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AUTHOR'S VIEW

Antiangiogenic resistance via metabolic symbiosis

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ABSTRACT
Several types of tumor are currently treated with antiangiogenic drugs. Unfortunately, most of these patients develop therapy resistance and succumb to the disease. Recently, a novel mechanism of resistance to antiangiogenics involving metabolic symbiosis of tumor cells has been described. Strategies to block resistance are emerging as a promising therapeutic approach.

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Several types of cancer are often treated with antiangiogenic drugs, which block angiogenesis and induce hypoxia, thus reducing the supply of nutrients and impairing tumor growth, progression, and dissemination. In most cases these antiangiogenic agents are disease stabilizing but resistance eventually develops over time; this involves acquired resistance related to various evasive/escape mechanisms that the tumor develops in response to therapy.

To investigate how current antiangiogenic treatments affect renal cell carcinoma (RCC) tumors, we developed a mouse model based on orthotopic implantation of human biopsies of RCC patients and evaluated new features acquired by the tumors after *VEGFR* multikinase signaling inhibition.

Surprisingly, emergence of resistance in these models was not associated with tumor revascularization but rather to a new mechanism of resistance to antiangiogenic therapies involving induction of metabolic symbiosis between subpopulations of tumor cells.[4] Besides us, 2 other groups recently described this new mode of resistance to antiangiogenic therapies in 2 different tumor types.[1,7]

Allen et al. found that the antiangiogenic inhibitors sunitinib and axitinib also elicit compartmentalization of cancer cells into symbiotic clusters in a pancreatic neuroendocrine tumor (PanNET) mouse model. They further described that co-inhibition of *MTOR* with rapamycin disrupts this symbiosis, in part by upregulating glucose transport in normoxic cells. Pisarsky et al. examined the role of metabolic symbiosis as a mechanism underlying evasive resistance to antiangiogenic therapy by the multikinase inhibitors nintedanib and sunitinib in a preclinical mouse model of breast cancer. In this study, inhibition of glycolysis or genetic ablation of the lactate exporter *SLC16A4* (*SLC16A4*, best known as *MCT4*) in tumor cells disrupted metabolic symbiosis, overriding therapy resistance and suppressing tumor growth.

In order to resist cytotoxic therapy, tumor cells coordinately rewire their metabolism to establish metabolic symbiosis: tumor cells in hypoxic areas upregulate glycolysis, increase lactate production, and export lactate through MCT4. Conversely, lactate is taken up by tumor cells in more oxygenated areas of the tumor via SLC16A1 (SLC16A1, best known as MCT1) and aerobically metabolized via mitochondria.[8]

The tumor microenvironment is heterogeneous, containing regions of low or high levels of oxygen. Moreover, the altered metabolism of cancer cells induces metabolic reprogramming through which activation of target genes by hypoxia-inducible factor (*HIF*) decreases the dependence of the cell on oxygen whereas *RAS, MYC*, and *AKT* can upregulate glucose consumption and glycolysis. Loss of phosphorylated tumor protein TP53 (TP53, best known as p53) may also recapitulate features of the Warburg effect, that is, the uncoupling of glycolysis from oxygen levels.[3] Indeed, tumor hypoxia appears to be strongly associated with tumor progression and resistance to therapy and has become a central issue in tumor physiology and cancer treatment. Thus, the detected compartmentalization upon treatment, with mutually exclusive patterns of perivascular MCT1 and perinecrotic/hypoxic MCT4 areas, is strongly suggestive of a metabolic symbiosis phenotype as a mechanism of metabolic tumor adaptation to therapy that allows the tumor to grow under hypoxia conditions. The compartmentalization between glycolytic cells and oxidative cells in different areas allows exchange of glucose and lactate for their mutual survival.

The altered metabolism of cancer cells is likely to confer several proliferative and survival advantages, such as enabling cancer cells to execute the biosynthesis of macromolecules, to avoid apoptosis, and to engage in local metabolite-based paracrine and autocrine signaling.[3] Indeed, increased expression of *MCT4* has been correlated with poor prognosis in renal cell carcinoma patients[2] and overexpression of *MCT1* and *MCT4* predicts tumor progression.[5] Reversing the Warburg effect by targeting the lactate transporters may be a useful strategy to prevent metabolic symbiosis resistance to antiangiogenics.

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The strategic location of normoxic cells and their signaling pathways make them vulnerable to metabolic pathway inhibitors and implicate their potential as therapeutic targets. Thus, at the time that resistance to antiangiogenic drugs emerges, metabolic symbiosis between tumor cells can be blocked using *MTOR* inhibitors, affecting cells close to vessels and killing the hypoxic regions and impairing tumor growth. Indeed, it has recently been described that urologic malignancies modulate sunitinib resistance through expression of *PTEN*, which serves as a gatekeeper of the PI3KCA (PIK3CA, best known as PI3K3)-AKT-MTOR signaling pathway.[6]

Clinical Relevance

Is this phenomenon also present in patients? To clearly address this question we validated this biologic process in human samples of 15 RCC patients pre- and post-antiangiogenic treatment and observed a metabolic symbiosis pattern in 100% of patients with disease in progression, confirming our observations in orthoxenograft mouse models. Furthermore, to investigate the implicated MTOR pathway we evaluated the pattern of expression of *MCT1* and *MCT4* in one patient who received MTOR inhibitor after antiangiogenic progression and found no compartmentalization patterning. The data obtained from this single but very informative patient are consistent with the results of our animal models in which mTOR inhibition selectively eliminated the MCT1 compartment, leaving the MCT4-positive tumor compartment comparatively intact. Thus, these data strongly suggest that the MTOR pathway might be involved and its inhibition may prevent the occurrence of resistance to antiangiogenic therapies in RCC patients.

The importance of our study lies in the validation of results obtained from experimental animal models in patient samples of renal cancer carcinoma, where we observed the mechanism of metabolic symbiosis in all patients who developed resistance to antiangiogenic treatment and disruption of this metabolic symbiosis in a single patient treated with an *MTOR* inhibitor. This demonstrates the therapeutic value and potential applicability of using an approved drug for a new therapeutic approach.

This new strategy can be used in clinical practice in the short term; however, identifying new predictors of response or biomarkers of resistance to antiangiogenic therapies would be of great applicability in cancer patients who are currently treated with these types of therapies.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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