

Goh, J., Enns, L., Fatemie, S., Hopkins, H., Morton, J., Pettan-Brewer, C. and Ladiges, W. (2011). Mitochondrial targeted catalase suppresses invasive breast cancer in mice. BMC Cancer 11, 191

Gupta, G.P. and Massague, J. (2006). Cancer metastasis: building a framework. Cell 127, 679-95

Hess, K.R., Varadhachary, G.R., Taylor, S.H., Wei, W., Raber, M.N., Lenzi, R. and Abbruzzese, J.L. (2006). Metastatic patterns in adenocarcinoma. Cancer 106, 1624-33

Hoffman, P.C., Mauer, A.M. and Vokes, E.E. (2000). Lung cancer. Lancet 355, 479-85

Ishikawa, K. et al. (2008). ROS-generating mitochondrial DNA mutations can regulate tumor cell metastasis. Science 320, 661-4

Isidoro, A., Martinez, M., Fernandez, P.L., Ortega, A.D., Santamaria, G., Chamorro, M., Reed, J.C. and Cuezva, J.M. (2004). Alteration of the bioenergetic phenotype of mitochondria is a hallmark of breast, gastric, lung and oesophageal cancer. Biochem J 378, 17-20

Karbowski, M. (2010). Mitochondria on guard: role of mitochondrial fusion and fission in the regulation of apoptosis. Adv Exp Med Biol 687, 131-42

Karrison, T.G., Ferguson, D.J. and Meier, P. (1999). Dormancy of mammary carcinoma after mastectomy. J Natl Cancer Inst 91, 80-5

Kulawiec, M., Owens, K.M. and Singh, K.K. (2009). Cancer cell mitochondria confer apoptosis resistance and promote metastasis. Cancer Biol Ther 8, 1378-85

Lambert, A.J. and Brand, M.D. (2009). Reactive oxygen species production by mitochondria. Methods Mol Biol 554, 165-81

Lee, H.C. et al. (2005). Mitochondrial genome instability and mtDNA depletion in human cancers. Ann N Y Acad Sci 1042, 109-22

Mambo, E., Chatterjee, A., Xing, M., Tallini, G., Haugen, B.R., Yeung, S.C., Sukumar, S. and Sidransky, D. (2005). Tumor-specific changes in mtDNA content in human cancer. Int J Cancer 116, 920-4

Martinou, J.C. and Youle, R.J. (2011). Mitochondria in apoptosis: Bcl-2 family members and mitochondrial dynamics. Dev Cell 21, 92-101

Mehlen, P. and Puisieux, A. (2006). Metastasis: a question of life or death. Nat Rev Cancer 6, 449-58

Mizumachi, T. et al. (2008). Increased distributional variance of mitochondrial DNA content associated with prostate cancer cells as compared with normal prostate cells. Prostate 68, 408-17

Modica-Napolitano, J.S., Kulawiec, M. and Singh, K.K. (2007). Mitochondria and human cancer. Curr Mol Med 7, 121-31

Murphy, M.P. (2009). How mitochondria produce reactive oxygen species. Biochem J 417, 1-13

Paget, S. (1989). The distribution of secondary growths in cancer of the breast. 1889 [classical article]. Cancer & Metastasis Reviews 8, 98-101

Patanaphan, V., Salazar, O.M. and Risco, R. (1988). Breast cancer: metastatic patterns and their prognosis. South Med J 81, 1109-12

Scatena, R. (2012). Mitochondria and cancer: a growing role in apoptosis, cancer cell metabolism and dedifferentiation. Adv Exp Med Biol 942, 287-308

Schmidt-Kittler, O. et al. (2003). From latent disseminated cells to overt metastasis: genetic analysis of systemic breast cancer progression. Proc Natl Acad Sci U S A 100, 7737-42

Selvanayagam, P. and Rajaraman, S. (1996). Detection of mitochondrial genome depletion by a novel cDNA in renal cell carcinoma. Lab Invest 74, 592-9

Sotgia, F. et al. (2012). Mitochondrial metabolism in cancer metastasis: visualizing tumor cell mitochondria and the "reverse Warburg effect" in positive lymph node tissue. Cell Cycle 11, 1445-54

Steeg, P.S. (2006). Tumor metastasis: mechanistic insights and clinical challenges. Nat Med 12, 895-904

Taanman, J.W. (1999). The mitochondrial genome: structure, transcription, translation and replication. Biochim Biophys Acta 1410, 103-23

Tarassov, I., Kamenski, P., Kolesnikova, O., Karicheva, O., Martin, R.P., Krasheninnikov, I.A. and Entelis, N. (2007). Import of nuclear DNA-encoded RNAs into mitochondria and mitochondrial translation. Cell Cycle 6, 2473-7

Tseng, L.M., Yin, P.H., Chi, C.W., Hsu, C.Y., Wu, C.W., Lee, L.M., Wei, Y.H. and Lee, H.C. (2006). Mitochondrial DNA mutations and mitochondrial DNA depletion in breast cancer. Genes Chromosomes Cancer 45, 629-38

Weber, K., Ridderskamp, D., Alfert, M., Hoyer, S. and Wiesner, R.J. (2002). Cultivation in glucose-deprived medium stimulates mitochondrial biogenesis and oxidative metabolism in HepG2 hepatoma cells. Biol Chem 383, 283-90

Witkiewicz, A.K. et al. (2012). Using the "reverse Warburg effect" to identify high-risk breast cancer patients: stromal MCT4 predicts poor clinical outcome in triplenegative breast cancers. Cell Cycle 11, 1108-17

Yin, P.H. et al. (2004). Alteration of the copy number and deletion of mitochondrial DNA in human hepatocellular carcinoma. Br J Cancer 90, 2390-6

Yu, M. et al. (2007). Reduced mitochondrial DNA copy number is correlated with tumor progression and prognosis in Chinese breast cancer patients. IUBMB Life 59, 450-7