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Rationale for mitochondria-targeting strategies in cancer bioenergetic therapies☆

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ABSTRACT

In the 1920s, Otto Warburg first hypothesized that mitochondrial impairment is a leading cause of cancer although he recognized the existence of oxidative tumors. Likewise, Weinhouse and others in the 50s found that deficient mitochondrial respiration is not an obligatory feature of cancer and Peter Vaupel suggested in the 1990s that tumor oxygenation rather than OXPHOS capacity was the limiting factor of mitochondrial energy production in cancer. Recent studies now clearly indicate that mitochondria are highly functional in mice tumors and the field of oncobioenergetic identified MYC, Oct1 and RAS as pro-OXPHOS oncogenes. In addition, cancer cells adaptation to aglycemia, metabolic symbiosis between hypoxic and non-hypoxic tumor regions as well the reverse Warburg hypothesis support the crucial role of mitochondria in the survival of a subclass of tumors. Therefore, mitochondria are now considered as potential targets for anti-cancer therapy and tentative strategies including a bioenergetic profile characterization of the tumor and the subsequent adapted bioenergetic modulation could be considered for cancer killing.

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Introduction: Mitochondrial impairment in cancer and one century of Warburg hypothesis

In the 1920s, Otto Warburg evidenced that tumor cells consume large amounts of glucose and convert it mostly to lactic acid despite the presence of oxygen (Warburg, 1930), observation we now unanimously call the "Warburg effect". This Warburg effect seduced the medical community in that a single metabolic specificity of cancer cells, the high dependency on glycolysis for energy production, could eventually be targeted to cure the disease. He then proposed that the cause of the increase aerobic glycolysis, i.e., the Warburg effect, was due to an impairment of mitochondrial oxidative metabolism. "*The aerobic glycolysis of the tumour cell is derived in any case from a disturbance of the respiration.*" Over ninety years of cancer biology research has been conducted with the basis of this predominant Warburg hypothesis. The exclusive respiratory impairment hypothesis is now challenged by an increasing number of bioenergetic studies which already started in the 1950s, when Sidney Weinhouse published experimental evidences in opposition to the Warburg hypothesis (Weinhouse, 1951, 1955). The major argument raised by Weinhouse was that tumors and non-neoplastic tissues show no difference in their ability to convert glucose and fatty acids to carbon dioxide, a process that requires respiration and functional mitochondria. It is noteworthy that Warburg himself recognized that respiration was not totally impaired and could even be efficient in a subset of tumors, the frequency of which still remain undetermined. "*As a rule, the respiration of the tumour cell is small, but in recent years tumour cells with a large respiration have also been found*. . .". Yet, this finding of Warburg remained underestimated so that an accepted consensus on a general mitochondrial impairment in cancer cells had emerged in the 1990s and remained highly cited since then. Nevertheless, in the last decade, several groups reported accumulating evidences of functional mitochondria in tumors and demonstrations of a strong dependency of cancer cells survival on mitochondrial oxidative metabolism. This short *argumentum* aims to clarify the implication and the importance of mitochondria in cancer biology and to discriminate the Warburg hypothesis (mitochondrial impairment) from the Warburg effect (aerobic glycolysis), both notions been not exclusive. We discuss the status and the variability of mitochondrial content and functionality in cancer. A special attention was given to the rationale for targeting mitochondria in anti-cancer strategies.

1. Mitochondrial content and efficiency is enhanced in a subset of human tumors

The changes in mitochondrial content, composition and bioenergetics parameters including respiration and proton-motive force observed in various tumor-derived cell lines were extensively

Abbreviations: CDK, cyclin; OXPHOS, oxidative phosphorylation; PGC1, peroxisome proliferator-activated receptor-γcoactivator; ROS, reactive oxygen species; PET scan, positron emission tomography; ETC, electron transport chain; PDH, pyruvate dehydrogenase; SV40, simian virus 40.

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reviewed in previous articles (Jose et al., 2011b; Smolkova et al., 2011; Bellance et al., 2009b). However, a large number of those studies were performed on tumor derived cell culture models, which might exhibit a strong dependency on glycolysis not only due to their cancer nature. Indeed, there is a strong impact of the artificial culture conditions on energy metabolism and on mitochondrial physiology, as revealed by cell biology investigations in senescence research. One example of the impact of cell culture on cell biology is the so-called "culture shock" (Gnaiger and Kemp, 1990; Gstraunthaler et al., 1999; Sherr and DePinho, 2000) which modulates the activity of the CDK inhibitors p16INK4a and p21Cip1, the p53 inducer p19ARF, and p53 itself. For this reason, we focused our argumentation on the few reports of mitochondrial changes in excised human and mice tumors as well as in vivo mice studies. Firstly, to evaluate mitochondrial representation in tumors different groups have measured the mitochondrial DNA (mtDNA) content in cancer regions and performed a comparison with normal cells. In this manner, a decrease in mtDNA copy number was reported in many types of cancers, including gastric (Wu et al., 2005) and hepatocellular carcinoma (Yin et al., 2004), suggesting that the decreased mtDNA copy number may contribute to, or associate with tumorigenesis. In ovarian cancer, despite an increase in mtDNA content in tumor *versus* normal ovary cells, there was a decrease in mtDNA copy number associated with tumor aggressiveness (Wang et al., 2006). Furthermore, Meierhofer et al. (2004) reported a significant reduction of mitochondrial enzyme activities and of mtDNA copy number in 34 out of 37 renal cell carcinoma tissues, as compared with adjacent noncancerous tissues. Similar observations were made on the reduced activity of respiratory chain complexes and the diminished mtDNA content in renal tumors (Simonnet et al., 2002; Capuano et al., 1996; Heddi et al., 1996). This alteration of OXPHOS capacity was related to the aggressiveness of the tumors, suggesting a progressive shift of energy metabolism toward glycolysis during tumorigenesis in kidney tumors.

However, other authors have observed opposite results in favor of an increase of mitochondrial capacity, notably in breast cancer (Shen et al., 2010). This controversial situation was found for other types of cancer as an increased mtDNA content was reported both in chronic lymphocytic leukemias, (Carew et al., 2004) and in lung cancer (Hosgood et al., 2010). These opposite findings do not permit to conclude unequivocally on the status of mitochondrial content in cancer and point toward a variability of mitochondrial content and capacity in tumors, rather than a simple general repression. The field of mitochondrial-cancer research still lacks of large-scale studies on different types of tumors, which could allow estimating the variability of mitochondrial content and functionality as well as solicitation in cancer tissues. Alternatively, prospective cohort studies have tried to assess the possible role of mtDNA copy number in blood cells as a risk factor for cancer. The results were extremely variable and suggested again a large disparity between cancer types and even within one type of tumor between different individuals. Some authors found a positive association between high mtDNA content and the risk of both lung (Hosgood et al., 2010) cancer and non-Hodgkin lymphomas (Lan et al., 2008). Lynch et al. also found an association between high mtDNA copy number and pancreatic cancer incidence (Lynch et al., 2011). This association was significant for the cases diagnosed during the first 7 years of follow-up. In striking contrast, no association between leukocyte mtDNA copy number and the risk of developing gastric cancer has been found on a large population-based prospective cohort (Liao et al., 2011). Interestingly, the authors found an association between low levels of mtDNA copy number and the risk for gastric cancer among earlier diagnosed cases (and not when the time between sample collection and cancer diagnosis increased). These authors concluded on a possible early disease effect on mtDNA copy number levels. Yet, such association studies lack of demonstration so that a causality link between mitochondrial content and cancer risk could be clearly shown. Of note, in the above cited studies, mitochondrial DNA content does not necessarily reflect the organelle content as defects in mtDNA translation, replication or in nuclear-encoded mitochondrial protein content alteration as well as mitophagy, may decrease the number of mitochondria or the OXPHOS protein content. To understand the underlying mechanism of mitochondrial content variability in tumors, some authors have analyzed the status of mitochondrial biogenesis, notably by measuring the expression level of the master regulator PGC1α. Once again different authors have shown opposite results since the mitochondrial biogenesis was up-regulated in tumors *versus* healthy tissues in some cancer types and down-regulated in others (Table 1). For example, it has been reported that in renal cell carcinomas PGC1α was expressed at lower levels as compared to normal background tissue (Simonnet et al., 2002). This could suggest an important role for this factor in refining the cancer cell's metabolic profile and also that a therapeutic gain might be obtained from the reactivation of mitochondrial biogenesis in those cancer cells. This hypothesis was tested with success in different studies using resveratrol, pioglitazone, AICAR or bezafibrate that are known to induce mitochondrial biogenesis *via* PGC1 α (Bellance et al., 2009a; Jose et al., 2011a; Wang and Moraes, 2011). However those drugs may produce off-targets effects responsible for cancer killing.

Table 1
Variation of mitochondrial biogenesis in tumors.

Cancer type	Up-regulated	Down-regulated	References
Type I endometrial cancer	X		Cormio et al. (2009) and Jose et al. (2011a)
Primary leukemia cells	X		Carew et al. (2004)
Arsenical skin cancer	X		Lee et al. (2011)
Thyroidoncocytoma	X		Baris et al. (2004) and Savagner et al. (2003)
Kidney carcinoma		X	Hervouet et al. (2005)
Renal cell carcinoma		X	Simonnet et al. (2002)
Lung carcinoma		X	Bellance et al. (2009a)

In addition to biogenesis reduction the low efficiency of the OXPHOS system observed in the Warburg type of cancer cells could be explained by the alteration of respiratory chain complexes specific activity, possibly caused by cancer specific protein regulations such as post-translational modifications or ROS-induced alterations. Yet little is known on this particular aspect of OXPHOS dysregulation and only one study reported a functional alteration of the respiratory chain complex I in cancer (Simonnet et al., 2003). Furthermore, abnormalities in the overall morphology of the mitochondrial network and its internal organization have been reported in numerous cancers, including human astrocytomas (Arismendi-Morillo and Castellano-Ramirez, 2008), carcinomas (Springer, 1980), Warthin's tumor (Kataoka et al., 1991), xenografted gliomas (Oudard et al., 1997), malignant glioma cells (Steinbach et al., 2003) and HeLa cells (Rossignol et al., 2004). Most of these studies reported heterogeneous ultrastructural abnormalities, such as organellar swelling with a disorganization and distortion of the cristae and partial or even total cristolysis. Those might underline an activity defect of the OXPHOS system as such ultrastructural alterations of the mitochondrion are commonly found in mitochondrial diseases. Abnormalities in mitochondrial fusion–fission were also proposed from the analysis of astrocytomas sections by electron microscopy (Arismendi-Morillo and Castellano-Ramirez, 2008). Such structural defects in the mitochondria are frequently seen in cancer cells, although their precise origin and participation in tumor progression are not well understood. Analyses of