Editorial

Mitochondrial calcium: a crucial hub for cancer cell metabolism?

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Introduction

According to the current concept, a typical tumor contains "driver gene" mutations that establish a growth advantage to the tumor cell (1). It was proposed that one of the first mutations must have either a mutation that introduces a selective growth advantage to a normal cell (1) or one of the first mutations results in genomic instability, thus, increasing the chance for the accumulation of further mutations (2). Recent data indicate that metabolic reprogramming by (somatic) mutations of key metabolic genes promotes cancer growth (3). In this context metabolic adaptations upon aging need to be considered as hallmark of cancer (4). Since the landmark discovery of cancer-specific enhancement of glycolysis with concurrent small respiration (5), abnormalities in mitochondrial functions as a key phenomenon of the metabolic peculiarities of cancer cells has been postulated. Otto Warburg assumed that the accumulation of lactate in cancer tissue is the result of enhanced anaerobic glycolysis and dysfunctional mitochondrial respiration. This assumption was lately challenged by still controversial findings of a reduced conversion of phosphoenolpyruvate to pyruvate by the less active, cancer-specific isoform pyruvate kinase 2 (PKM2) (6), which might limit the production of ATP from glycolysis, but boosts the accumulation of intermediate products like nucleic acids and phospholipids for cancer cell growth (7). Nevertheless, Otto Warburg was prophetic in his view on the role of metabolism for cancer. Recent work highlights alterations of mitochondria-associated genes to play an essentially role in the metabolic reprogramming in cancer cells that play a supportive, if not causative role in tumorigenesis (8). The latter hypothesis was stressed by a recent work where mitochondria/cytosolic transfer from a cancer cell into a somatic cell turned the latter one to a cancer cell as well (9). While the interpretation of this work is complex, mitochondrial metabolic and signal functions that undergo a cancer-specific transformation (4) involving mitochondria-endoplasmic reticulum (ER) settings (10,11) are known to be essential to meet the enhanced energy demand of a cancer cell. The study "MICU1 drives glycolysis and chemoresistance in ovarian cancer" by Chakraborty *et al.* recently published in *Nature Communications* (12) describes important new findings supporting the current hypothesis on mechanistic/functional mitochondrial adaptations to be crucial for cancer cell development. Importantly this work points to a crucial role of mitochondrial calcium uptake 1 (MICU1), the gatekeeper of mitochondrial Ca^{2+} uniport (MCU) (13), for glycolysis and chemoresistance in ovarian cancer. Notably, this work considerably fuels current hypothesis on the importance of mitochondrial Ca^{2+} uptake for cancer cell survival and growth (10,11,14) and points to adaptations in mitochondrial Ca^{2+} as a hallmark in the adjustment of mitochondrial activity in cancer cells.

All about mitochondrial calcium?

Chakraborty and coworkers also described an obvious role of MICU1 in the regulation of pyruvate dehydrogenase (PDH) by affecting the phosphoPDH: PHD ratio. They further describe a strong impact of MICU1 depletion on the anti-tumor effects of cisplatin. Notably, these particular findings were acquired under conditions of MICU1

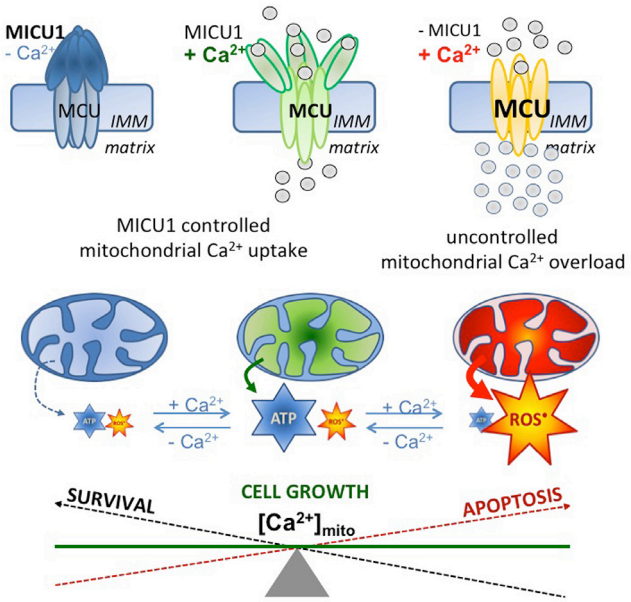

Figure 1 ATP and ROS production is under the control of mitochondrial Ca^{2+} uptake. MICU1 prevents mitochondrial Ca^{2+} loading under resting conditions (left blue panels). Physiological Ca^{2+} signals activate MCU via Ca^{2+} binding to MICU1, which allows controlled mitochondrial Ca^{2+} sequestration and consequently stimulates mitochondrial ATP production (middle green panels). Diminished MICU1 expression levels can lead to an uncontrolled mitochondrial Ca^{2+} overload, which has the potency to trigger enhanced ROS production and cell death pathways (right red panels). MICU1, mitochondrial calcium uptake 1; MCU; mitochondrial Ca^{2+} uniport.

silencing, conditions where mitochondrial Ca^{2+} uptake is strongly enhanced (12), due to the protein's gatekeeper function in most cells (15). Hence, because the activity of the mitochondrial oxidative phosphorylation (OXPHOS) crucially depends on Ca^{2+}-dependent dehydrogenases in the citrate cycle in the mitochondrial matrix, Ca^{2+} acts a main regulator for mitochondrial ATP synthesis (16), thus, a regulatory role of mitochondrial Ca^{2+} appears likely even in case of PDH activity (17). Such central role of mitochondrial Ca^{2+} in the regulation of mitochondrial processes and function appears a consequence of the tight physical and functional coupling of ER-released Ca^{2+} and mitochondrial Ca^{2+} sequestration. Recently, an optimized physical coupling between the ER and mitochondria was described in cancer cells (10,11). Notably, while the constitutive Ca^{2+} flux from the ER to mitochondria was demonstrated to be essential to maintain viability of cancer cells with high proliferation activity (10), mitochondrial Ca^{2+} overload (*Figure 1*) due to e.g., uncontrolled mitochondrial Ca^{2+} uptake, like under conditions of MICU1 depletion, yields activation of apoptotic pathways and, ultimately, cell death (11). The importance of the ER-mitochondrial Ca^{2+} transfer in cancer cells was further highlighted by the finding that certain oncogenes manipulate contact sites between these two organelles thereby affecting mitochondria-associated-ER membranes (MAMs) (18). In contrast the cancer testis antigen, FATE1 antagonizes cancer apoptosis by physically uncoupling the ER from mitochondria (19).

Accordingly, there is a large body of evidence that mitochondrial Ca^{2+} is of utmost importance for (cancer) cells homeostasis, functions, growth, migration, and, ultimately, survival. The contribution of Chakraborty *et al.* convincingly demonstrates that besides cancer cell survival, their glycolytic activity and chemoresistance are also critically associated with mitochondrial Ca^{2+} uptake (12).

Mitochondrial Ca^{2+} uptake in cancer: the balance between energy and death

Chakraborty *et al.* described a poor prognosis of cancer patient suffering from ovarian cancer with elevated expression of MICU1 (12). These data point to a protective effect of elevated MICU1 on cancer cell survival by preventing mitochondrial Ca^{2+} overload and, subsequently the initiation of the machinery for apoptotic cell death (*Figure 1*). These data further indicate that cancer cells benefit from reduced mitochondrial Ca^{2+} uptake, thus, illustrating the obvious risk of tumor cells for mitochondrial Ca^{2+} overload. Recently, cancer cells were found to exhibit a stronger tethering between mitochondria and ER in comparison to non-cancerous cells (11). While this enforced intra-organelle communication fosters e.g., mitochondrial ATP supply for the ER's protein folding machinery and, thus, meets the high energy demand of cancer cells, such settings makes them more vulnerable for mitochondrial Ca^{2+} overload.

Notably, cancer cells developed multiple unique strategies to protect themselves against lethal mitochondrial Ca^{2+} overload:

(I) Via the protein arginine methyl transferase 1 (PRMT1) MICU1 gets methylated yielding a strong sensitivity loss of the mitochondrial Ca^{2+} uptake machinery. In cancer cells methylated MICU1 protects from mitochondrial Ca^{2+} overload (14).

(II) Tumor cell physiology and plasticity is regulated

by cancer-specific mitochondrial dynamics (20).

(III) Most cancer cells develop a unique redox handling by enhancing NADPH-dependent scavenging enzymes (21).

(IV) Cancer cells can actively untether their mitochondria from the ER (22).

(V) Cancer cells modulate ER Ca^{2+} release by regulating inositol-1,4,5 trisphosphate receptors (IP3R), the constitutive receptors for ER Ca^{2+} release (23).

(VI) The permeability of the outer mitochondrial membrane (VDAC) is regulated (24).

(VII) Cancer cell suppress mitochondrial K^+-channels and its normalization promotes apoptosis and hampers cancer growth (25).

This incomplete list illustrates the flexibility of cancer cells to address the issue of keeping the balance between enough mitochondrial Ca^{2+} uptake to meet the cell's ATP demand while to avoid mitochondrial Ca^{2+} overload in order to stay clear from the initiation of apoptotic processes that ultimately would cause cancer cell death.

Mitochondrial Ca^{2+} uptake as therapeutic target

Many authors including Chakraborty *et al.* (12,26) have indicated the potential of targeting mitochondrial Ca^{2+} uptake to fight against cancer growth. In this regard, three approaches appear most promising to be effective to introduce mitochondrial Ca^{2+} overload leading to apoptotic cancer cell death:

(I) Directly affecting constituents of the MCU complex yielding uncontrolled Ca^{2+} uptake;

(II) Manipulating the vicinity between the mitochondria and the ER resulting in an harmful enhancement of mitochondrial Ca^{2+} sequestration;

(III) Disturbing the main Ca^{2+} regulators of the ER (i.e., SERCA and IP3R) to trigger exhaustive ER Ca^{2+} depletion and subsequently mitochondrial Ca^{2+} overload.

Conclusions

While controlled mitochondrial Ca^{2+} uptake promotes cancer cell growth, the adequate transfer of Ca^{2+} into mitochondria is also of utmost importance for the proper functioning of somatic cells and tissues. Therefore, future work essentially needs to be aimed on the identification of cancer specificities in mitochondrial Ca^{2+} handling that can be therapeutically targeted to selectively fight cancer cells without affecting non-cancerous cells.

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