



Natural Compounds Target Mitochondrial Alterations in Cancer Cell: New Avenue for Anticancer Research

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Mitochondria are semi-autonomous organelles that play essential roles in cellular metabolism and programmed cell death pathways. Functional, structural and genomic alterations in mitochondria have been associated with carcinogenesis in different cells. Some of those alterations may provide a selective advantage to cells, allowing them to survive and grow under different stresses. Due to the specific alterations that occur in cancer cell mitochondria, these organelles may provide promising targets for cancer therapy. The development of drugs that specifically target metabolic and mitochondrial alterations in tumor cells has become a matter of interest in recent years, with several molecules undergoing clinical trials. This Editorial focuses on the most relevant mitochondrial alterations found in tumor cells, for cancer therapy.

Since transformed cells have metabolic and mitochondrial needs that differ from their normal counterparts, mitochondrial alterations in cancer cells can offer a window of opportunity for efficient and selective anti-cancer therapy. This principle of oncogenic alterations is in fact the basis for new anticancer research and can also be used with success when targeting altered aspects of tumor cell mitochondria. All the previous published works in this regard suggest that there is no mitochondrial alteration common to all cancer types, which excludes the use of a single mitochondrial-acting agent for all cancers. There are candidate natural compounds, in different stages of drug development, which have been described to interfere with mitochondrial functions in tumor cells, leading to cell cycle arrest and/or death by apoptosis or necrosis.

Natural compounds have long been studied for their anticancer properties. Chemicals resemble ubiquinone can act to inhibit complex II via competitive binding such as vitamin E analogs. For instance, agents such as α -tocopherol succinate (α -TOS) a vitamin E analog, represent excellent candidates for cancer therapy. α -TOS competes with ubiquinone in binding to Q sites on complex II of the respiratory chain. This connection disrupts the electron flux, destabilizes the mitochondrial membrane consequently and generates superoxide anion. Furthermore; α -TOS promotes Bax translocation to the mitochondrial outer membrane and subsequent cytochrome c release resulting in programmed cell death. Resveratrol, a natural stilbene, was shown to act as a mitocan, compounds which specifically target mitochondria in tumor cells. Resveratrol can act directly at several different sites from complexes I to III, possibly competing with ubiquinone binding sites. Moreover, it interacts with complex V, the F₀-F₁ ATP synthase. Although Resveratrol is generally considered a potent antioxidant, it can also act in favor of oxidative status in cells, inducing apoptosis through the mitochondrial pathway. The chemotherapeutic properties of Curcumin, the major constituent of turmeric powder, have been reported as inducing lung cancer cell death through Bax up regulation

and Bcl-2, Bcl-XL down regulation, causing AIF and cytochrome c release. Curcumin is currently undergoing phase II/III clinical trials in different types of cancer, including colon and cervical cancers, with promising results in some Cases.

Sanguinarine, a natural benzyloquinoline alkaloid, interferes with mitochondrial calcium loading capacity and causes an increase in p53 expression. It was reported that complex II is a mitochondrial target for Sanguinarine, which may explain the effects on the respiration. Other studies confirmed that Sanguinarine causes apoptosis via mitochondrial depolarization and cytochrome c release, ROS-induced DNA damage, glutathione depletion, and cleavage of poly (ADP-ribose) polymerase and β -catenin. Berberine, an alkaloid derived from plants of the Berberidaceae family, has also been described to act as an anticancer agent, exerting several direct effects on mitochondria function, including inhibition of mitochondrial complex I and interaction with the ANT.

Mitochondrial alterations in the context of metabolic reprogramming in cancer cells are attractive targets for a novel therapeutic approach. However, there are still many obstacles to a full application of this approach. Not only it is important to identify the specific mitochondrial alteration in each tumor type for better therapeutic achievement but it is also critical to understand how untargeted tissues are affected by these new therapies. As described in this article, there are natural compounds with the specific potential of targeting tumor mitochondria and act as mitocans. Although only a few of these compounds move to subsequent clinical trials. Also, mitochondria have key roles in both cell life and death, which makes a challenge to selectively targeting of mitochondria abnormalities in tumor cells without any functional consequence for their normal counterparts. However, there are no extremely effective drugs to treat most cancers. There is a general call for new drugs that are highly effective, possess low toxicity, and have a minor environmental impact. Novel natural products offer opportunities for cancer therapy. For best effect and low toxicity, mitochondrial changes in cancer cells can be new potential targets for efficient and selective anti-cancer therapy.

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