

Metabolism: A new frontier in cancer research

Abstract

Alterations in metabolic pathways and enzymes are found in many human diseases, including metabolic, immune and central nervous system disorders, and recently in cancer. As tumors share the common phenotype of uncontrolled cell proliferation they have to efficiently generate energy and biomass components in order to expand and disseminate. The required metabolic changes influence both glucose and lipid metabolism.

Keywords: cancer, metabolism, glucose metabolism, lipid metabolism

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Introduction

Uncontrolled proliferation, immortalization, the ability to differentiate and migrate, among others, are common features in different types of cancer. These cellular alterations are energy demanding and require an increased synthesis of cellular metabolites, and often the metabolism is altered to keep up with these changes.¹ Therefore, it was expected that the enzymes responsible for the control of the metabolism should be up or down regulated. Research by several groups has verified such altered regulation in cancer, which leads to metabolic reprogramming.² This knowledge might reveal new targets to involve in cancer development and can be used by the pharmaceutical industry to generate novel drugs.

This is validated by the approval of Agas and Celgene's enasidenib by the FDA. This drug modulates the metabolism and is used as a medication against acute myelogenous leukemia. Enasidenib is an inhibitor of the mutated isocitrate dehydrogenase (IDH2), one of the main enzymes of the citric acid cycle (also known as Krebs cycle), a central pathway which converts molecules coming from all 3 main catabolic pathways into intermediate metabolites that finally fuel the respiratory chain, the main energy providing process in cells. IDH enzymes usually metabolize isocitrate into α -ketoglutarate, a crucial step in the citric cycle. When mutated in some cancers, this enzyme starts producing 2-hydroxyglutarate, a metabolite that causes cell differentiation defects and impairs histone demethylation.³ While this approval highlights the promising role of anticancer drugs modulating metabolism, researchers have struggled to find other therapeutically useful targets in metabolic pathways.

Tumor metabolism

Cell metabolism as well as cancer development and growth is complex. The intermodulation between metabolic pathways and the plasticity of these routes, plus the capacity of tumor cells to adapt are factors that slow down the advances in their understanding. Factors

such as poor oxygenation, acidity and deprivation of nutrients, which normally cause cell death, are rapidly converted into promoters by tumor cells.^{4,5} The reprogramming of the glucose metabolism is a good example for this flexibility. Tumor cells typically exhibit a high uptake of glucose and are mainly metabolizing anaerobically. For many years, the explanation for that was attributed to the lack of oxygen, once the proliferation rate of tumor exceeds the angiogenesis. However, Otto Warburg (1927) verified that even in the presence of oxygen, tumor cells prefer to metabolize glucose into lactic acid. This process is known as anaerobic glycolysis and has been extensively studied throughout the years, but is still poorly understood.^{6,7} Recent studies demonstrated that tumor cells prefer the anaerobic metabolism because it more efficiently produces energy and basic metabolites for protein biosynthesis as compared to aerobic metabolism.^{8,9} These findings were confirmed in a study showing that one of the main molecule that control glycolysis and the anaerobic metabolism, the glucose-transporter (GLUT), was up regulated in breast tumor cell lines.¹⁰

To corroborate the complexity of cancer metabolism, it has been shown recently that some tumors also use the mitochondrial oxidative phosphorylations.^{11,12} Growing evidence of the importance of the glucose metabolism for tumor development and the need of new therapeutic targets, lead to the application of drugs inhibiting the glycolytic pathway as potential approach. Metformin for example, a drug already widely used in diabetes treatment, decreases glucose consumption and, consequently, also tumor growth.^{13,14}

Fatty acids also are extremely important for various cellular processes, as for example the synthesis of hormones, for the cell membrane lipids and serve as storable energy supply. Unlike normal cells that are dependent on lipid supply from the extracellular environment, e.g. extracellular medium or blood circulation, cancer cells use a pathway that allows an intracellular de novo lipid synthesis even if there is extracellular lipid supply.^{15,16} It has been shown that fatty acids participate in cellular renewal and in mitogenesis, and that

in cancer cells the de novo synthesis of fatty acids positively correlates with tumor aggressiveness.¹⁶ In support of this finding, Antalis et al.¹⁷ have shown that aggressive breast cancer cells (MDA-MB-231 and MDA-MB-436) revealed higher levels of cytoplasmic lipids, whereas Slebe et al.¹⁸ associated tumor migration with the uptake of exogenous lipids.

In several tumors, the withdrawal of antiangiogenic tyrosine kinase inhibitors resulted in increased lipogenesis, rapid tumor regrowth and metastasis. Sounni et al.¹⁹ found an increased lipid synthesis under these conditions, which, when blocked pharmacologically, inhibited the regrowth. This again strengthens the suggestion that inhibition of lipogenesis may be a way to tumor reduction.

Conclusion

Cancer is considered one of the leading causes of death worldwide, with approximately 14 million of new cases just in 2012. This number is expected to rise by 70% over the next 2 decades.²⁰ Tumor development and growth is a complex system and not yet fully understood system. It involves different cells, which can undergo cellular transformation or promote tumorigenesis by creating a unique microenvironment with a variety of different micro environmental factors as for example secreted bioactive molecules, hypoxia, acidification or low nutrition supply. In response to these factors the cellular metabolism undergoes several modifications to maintain all cellular functions. This adaptation capacity of cancer cells is one of the main problems in the development of new therapies using metabolic pathways. However, targeting more than only one pathway, common points to two or more pathways, might be a constructive strategy.

The results of many researchers in the field reinforce how important metabolism is for tumoral genesis and progression. Understanding the principles of cellular reprogramming may reveal new and more solid targets to antagonize this disease. In order to accelerate our gain of knowledge, tumor metabolism studies should be intensified and linked with epidemiological data, as a new frontier for research.

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Conflicts of interest

None.

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