Microreviews in Cell and Molecular Biology 2012

Mitochondria and Cancer

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Key Words:
Mitochondria, cancer, DNA, mtDNA, tumor, mutation

Mitochondria are the organelles of the cell that produce energy by cellular respiration and regulate cell death. This process uses steps such as glycolysis and the Krebs cycle to turn sugar molecules into chemical energy stored in the bonds of the molecules. Cancer cells show a decrease in sugar breakdown and perform glycolysis but do not perform the cycle of cellular respiration. Cancer cells ability to suppress further breakdown of sugar molecules by suppressing the function of mitochondria allow the cancer cells to reproduce uncontrollably. It was thought that cancer cells permanently damage mitochondria leaving them unable to function. Studies suggest that Dichloroacetate (DCA), an odorless, colorless, small molecule, causes regression of cancer cells. Researchers believe the use of this molecule in combination with other treatments will lead to curing several cancers[4].

Introduction

Mitochondria require oxygen to synthesize Adenosine Triphosphate (ATP) in oxidative phosphorylation for energy and cell regulation. The suppression of mitochondria allows cancer cells to grow and duplicate in low-oxygen environments that lack sufficient blood supply. When a cell does not undergo oxidative phosphorylation, glycolysis is used to produce ATP for the cell. Cancer cells have the ability to reproduce without apoptosis which suggests that mutations in the mitochondria not only allow the cancer cells to survive in low oxygen and in low blood environments, but also allow the cells to reproduce without any mechanism of regulation.

Cancer cells require a minimal level of activity from the mitochondria to perform glycolysis and duplicate. The ability of mitochondria to resume activity shows that mitochondria are not destroyed in cancer cells, but rather they are suppressed. Mutations in the mitochondrial genome such as methylated cytosine and hydroxymethyl cytosine act as an on/off switch in DNA methylation. The DNA of the mitochondria is distinct from the nuclear genome because it follows a strict maternal inheritance pattern. The mitochondria are able to duplicate in the absence of mtDNA by means of the nuclear DNA being transcribed and translated for replication. Nuclear DNA encodes many of the proteins found in the mitochondria, while mtDNA encode for some proteins of the nucleus they also encode for the 12s and 16s rRNA's and tRNA's that are required for the respiratory chain.

When mitochondrial reactive oxygen species (ROS) reach a high level in the cell it triggers apoptosis. When mitochondria are suppressed it allows the ROS to increase, which can contribute to cancer formation. The increase in ROS causes the inner membrane of the mitochondria to slow production of electrochemicals that regulate ROS production and redox balance. This "stalemate" between the inner and outer membranes of the mitochondria causes the production of ATP to be inhibited.

Recent Progress

Recent research shows defects in cancer-related mitochondria. These defects include altered expression and activity in the cellular respiratory chain, decreased oxidation of NADH, as well as mutations to the mitochondrial DNA[2]. With the role of mitochondria in the development of cancer, to resist apoptosis and avoid anticancer agents, more focus is being placed on this area of study to develop treatments not only for cancer but other diseases that suggest mitochondrial involvement. Studies have shown that when tumors were injected with normal functioning mitochondria there was a decrease in

tumor growth. The uptake of glucose by tumors is used as a diagnostic tool. The administration of DCA to cancer cells has shown to increase mitochondrial action and cause a regression in tumors[4].

Using straightforward laboratory techniques analysis of germline homoplasmic mutations can be achieved[2]. The challenge then is that the wild type gene function along with the mutant gene type may co-exist. There have been cancer cells linked to somatic and germline mitochondrial DNA mutations. This has increased the study of mitochondria's role in cancer development and a rise in a new field of epigenetics which studies the processes that control gene expression. This new field offers a bright future of developing new gene therapies to treat diseases. The DNA molecule and the process of replication are strongly influenced by environmental and chemical conditions in the early stages of development. This outside influence, such as radiation exposure and carcinogenic chemicals, alters the genes and can change the function of a gene. Cancer cells show a dysfunction in the epigenetic process.

Discussion

The presence of mtDNA found in cancer cells is consistent with alterations in the respiratory chain and apoptosis activity of the cell. The process of introducing normal mitochondria suggest that there is a possibility of developing new treatments by reactivating suppressed mitochondria to reduce tumor growth. Many of the mitochondrial gene mutations in cancer are linked to the oxidative phosphorylation and redox regulation. The importance of mitochondria's role with cancer development has been shown by the exchange of mtDNA between tumor cells and normal cells with a decrease in tumor activity. Environmental conditions increase the risk of developing cancer by increasing the occurrence of damage/mutations to the mtDNA. Mutations that suppress mitochondrial function allow cancer cells to replicate through glycolysis despite environments low oxygen and low blood supplies.

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