Mitochondrial ROS and cancer drug resistance

The repetitive and continuous circle of resistance to anti-cancer agents was a primary focus of the above-titled articles recently published in Pharmacological Research. Gaining a basic understanding of why so many (possibly all) drugs currently available against cancer eventually fail will provide important information that will hopefully minimize the occurrence of resistance. The unique and highly dynamic nature of each patient's cancer means that different therapies are applied in order to achieve the best response. These therapies, whether chemo, radio or targeted agents (targeted agents, such as gefitinib are typically used against a specific defective gene) provide relief via different mechanisms. However, decreased sensitivity towards these therapies remains a major problem that is common and occurs within cancer cells. Our article therefore sought to identify the emerging patterns and characteristics that strongly associate with drug resistance. Based on several research investigations from our lab, as well as other groups, a significant increase in the levels of cellular reactive oxygen species (ROS) is thought to be strongly linked with resistance. ROS are free oxygen radicals that can become involved in biochemical reactions in the body, and alter the "normal" functions or processes of the cell. In most animal cells, the mitochondria is the primary "engine room" tasked with the utilization of the food we eat to generate energy. The mitochondrial is involved with numerous metabolic reactions in order to provide energy in the form of adenosine triphosphate (ATP), which is the energy "currency" of the body. Taking a step back, we know that a major difference between cancer and non-cancer cells involves differences in metabolism. As would be expected, cancer cells require more energy (ATP), and so device alternative ways of making adequate supply which is critical to the survival and progression of the defective tumor cells. Hence, accompanying such metabolic alterations is the corresponding rise in ROS. Findings from our study using a specific anti-cancer agent showed that the structure, as well as function of the mitochondria was adversely impacted in response to long-term treatments with the drug. Accompanying the mitochondria defect was significant increase in cellular ROS. Such sustained high level of ROS has several implications within the cell. For example, in addition to driving unregulated signaling events, ROS can affect other "normal" genes or processes within healthy cells, thereby setting off a cascade of chain-reactions that promotes tumor growth and progression. It is thought that these events may potentially contribute to drug resistance or failure.

A major goal of our study is to identify, characterize and validate with a high degree of precision those genetic signatures, as well as cellular processes that will provide accurate and reliable determination of resistance as early as possible. Such knowledge will enable and empower doctors, and cancer management teams to understand the processes and hallmarks that predict resistance, and make alternative arrangements with treatment strategies. Early-stage cancer is often very responsive to therapy and offers the greatest chance of achieving a successful and complete cure. Late cancer detection and the resulting poor survival rates is linked to the spread of cancer to other secondary sites, thus making it difficult to achieve optimum targeting and therapeutic efficacy. In a similar vein, early and accurate detection of drug failure provides the best chance of alternative interventions in order to ensure the cancer cells are effectively targeted and

remain responsive to treatments.

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Publication

Mitochondrial ROS and cancer drug resistance: Implications for therapy.
Okon IS, Zou MH
Pharmacol Res. 2015 Oct