Impact of Ionizing Radiation on Mitochondria in Carcinogenesis and Radiosensitivity of Cancer Cells

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Objectives: Mitochondria posses' central power house for cells is a double helical structure. Inner folded membrane harbors the OXPHOS system (complex I-IV, F1F0 ATP synthase). Double stranded circular DNA molecule carries 16,569 base pairs that encode 37 genes. Ionizing radiation activates mitochondrial genes epigenetic control by transcription, translation of gene expression and protein synthesis. This researcher intend to observe the impact on Mitochondria morphology, epigenetics, signaling pathway, mitophagy in response to ionizing radiation (IR) that is also growing attention for cancer therapy.

Methods: Review mitochondria research in last five years from PubMed to overview the ionizing radiation both low linear energy transfer (LET; photons, X and γ-radiation) and high LET particles (protons. α-particles and heavy ions) on mitochondria and radiosensitivity for the further management of cancer patients.

Results: Last 10-20 years study explored IR impacts on mitochondria (MELODI & DoReMi study).

Low dose radiation (< 0.1 Gy) impact: Cellular biogenetics and biosynthesis induce specific gene can cause increase activation of proteins, intra and intercellular signaling, communication. Thus, induce ATP production, ROS, mitochondrial dynamics change, immune response (Inflammatory vs non inflammatory). Non linear responses also induce low dose hermetic and adaptive responses, non targeted effects (NTE), genetic instability, cell proliferation. Low LET IR can inducing big deletion like loss of 4977 base pairs (8470-13,446) coding vital for genes such as ATPase, NADPH dehydrogenase and cytochrome C oxidase. Less deletion observed in tumor cells.

High dose radiation (>1 Gy) impact: It can be received in human by radiotherapeutic doses or by accidents lead to epigenetic control on mitochondrial activity and functions. Effects cause structural changes in cells, Mutations, malignant transformation, cancer and cell death (apoptosis and even necrosis), programmed cell death. High-LET C ions cause more harms; keeps long lasting imprints on tumor cells separating from normal cells in same tissue.

Following IR exposure three pathways (intrinsic, extrinsic and ceramide dependent pathways) are activated. That leads to activation of Capcase3, 6 and 7 and subsequent cell degradation, apoptosis and cell death. Damaged mitochondria removed by mitophagy (activation of PINK protein). Mitophagy can induce radioresistance and can resist oxidative stress in irradiated tumor cells.

IR response in carcinogenesis and radiosensitivity on cancer cells: IR acts on DNA methylation and serve as a marker of radioresistance. Delayed effects induce genomic instability both in vivo and vitro that acts on cell transformation and carcinogenesis. Mitochondrial dysfunction is more evident in later years; mutation in complex II, excessive ROS production and cells are in oxidative stress and changes epigenetic regulation hallmarks of carcinogenesis. Even in aerobic condition ATP production occurs from glycolysis instead of OXPHOS (Warburg effect). Long term oxidative stress cause irreversible

damage; increase apoptosis. Mitochondria try to adapt in highly proliferative cancer cells. Lactate production and release linked to radio/chemo efficacy. In cancer cells, LDHA regulates lactate and inhibition of LDHA reduces tumor metastasis. Reduction of lactate efflux in gliomas (reduce Glutathione) increased sensitivity to IR. ROS also makes preferential target for anticancer therapy. On the other hand, hypoxia and glucose metabolism beneficial to RT. IR demethylated tumor cells and acetylation of histone in proteins. Maternal mitochondria is destroyed.

Radiosensitivity of tumor cells depends on several factors: type of tumor cells, presence of cancer stem cells, types and dose of radiation and tumors microenvironment. Dysfunctional mitochondrial enzymes also cause genetic instability insist metastasis. Metalloproteinases (MMPs) involve in translocation and metastasis. In reverse, radiosensitization is associated with a decrease MMP, increase ROS, decreases Gluathione levels and activation of Capcases. Cermaide production in C-ion radiation can cause early and late apoptosis in radiosensitive and delayed radioresistant cells respectively. Radioresistant cells (SQ20B) in head neck squamous cell carcinoma, face late apoptosis affected by high LET in every steps of degradation. Photon radiation significantly decreases SQ20B cell survival. Some cells still resist apoptosis process and anastasis.

Conclusion(s): Mitochondria play a central role in cellular homeostasis. Mitophagy, mROS, epigenetic control can be targeted for radiation therapy. Mitochondrial reprogramming can able to reverse cancer cell radiation resistance. Radioresistant U87 cells of Glioma usually radioresistant can be sensitized by reprogramming showed radiosensitivity in mice. OXPHOS to glycolysis increase radioresistance whereas, reverse paths increase radiosensitivity. Radiation quality, dose, cancer cell type are effective for cancer treatment.