DOI:10.33266/1024-6177-2024-69-2-12-17

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МЕХАНИЗМЫ ВЛИЯНИЯ МИТОХОНДРИЙ НА РАДИОРЕЗИСТЕТНОСТЬ ОПУХОЛЕЙ

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РЕФЕРАТ

Радиотерапия остается одним из основных методом лечения раковых заболеваний. При этом формирование радиорезистентности раковых клеток к ионизирующему излучению ведет к потере эффективности терапии. Токсичность радиотерапии определяется митохондриями, и использование митохондрий или их компонентов в комбинации с химио- радио- и иммунотерапией может увеличить эффективность лечения. В этом обзоре мы рассмотрели новые экспериментальные методы использования митохондрий в терапии рака. Данные литературы свидетельствуют, что хотя физиологический транспорт митохондрий способствует канцерогенезу и резистентности к химиотерапии, трансплантация экзогенных митохондрий наоборот индуцирует радиочувствительность и ингибирует рост опухолей в мышиных моделях рака. Следовательно, ингибирование эндогенного переноса раковых митохондрий или разработка методов доставки экзогенных митохондрий являются многообещающим направлением разработки противораковых лекарств.

Ключевые слова: *радиорезистентность, рак, перенос митохондрий, трансплантация митохондрий*

Для цитирования: Розенберг Ю.М., Максимов В.В., Кузьмин Д.В., Леонов С.В. Механизмы влияния митохондрий на радиорезистетность опухолей // Медицинская радиология и радиационная безопасность. 2024. Т. 69. № 2. С. 12–17. DOI:10.33266/1024-6177-2024-69-2-12-17

DOI:10.33266/1024-6177-2024-69-2-12-17

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Mechanisms of Mitochondrial Influence on Tumor Radioresistivity

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ABSTRACT

Radiotherapy remains one of the main methods of cancer treatment. At the same time, the formation of radioresistance (RR) of cancer cells to ionizing radiation leads to a loss of therapy effectiveness. The toxicity of radiotherapy is determined by mitochondria, and the use of mitochondria or their components in combination with chemo-radio and immunotherapy can increase the effectiveness of treatment. In this review, we have reviewed new, experimental methods for using mitochondria in cancer therapy. Literature data indicate that although the physiological transport of mitochondria promotes carcinogenesis and resistance to chemotherapy, transplantation of exogenous mitochondria, on the contrary, induces radiosensitivity and inhibits tumor growth in mouse models of cancer. Therefore, inhibition of endogenous transfer of cancer mitochondria or the development of methods for the delivery of exogenous mitochondria is a promising area for the development of anti-cancer drugs.

Keywords: *radioresistance, cancer, mitochondrial transfer, mitochondrial transplantation*

For citation: Rozenberg JM, Maximov VV, Kuzmin DV, Leonov SV. Mechanisms of Mitochondrial Influence on Tumor Radioresistivity. Medical Radiology and Radiation Safety. 2024;69(2):12–17. (In Russian). DOI:10.33266/1024-6177-2024-69-2-12-17

Introduction

Mitochondria play a pivotal role in all aspects of cancer. Classically, the primary mitochondria function is ATP generation through the Krebs cycle followed by the oxidative phosphorylation (OXPHOS). The mitochondria are sites of biosynthetic pathways, required for proliferation [1,2] and whose dysregulation contributes to cancer [3–5]. This can be exemplified by mutations of the Isocitrate dehydrogenase 2 (IDH2) gene, which cause synthesis of D-2-HG that inhibits activity of anti oxidative and gene regulation pathways and is a driver mutation in multiple cancers [6, 7]. Multiple mitochondrial proteins protect cells from damage, exemplified by the GLS2, synthesizing D-glutamate which is subsequently used for production of the major antioxidant glutathione or the Mn-SOD2 reducing superoxide to H_2O_2 [8].

Remarkably, mitochondria can be exchanged between cells (so-called horizontal transfer) by either intercellular tunneling nanotubes [9–12], or via large extracellular vesicles (EV) [13–15] or through the gap junctions [16].

The body of the literature suggests that consequences of such transfer promote cell survival and improve cardiomyocyte viability [14], survival of virus infected cells [17], tissue regeneration [18, 19] and acute myeloid leukemia cell resistance to apoptosis [20].

In addition, mitochondria are major players in regulating cell apoptosis mediated by the DNA damage, reviewed in [21]. Classically, activation of signaling cascades by the DNA damage triggers ATM activation leading to transcriptional activation of pro-apoptotic genes reviewed in [21], BAX protein oligomerization and pore formation in the mi-

tochondrial membrane [22], followed by cytochrome C release to the cytoplasm and caspase activation [23, 24]. The Bax-mediated release of the cytochrome C is inhibited by the Bcl-2 protein family (Bcl-2, Bcl-XL, Mcl-1, Bcl-w, A1, Bcl-L10, Bcl-G and Bcl-Rambo). In turn, the Bcl-2 anti-apoptotic functions are inhibited by the BH3-only family of proteins (Noxa, Puma, Bid, Bad, Bim, Bik, Hrk and Bmf) [25]. These processes are tightly regulated and gamma irradiation can induce apoptosis in a cell dependent manner. For example, in the lung cancer cell line, radiation induced apoptosis in the majority of cells but not in the stem cell enriched side population [26].

In addition, mitochondria induce immune response to radiation damage by releasing damaged mitochondrial DNA and RNA to the cytoplasm [27–29].

Thus, mitochondria has a dual role in cell physiology promoting cell survival or apoptosis.

Indeed, it has been observed in multiple cancer models that transplantation of mitochondria inhibits proliferation [30–33] and induces radiosensitivity [34].

Currently, drug targeting of mitochondrial proteins involved in the regulation of apoptosis has led to successful development of drugs for cancer treatment, such as BCL-2 inhibitor venetoclax [35–37]. However, the mechanisms by which exogenous mitochondria can either induce death or promote survival are currently unknown and therefore development of cancer treatment approaches using mitochondrial transport is in it's infancy.

In this mini-review, we briefly discuss the mitochondrial mechanisms of radioresistance and then focus on cancer radiosensibilization by the mitochondrial transport.

Accumulating data suggest that mitochondrial transplantations can induce tumor cell radiosensitization. Research focused on the better understanding of underlying mechanisms is an exciting field leading to improved treatment of cancer.

Mitochondria in cancer radioresistance

Mitochondria modulate radioresistance by regulating cell proliferation and apoptosis

Mitochondria are essential for cancer cell proliferation and radioresistance (RR). It is possible to generate cells without mitochondria, although these cells will not form tumors *in vivo* until they acquire the mitochondria from the surrounding host cells [1]. Moreover, ATP production was dispensable whereas pyrimidine biosynthesis was required for tumor occurrences [1]. Accordingly, a recent study has found that even though radioresistant cells have higher oxidative metabolism, the OXPHOS itself is not responsible for the radioresistance. [2]. Moreover, resistant cells have the same ATP production, ROS, DNA damage and ATM activity as control cells [2]. What was the exact mechanism of radioresistance was not clear, except radioresistant cells have about 1.5 higher mitochondria counts.

Notably, it was shown that across different organisms, including bacteria, fungi or human cells, RR is extremely strongly associated with complexes of Mn2+ with small metabolites (such as orthophosphates or organic compounds) but not with big chelating agents or proteins [38, 39]. These small Mn2+ complexes largely determine O2• – scavenging capacity after irradiation and their role is largely in protecting proteins [40].

Taking in the account that significant fraction of Mn is accumulated in the mitochondria [41, 42] and reference therein, it is possible to speculate that the increase of RR can be partially attributed to the increase of the low molecular weight Mn2+ complexes within mitochondria. However, despite of the fact that this mechanism is well demonstrated in bacteria [38,43], the eukaryotic cells are much more sensitive to irradiation and the data quantifying this mechanism in eukaryotes are just emerging [38, 39].

Multiple investigations describe mechanisms of mitochondria-regulated cell survival and radiation response. For example, Irradiation of breast, colon and glioblastoma cell lines with 5 Gy caused mitochondrial mTOR translocation. In breast cancer 4T1 cell mTOR translocation inhibited mitochondrial bound Hexokinase2 and repressed glycolysis at the same time inducing OXPHOS [44]. This was associated with G2/M cell cycle arrest at 24h post irradiation and increased mitochondrial ATP production. Inhibition of mTOR mitochondrial translocation by rapamycin completely inhibited these effects and caused 2x reduction of colony formation, suggesting that induction of mitochondrial metabolism by this mechanism is important for RR [44]. However, effects of rapamycin on the cell cycle and DNA damage were not examined.

Another possible mechanism is mediated by the mitochondrial damage upon irradiation and this damage can contribute either to the cell death or conversely, to the survival of radioresistant cells. An interesting study systematically evaluated kinetics of mitochondrial OXPHOS and glycolytic energy generation in multiple cancer cell lines (lung, colon, liver, brain, prostate, breast) in response to 3 Gy (and 2–8 Gy in selected experiments) doses of irradiation [45]. They observed that OXPHOS and glycolysis are decreased by two times or more within one hour after irradiation together with increase in DNA damage (maximum at 30 minutes after irradiation), which are caused by the oxidative effects of Fe^{3+} peaking at one hour after irradiation. Glycolysis was restored in six hours after irradiation while OXPHOS – in 24 hours after irradiation. Inhibition of glycolysis reduced oxygen consumption rate (OCR), ATP production and increased residual DNA damage while reducing survival of all tested cell lines after irradiation [45]. In turn, inhibition of the mitochondria only increased DNA damage in six hours after irradiation. The loss of p53 in HCT116 cells reduced respiration recovery and recovery of DNA damage in 24 hours after irradiation. These data suggest that glycolysis is the primary fuel source for the DNA repair during mitochondrial shutdown after irradiation.

Accordingly, mitochondria membrane potential decreased in the irradiated human liver cancer HepG2 cells, leading to damage of mitochondrial DNA, apoptosis and decreased cell proliferation. This effect was inhibited by pharmacological pre-inactivation of NADPH or application of mitochondria targeted antioxidant MitoQ [46]. In addition, depletion of mitochondria by incubation with low concentrations of ethidium bromide inhibited DNA damage however cell colony formation was decreased. Thus, protection of mitochondria improved cell survival and mitochondria promoted RR [46].

In contrast, in MiaPaCa pancreatic cancer cells, mitochondrial depletion increased RR and colony formation (and lower proliferation rate without irradiation) with unclear mechanisms, although higher G2/M transition proteins were reported after irradiation in cells without mitochondria [47].

Accordingly to the above report, mitochondria depletion in H1299 lung cancer cells promote RR accompanied by activation of the NF-κB/PI3K/AKT2/mTOR pathway, however, direct effects of pathway inhibition on apoptosis or RR were not examined [48].

To summarize, the effects of mitochondria on RR and growth are cancer cell line specific. In liver HepG2, breast cancer MCF-7, colon cancer HCT116 and glioblastoma U87

(all p53 wt) mitochondria promote RR whereas in H1299 and MiaPaCa (both are p53 null) cancers mitochondria inhibit RR.

Mitochondria induce immune reaction to radiation

Mitochondrial content, especially IR-damaged or IR-oxidized components, can act as damage-associated molecular patterns (DAMPs), activating an inflammatory response upon release in the cytosol or from the cells [49].

Specifically, apoptotic cells release mitochondria that are highly inflammatory in terms of recruiting macrophages and neutrophils [50]. It was demonstrated that mitochondria specific lipid cardiolipin acts as a main mtDAMP molecule [50].

The mitochondrial antiviral signaling protein (MAVS) is an innate antiviral immune signaling molecule, which is overexpressed in multiple cancers and which depletion reduces cancer cell proliferation, inflammasome expression and activation [51]. This molecule is involved in radiation response via its oligomerization mediated by radiation-induced ROS [52]. MAVS participates in radiation induced IFN-β and IFN-stimulated gene expression. MAVS complexes promote the nuclear translocation of the NF-κB and IRF3/7 transcription factors and thereby elicit the innate antiviral response [52].

Moreover, mitochondria regulate innate immunity in response to irradiation by releasing of the damaged mitochondrial DNA and RNA to cytoplasm, causing the induction of type-I interferon response by RIG-I–MAVS pathways synergising with cGAS/STING response and DNA-DSBs [27–29].

It would be important to further understand how mitochondria regulates macrophage polarization and T-cell differentiation in response to radiation in cancer microenvironment.

Mitochondria transfer and transplantation in cancer

Effects of mitochondria transfer on cancer cell survival

Intriguingly, mitochondria can be exchanged between cells by either intercellular tunneling nanotubes (TNT) [9–12], via large extracellular vesicles (EV) [13–15] or by the gap junctions [16, 53].

Mitochondrial transfer promotes cell survival including cardiomyocytes [14], virus infected cells [17], promotes brain regeneration after chemotherapy [19] or after cardiac arrest [54], repair injured glomerular endothelial cells [55] or promote bone formation [56].

In the cases of cancer cells, mitochondrial transfer increases apoptosis resistance of the acute myeloid leukemia cells [20, 57] and confers glioblastoma resistance to TMZ [58, 59]. The mitochondrial transfer between astrocytes and GBM cells promotes self renewal and proliferative properties of GBM and depends on actin and GAP43 [60].

Apparently, mitochondrial transfer occurs when recipient cells have deficiency in the mitochondrial functions [61–64].

Typically, the source of the mitochondria are stromal cells such as endothelial cells, MSCs or pericytes [65], which are capable of migrating to cancer sites [59], generating a huge amount of EV that contain mitochondria [13–15] and which EV have cancer homing ability itself [66, 67].

Importantly, mitochondrial transfer from the MSCs to macrophages induced certain M2 markers and repressed pro inflammatory cytokine production including TNF-a, protecting lungs from the LPS induced injury [13, 68].

Accordingly, in the lung fibrosis model, mitochondrial biogenesis in MSC was enhanced by the combination of iron nanoparticles and pioglitazone leading to enhanced mitochondrial transfer and effective therapy of pulmonary fibrosis [69].

In addition to the effects on the innate immune system, MSC mitochondria transfer transdifferentiates Th17 cells towards Treg phenotype [70].

All together, effects on immune cells by the mitochondria transfer resemble a pro-cancerogenic microenvironment, however direct experiments are needed. Moreover, inhibition of mitochondrial transfer or effects of such transfer might be beneficial for cancer treatment [59].

So far, we have found only one paper describing the effect of radiation of the TNT mitochondrial transport from GBMs stem-like cells from a single patient in which TNT formation was mitochondria transfer was accessed after irradiation in 3-D structures with mixed results [71].

Effects of mitochondrial transplantation on cancer cell survival and radioresistance

Mitochondria transfer promotes cancer development and RR. In contrast, exogenous mitochondria transplantation can suppress cancerogenesis and promote radioresistance.

Specifically, it has been observed in multiple cancer models that transplantation of mitochondria inhibits proliferation [30–33] and induces radiosensitivity [34].

In the pioneering work of Chao Sun isolated mitochondria from human astrocytes retained its membrane potential and was endocytosed into glioma U87 cells [34]. Transferred mitochondria enhanced TCA pathway and aerobic respiration but also attenuated glycolysis and decreased proliferation of cells, xenograft tumors and increased apoptosis. The radiosensitivity of cells and xenografts was also increased [34]. This is in agreement with a report that glycolysis plays a pivotal role in radioresistance [45]. In addition, this prompte the hypothesis that depletion of endogenous mitochondria is not equal to repletion by exogenous mitochondria in terms of evaluating mitochondrial effects on RR.

Accordingly, mitochondria freshly isolated from mice livers retained membrane potential and were consumed by H22 cells and promoted apoptosis annexin staining [31]. The growth of hepatocellular carcinoma with exogenous mitochondria was half as much as control and more apoptotic cells were detected in the tumors. Consistently, more Bap and activated caspases and less p-Bad were detected in the tumor. Notably, hexokinase activity and lactate dehydrogenase activity among other glycolytic enzymes were lower in tumor tissue with mitochondria again pointing at reduction of glycolysis function [31].

The same group studied the effect of mitochondria transplantation on the malignant melanoma [32]. Accordingly, mitochondria transfer to the cell inhibited ATP, lactate and pyruvate production and cell proliferation while increasing apoptosis stain. In comparison to control, female mitochondria was more effective than the male one. Accordingly, the growth of subcutaneous melanoma was substantially reduced and corresponding reduction of glycolytic enzymes induction of apoptosis related protein and autophagy were detected in tumors with female mitochondria being much more effective than male [32].

Consistent with in vitro observation indicating that the absence of mitochondria might promote cancer growth and radioresistance, in vivo, in breast cancer, histological evaluation of electron microscopy images revealed that in the majority of cases (59 %) the mitochondria was absent and this correlated with the more anaplastic phenotype, while cells were more differentiated when mitochondria appeared normal [72].

Accordingly, mitochondrial transport into MCF-7 breast cancer cells induced apoptosis and drug sensitivity [33]. The further investigation revealed that mitochondria conjugated

with internalizing peptide induced necrosis in the model of triple negative breast cancer [73, 74].

Conclusions

Our analysis of the published data highlights two somewhat contradictory sets of results.

First – cell mitochondria or mitochondria acquired from the intercellular transfer promote cell survival and induced chemo or radioresistance in the majority of cases.

Second – in a few cases, cell mitochondria or mitochondria acquired by mitochondria transplantation repressed cell survival, chemo or radioresistance.

It shall be noted that the cases associated with mitochondria induced cell death upon transplantation were associated with partial reversal of the Warburg effect [31, 32, 34, 75]. Considering that glycolysis is pivotal for the repair of the DNA damage and cell survival, it is possible that this effect is deterministic in the success of mitochondrial transplantation [45]. One exception is the mTOR mediated repression of the HK2 in which increased lactate production was associated with decreased radiosensitivity. However, in this case the quantity of mitochondria was at physiological level and *in vivo* effects were not observed.

The results of mitochondrial transplantation inhibiting the cancer growth will need to be compared with other developing approaches and standard treatment [76].

The question of mitochondria delivery to tumors is yet to be addressed and one of the possible options is delivery by the MSCs, which have an ability to travel to tumor and metastatic sites, produce a large quantity of exosomes including those containing mitochondria and also can be loaded with nanoparticles with treatment modalities including radiosensitizers or drugs [67, 77].

In the majority of cases, physiological mechanisms of mitochondrial transfer are beneficial for normal or cancer cell survival and metastasis [78–80]. A few reports suggest that inhibiting the natural mitochondrial transfer [20, 78] or consequences of such transfer [59] represses tumor formation and we believe that deeper investigation of these mechanisms will lead to the development of anticancer drugs.

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Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Финансирование. Исследование выполнено при финансовой поддержке гранта Российского научного фонда (No 23–14–00220).
Участие авторов. Статья подготовлена с равным участием авторов.
Поступила: 20.11.2023. Принята к публикации: 27.12.2023.

Conflict of interest. The authors declare no conflict of interest.
Financing. The research was carried out with the financial support of a grant from the Russian Science Foundation (No. 23–14–00220).
Contribution. Article was prepared with equal participation of the authors.
Article received: 20.11.2023. Accepted for publication: 27.12.2023.