Hypothesis

Guardian of the Furnace: Mitochondria, TRAP1, ROS and Stem Cell Maintenance

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Abstract

Mitochondria are key to eukaryotic cell survival and their activity is linked to generation of reactive oxygen species (ROS) which in turn acts as both an intracellular signal and an effective executioner of cells with regards to cellular senescence. The mitochondrial molecular chaperone tumor necrosis factor receptor associated protein 1 (TRAP1) is often termed the cytoprotective chaperone for its role in cancer cell survival and protection from apoptosis. Here, we hypothesize that TRAP1 serves to modulate mitochondrial activity in stem cell maintenance, survival and differentiation. © 2013 IUBMB Life, 66(1):42–45, 2014

Keywords: *mitochondria; stem cells; cancer; TRAP1; reactive oxygen species*

Introduction

Tightly regulated external and internal signal processing control the two basic characteristics of stem cells: first, the ability to self-renew and second, differentiation into diverse specialized cells. Extensively interlinked signaling pathways control self-renewal through activation of defined sets of genes regulating the fine balance between self-renewal and differentiation (1, 2). Under normal physiological conditions, controlled imbalances in these signaling systems induce differentiation. Similarly in differentiated cells uncontrolled changes in these signaling systems can induce and drive cellular transformation and oncogenesis (3). Seemingly, stem cell phenotypes have also been observed in cancer as so-called cancer stem cells (4, 5).

Abbreviations: *ROS, reactive oxygen species; TRAP1, tumor necrosis factor receptor associated protein 1*

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Homeostatic balance in normal aerobic eukaryotic cells is required to maintain mitochondria, and fine-tuning the bioenergetic systems within stem cells becomes extremely important to maintain phenotype (6). Reactive oxygen species (ROS) produced as a by-product of mitochondrial activity, is often detrimental to cells as it causes DNA and protein damage, but this viewpoint is shifting slightly due to the role ROS plays in signaling and differentiation (7–9). Under hypoxic conditions, cells can shift from mitochondrial oxidative phosphorylation to cytosolic aerobic glycolysis, known as the Warburg effect, to produce ATP (10–12). The Warburg effect, thought to provide the building blocks required by the rapidly proliferating cells and protect the mitochondria from ROS-induced membrane damage and initiation of apoptosis, has been reported in rapidly proliferating cancer, cancer stem cells and normal stem cells (13–16). Molecular chaperones play a strong role in preventing apoptosis and the mitochondrial molecular chaperone, TRAP1, has been shown to protect cells against ROS-induced damage in cancer cell models (17–20).

Mitochondria and ROS—The Cellular Furnace

Beside their vital role in energy generation, mitochondria also play essential roles in processes such as apoptosis, cellular proliferation, calcium homeostasis and steroid metabolism (21). During oxidative phosphorylation, the respiratory complexes leak electrons to oxygen producing the free radical superoxide