Review of “MYC/PGC-1a Balance Determines the Metabolic Phenotype and Plasticity of Pancreatic Cancer Stem Cells”

This paper addresses one of the hot topics in cancer research, how cancer cells modify their metabolism to allow uncontrolled growth. The dependence of cancer cells on anaerobic glycolysis rather than aerobic glycolysis and oxidative phosphorylation has been known for 50 years (The Warburg Effect).

In this paper then authors attempt to demonstrate that pancreatic cancer stem cells are in fact dependent on mitochondrial oxidative phosphorylation for the generation of energy.

Treatment with metformin which inhibits mitochondrial respiration leads to apoptosis of the pancreatic cancer stem cells. However alterations in the myc signaling leads to the development of resistance in this population.

The paper is particularly topical because of the recent interest in repurposing metformin, a drug usually used to treat type 2 diabetes, for use as an anti-cancer agent. There is some epidemiological evidence to suggest that those people on metformin are less likely to develop pancreatic cancer and to have improves survival if they are on this drug.

Preclinical animal studies have also shown a possible anti-tumour effect of metformin. However recent randomized trials have failed to show a benefit of metformin with current dosing regimens. The paper by Sancho et al. adds a further piece to this puzzle and potentially explains how resistance to such treatments can develop.

Finally, the other interesting aspect of this paper is the focus on pancreatic cancer stem cells. The existence of a stem cell hierarchy within pancreatic cancer remains a controversial subject.

There have been some papers that have suggested that pancreatic cancers may contain a small population of multipotent cells which have the capacity for self-renewal and potent tumorigenicity.

These cells are thought to also give rise to the great bulk of cells within the tumor which are more differentiated, have a limited life-span and hence are not in themselves tumorigenic.

The authors would appear to believe that this controversy has been settled and suggest that the use of anchorage independent growth or expression of CD133 is sufficient to isolate a pure population of pancreatic cancer stem cells.

Given that culture of cells in vitro is likely to significantly alter the behavior of these cells, the first methods has some issues. Furthermore CD133 selection has not yet been used in the context of freshly isolated primary pancreatic cancer cells to demonstrate that selection of pancreatic cancer cells based on this marker leads to an enrichment of tumorigenicity in a xenograft model.

I suspect that further work needs to be done before we can establish the nature of the pancreatic stem cell population if such a population exists.

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