Mitochondrial mass and DNA repair in breast cancer stem cells

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Two recent studies by Lisanti and co-workers provide new insights into the importance of mitochondria and the cancer stem cell and its resistance to therapy. Lisanti demonstrated that WNT1/FGF3 enhances breast cancer stem cell (BCSC) expansion via a paracrine loop associated with the induction of mitochondrial biogenesis [1]. Furthermore, Lisanti showed that mitochondria are enriched within BCSC, and that mitochondrial enriched human BCSC are resistant to DNA damage [2]. These finding are consistent with the prior findings that stem cells are resistant to current therapies due to increased DNA repair capacity. The findings by Lisanti are also consistent with prior studies in which an RNAi screen identified Wnt as an inducer of mitochondrial biogenesis [3]. Importantly these studies add to the growing understanding that, in contrast with the reduction in mitochondrial mass in normal stem cells, mitochondrial protein abundance is increased in cancer stem cells.

The studies by Lisanti provide important evidence for a direct link between cancer stem cells and altered mitochondrial metabolism within a heterogeneous breast tumor population. CSCs preferentially perform oxidative phosphorylation over glycolysis compared to non-CSCs and several mechanisms have been described. Firstly, oncogenes, including c-Myc, are sufficient for the induction of OXPHOS and the induction of CSCs [4, 5]. Secondly, metabolic genes are mutated in CSCs in different cancer types. Those mutations in metabolic enzymes may cause gain of function or loss of function. The normal function of isocitrate dehydrogenase-1 (IDH1) and IDH2 is to metabolize isocitrate and NADP+ to yield α-ketoglutarate (αKG) and NADPH [6], [7]. Mutations in IDH1 and IDH2 have recently been identified in a number of different tumor types including prostate cancer. These alterations are gain of function mutations because they drive the synthesis of the 'oncometabolite’ R-2-hydroxylglutarate (2HG). 2HG-producing IDH mutants repress FBP1 in breast CSC? As Snail is increased in luminal and basal breast cancer, perhaps the Snail/G9a mediated repression of FBP1 which reduces ROS, may thereby promoting self-renewal potential of CSCs which are exquisitely sensitive to the level of ROS. Given the increased biogenesis of the mitochondria of tumor initiating cancer stem cells and reduced biogenesis of normal stem cells future studies may provide important insights into the distinct mechanisms governing these key cell types.

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