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Perspective

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# Recent Developments in Cancer Metabolism

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To identify metabolic vulnerabilities in cancer is of a major importance to better understand the dependence of cancer cells on certain metabolic rewiring, and thus to identify new therapeutic targets. The majority of data provided in the past years relied on *in vitro* studies. Yet, to reach clinically effective conclusions there is a strong need for powerful systems that recapitulate the complexity of the *in vivo* environment. Notable examples that qualitatively changed the state of art are recent studies that highlighted the vast cancer metabolic heterogeneity in the *in vivo* environment, and the poor correlation between data observed in *in vivo* versus *in vitro* conditions [1,2]. Just to mention other relevant facts, the role of anaplerotic glutamine addiction was indeed shown to be overrated in culture conditions. It seems, in fact, that pyruvate carboxylation can support anaplerosis better than glutamine [3,4] and that *in vivo,* glutamine poorly contributes to TCA cycle in mouse lung tumors [1]. Considering that metabolic alterations have been suggested as criteria for patient stratification [5], the concept of "glutamine addiction" has been revisited and it is clear that reliable *in vivo* systems are strongly needed. In turn, cellular metabolism of cancer has been dramatically changing. It is now accepted that metabolites like lactate and ammonia are not only by-products of metabolism with limited biological functions, but rather important contributors for cancer cells growth. More specifically, lactate was recently suggested to bridge glycolysis with mitochondria feeding the TCA cycle [6]. Remarkably, ammonia seems to account for more than 20% of the glutamine synthesis in breast cancer cells [7].

A recent work done in Dr. Vander Heiden's laboratory echoed the findings in refs [1,2].

Authors showed that despite the same mutational initiating events, isogenic (K-Ras, p53 null) lung and pancreatic tumors use a different amino acids metabolism [8]. Tumor metabolism is regulated by a complex and poorly defined combination of cell intrinsic and extrinsic factors. Genetic alterations are sufficient to reprogram metabolism of cancer cells. Nevertheless, the *in vivo* environment may constrain the influence of genetic mutations on the metabolic phenotype [1,2,8]. This also suggests that rather epigenetic changes within the primary site may account for the evolution of tumors. In the future, it would be relevant for researcher to address thoroughly the role of the environment in influencing the epigenetics of cancer cells. A recent work published by Dr. Christian Frezza's group specifically shed light on this issue. Authors showed that TCA cycle metabolite fumarate can induces epithelial to mesenchymal transition (EMT) in cancer cells through epigenetics [9]. The connection between metabolism and EMT is quite fascinating being a phenomenon tightly connected to the acquisition of stemness traits in cancer.

Classical therapeutic approaches based on genetics have shown severe limitations in providing long-term remission for most cancers and especially advanced disease. This suggests that other factors than the mere genetic background may be better in predicting the evolution of tumors and for the design of new cancer treatments.

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