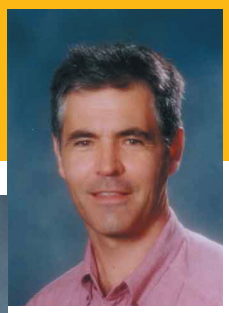
Editorial



Stephen J. Ralph (above) and Jiri Neuzil (left)

Mitocans, a class of emerging anti-cancer drugs

A significant number of the current anti-cancer drugs in use originated from traditional remedies and medicines sourced from nature. Starting with these crude products has been the basis for novel anti-cancer drug discovery, leading to the development of more highly refined derivatives with greater activity and reduced toxicity to normal tissues. This issue of *Molecular Nutrition & Food Research* is devoted to a new way to fight cancers based on drugs, many of which originate as nutritional or natural compounds, and which share in common their ability to disrupt energy flows inside cancer cells, particularly by acting on the mitochondria – the powerhouses inside cells. The goal of this issue is to highlight the underlying principles by which such agents show strong selectivity for killing primarily the cancer cells, with minimal side-effects on the body's normal cells and tissues. The advantage of targeting mitochondria is that it can be likened to an electrical overload that shorts out the power circuits and blows the fuse. In effect, this often manifests as a high level of reactive oxygen species (ROS) that upset the redox balance of cellular systems, activating programmed cell death pathways (apoptosis) leading to destruction of the cancer cells.

> *"This issue should provide the reader with a solid overview of (…) mitocans – the development of novel drugs, many derived from natural compounds that target the mitochondria to selectively kill cancer cells."*

Each of the articles reviews the different modes of action of the novel natural and synthetic drugs and their relationship to the mitochondria as the ultimate destruction target for selectively inducing death of cancer cells by apoptosis. In the first article we summarize a classification system based on eight groups belonging to the family of mitochondrially targeted anti-cancer agents (mitocans). The article largely concerns the nature of mitochondria and their properties in cancer cells that makes them an ideal candidate as a drug target by which cancer cells can be killed *via* the activation of the cell death (apoptotic) signalling pathway. Rodríguez-Enríquez *et al*. then focus on the differences in energy metabolism, including glycolysis and oxidative respiration levels operating inside cancer cells compared to normal cells. The authors provide support for strategies aimed at deleteriously affecting the energy flows in cancer cells, including both cytoplasmic glycolysis as well as the mitochondrial metabolic pathways.

The next three articles deal with related topics in terms of different mitocans and the way in which they work to bring about death in cancer cells by affecting various components important to mitochondrial function. Hail and Lotan consider the use of chemopreventative agents that will slow the progression of, reverse, or inhibit cancer development, reviewing the intrinsic apoptotic pathway and agents that target mitochondrial bioenergetics. The list of agents described include many natural and synthetic derivatives such as retinoids based on vitamin A, vanilloids such as the chilli plant derived hot spice, capsaicin, the natural pesticide agents, rotenoids, and the polyphenolic compounds like the green tea derivatives and curcumin, a compound derived from yellow curry spice, tumeric. Kurtoglu and Lampidis discuss the role of positively charged moieties that facilitate drug uptake by cancer cells into mitochondria and associated toxicity to cardiac tissue. They also discuss the problem of the multidrug resistance genes in preventing drug access into cells and the importance of delocalised cationic structures in targeting the mitochondria of cancer cells. The article concludes with the benefits of combining a number of different agents together. The aim is that by inhibiting dependency on the glycolytic pathway for energy production in cells with other drugs that disrupt mitochondrial energy flow or other vital functions may provide opportunities for enhancing the selective killing of the "difficult to treat" hypoxic cancer cells residing inside tumours. The article by Berridge *et al*. is devoted to the process of pore opening in the mitochondria and discusses the nature of the pore complexes that bridge between the mitochondrial cytoplasmic face and the inner matrix. Compounds that disrupt the integrity of this mitochondrial permeability channel and that exhibit anticancer activity are also discussed. Tonissen and Di Trapani consider the major redox control mechanism affecting many viscinal thiol containing enzymes and proteins. Known as the thioredoxin system,

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this series of thiol containing molecules exists in both the mitochondria and cytoplasm to help regulate the redox balance. This system can act as an anticancer target because disrupting redox control *via* thiol-disulfide exchange affects many of the regulatory circuits operating inside the cell and if specifically disrupted in cancer cells, can selectively induce their death. There are many different compounds, either metal based or organic in nature, or mixtures of both that have the ability to disrupt thiol redox mechanisms in this manner.

The article by Kagan *et al*. concerns one of the earliest events in the capitulation of cancer cells as they become committed to undergo apoptosis in response to overburdening with ROS. This event is localised to occur in the inner membraneous space between the two lipid bilayers of the mitochondria, when cytochrome *c* is released from a complex with cardiolipin as one of the early trigger signals leading to cell death. Several potential strategies are discussed for designing drugs that may interfere with the cytochrome *c*/cardiolipin complex in cancer cells as a possible means for activating cancer cell apoptosis. The next three articles review three different mitocans that each target and kill cancer cells. The first of these (by Aggarwal *et al*.) concerns a very interesting nutritional substance, resveratrol, found in red pigmented foods like grapes and berries that exerts a wide range of anticancer effects. Zhao *et al*. then discuss the actions of vitamin E analogues as potent pro-oxidant compounds that can selectively act in cancer cells to increase ROS production in mitochondria leading to apoptosis. Finally, Fulda describes the properties of betulinic acid, a drug derived from the bark of certain plants that exhibits potent antitumour properties and has a range of activities inside cancer cells, with little effect detected on normal cells and tissues.

The last article in the series is devoted to the very important concept of targeting the cancer stem cell population in tumours with mitocans. These cells have proven very resilient to drug treatment and as a result, tumours regrow because the stem cells have the capacity to continually repopulate the tumour. Hence, it becomes vital to find anticancer therapies that will eliminate the tumour stem cells. This has recently proven to be achievable and will no doubt become an area of great interest in future developments in this subject. This issue should provide the reader with a solid overview of the many facets of this burgeoning field of mitocans – the development of novel drugs, many derived from natural compounds that target the mitochondria to selectively kill cancer cells.

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