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Cancer stem cells metabolism – Therapeutic opportunities

Amit Subedi

It is widely considered that in cancer cells escape cell cycle regulation and continues freaky cell proliferation. Further, free uptake of glucose by cancer cells and conversion to lactate, termed Warburg Glycolysis, has been considered universal mode of cell cycle proliferation in tumor cells. However, this theory has been questioned with the emergence of tumor heterogeneity. Such heterogeneity do not exist as genetic heterogeneity but also functional heterogeneity where cells with same genetic make-up acts differently. Cancer cells with Warburg Glycolysis has enhanced proliferation and thus are likely to be a dominant population within a huge tumor mass. But are those proliferating cells really tumorigenic or are just soldier cells directed by other leader cells? Why can't tumor be cured by so many potent drugs against those rapidly proliferating cells? We must think out of box to answer these questions and accept every possibilities. In this paper, author has shown that indeed those proliferating glycolytic cells do not determine tumorigenicity. Author showed that indeed the tumor driving cancer stem cells rely more on OXPHOS. Further, those CSCs are again heterogeneous and inefficient targeting of CSCs could lead to selection and expansion of fittest CSCs clone leading to relapse. Indeed those resistant clone used Myc driven glycolytic pathway for their expansion with decreased tumorigenicity. This showed that oncogene like Myc do not have universal effect and are indeed context specific.

Introduction

MYC/PGC- Balance Determines the Metabolic Phenotype and Plasticity of Pancreatic Cancer Stem Cells

Sancho P. et al., Cell Metabolism, Oct. 6, 2015, Queen Mary University of London

Abstract

The anti-diabetic drug metformin targets pancreatic cancer stem cells (CSCs), but not their differentiated progenies (non-CSCs), which may be related to distinct metabolic phenotypes. Here we conclusively demonstrate that while non-CSCs were highly glycolytic, CSCs were dependent on oxidative metabolism (OXPHOS) with very limited metabolic plasticity. Thus, mitochondrial inhibition, e.g., by metformin, translated into energy crisis and apoptosis. However, resistant CSC clones eventually emerged during treatment with metformin due to their intermediate glycolytic/respiratory phenotype. Mechanistically, suppression of MYC and subsequent increase of PGC-1α were identified as key determinants for the OXPHOS dependency of CSCs, which was abolished in resistant CSC clones. Intriguingly, no resistance was observed for the mitochondrial ROS inducer menadione and resistance could also be prevented/reversed for metformin by genetic/pharmacological inhibition of MYC. Thus, the specific metabolic features of pancreatic CSCs are amendable to therapeutic intervention and could provide the basis for developing more effective therapies to combat this lethal cancer.