

Are Macrophages Responsible for Cancer Metastasis?

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Introduction

Despite the decades of basic and clinical research and countless scientists and laboratories involved, the origin of cancer and metastasis still remain unresolved. Currently, there are two dominating theories of the origin of cancer: genetic and metabolic [1,2]. The proponents of “the cancer as a genetic disease” theory postulate that various factors or a combination of factors such as heredity, random mutagenesis, hypoxia, radiation, inflammation, age, carcinogens, oncogenes or viruses, cause damage/changes to nuclear DNA and these in turn lead to the transformation of normal cells into cancer cells. In contrast, the advocates of “the cancer as a metabolic disease” theory believe that the acquisition of cancer phenotype is a consequence of mitochondrial and cell respiration defects—the so called Warburg effect when cancer cells produce energy by lactic acid fermentation in contrast to normal cells, which oxidize pyruvate in mitochondria [1-4] and that the genetic/DNA changes observed in cancer cells are just the secondary effects of respiratory malfunctions. In many cancers the deficient oxidative phosphorylation in mitochondria correlates with disappearance of mitochondrial cristae [5]. It is worth mentioning here that mutations in tumor suppressor genes such as for example p53 are also known to cause mitochondrial and respiratory damage [6,7]. The results of nuclear or cytoplasm and mitochondria transplantation experiments between cancer and normal cells support the metabolic/mitochondrial theory of cancer origin: cytoplasm or mitochondria from normal cells transplanted into cancer cells suppress cancer phenotype and mitochondria from cancer cells transplanted into normal cells induce tumorigenesis [2].

Similarly vague and unresolved are the mechanisms and origin of metastasis, which is a primary cause of cancer mortality [8, 9]. Metastasis is the spread of cancer cells from the primary tumor to surrounding tissues and, via circulation, to distant organs. It involves a combination of many steps: cancer cells have to detach from the primary tumor, enter and exit circulation and infiltrate target/distant organs. Subsequently, metastatic cells have to establish a new microenvironment favourable for cell proliferation and angiogenesis, which lead to development of secondary tumors. Until recently the generally accepted model of metastasis has been the epithelial/mesenchymal and mesenchymal/epithelial transition model [9]. This model proposes that non-mobile cells of benign (pre-cancerous) tumor loose cell-cell adhesion and undergo epithelial/mesenchymal transition (EMT), which together with the disruption of the underlying basement membrane allows them to become migratory, leave primary tumor, intravasate into the circulatory/lymphatic systems and extravasate in distant locations where, after mesenchymal/epithelial transition (MET), they form secondary tumors [9]. However this theory is unable

to explain for example how the random mutations (often different in different cancers) can lead to such an intricate and multistep events (identical in different cancers) and why genetic changes observed in EMT are also present in non-metastatic benign tumors. On the other hand, some time ago scientists noticed that normal leukocytes have all hallmarks of metastatic cells: they are motile, they intra- and extravasate and infiltrate various distant organs.

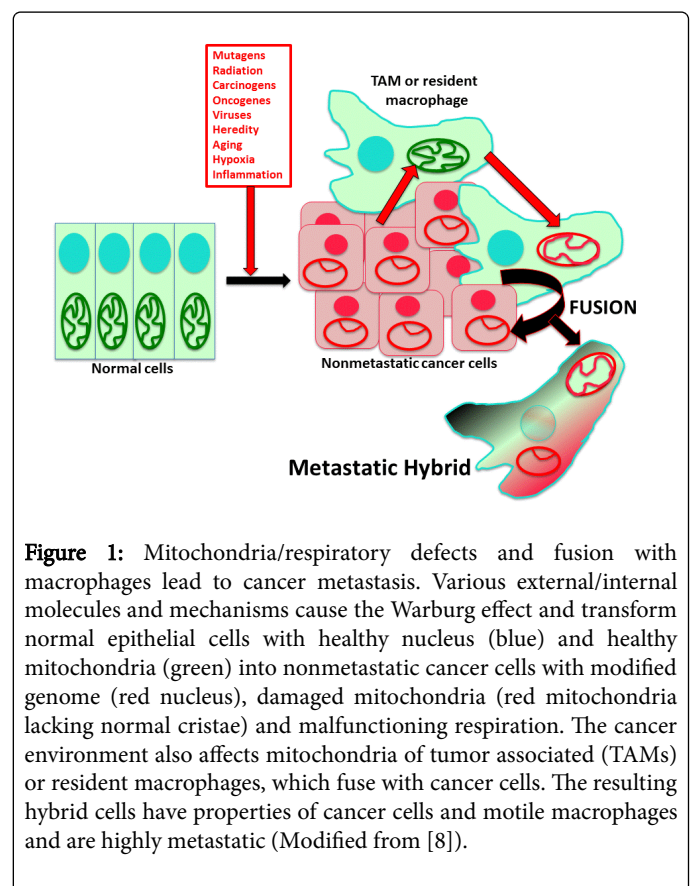


Figure 1: Mitochondria/respiratory defects and fusion with macrophages lead to cancer metastasis. Various external/internal molecules and mechanisms cause the Warburg effect and transform normal epithelial cells with healthy nucleus (blue) and healthy mitochondria (green) into nonmetastatic cancer cells with modified genome (red nucleus), damaged mitochondria (red mitochondria lacking normal cristae) and malfunctioning respiration. The cancer environment also affects mitochondria of tumor associated (TAMs) or resident macrophages, which fuse with cancer cells. The resulting hybrid cells have properties of cancer cells and motile macrophages and are highly metastatic (Modified from [8]).

abundant population of tumor associated macrophages TAM1 and TAM2, which are known to produce inflammatory microenvironment and cause DNA and mitochondrial damage as well as promote tumor growth, angiogenesis and metastasis [1,10-15]. Thus, the fusion of non-metastatic non-motile cancer cells with TAMs or other resident macrophages may create motile and metastatic hybrids. In addition, it is possible that cancer cells or/and tumor environment causes damage to TAMs or other resident macrophages mitochondria, resulting in Warburg effect and causing the hybrids to be highly metastatic [8]. Numerous studies showed that cancer cells from majority of tumor types possess characteristics (phagocytosis and fusogenicity) and protein and gene expression markers typical for macrophages [16-20] and circulating macrophage-cancer hybrid cells have been detected in melanoma and pancreatic and colorectal cancers [11,21,22] Recently, Shabo et al. [23] showed that breast and colorectal cancer cells express macrophage-specific antigen CD163 and proved experimentally that cancer cells acquire this trait by direct fusion with macrophages. The revival of metabolic theory of cancer origin, hybrid theory of cancer metastasis and participation of macrophages in the formation of highly metastatic hybrids (Figure 1) may lead to novel anticancer therapies, which either target/ rescue/prevent the metabolic disease of mitochondria or directly target macrophages for example by interfering with pathways such as RhoA pathway, which regulates actin-dependent macrophage motility and fusogenicity. In addition, the fact that circulating macrophage/cancer cell hybrids can be detected in histologically cancer negative patients [24] may lead to the early detection and prevention of metastasis.

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