Endothelial cell metabolism inhibition: A new approach to the treatment of resistant metastatic colorectal carcinoma

Shaimaa I. Eltanani¹, Ahmed S. Ibrahim²

¹ Department of Clinical Pathology, Faculty of Medicine, Mansoura University, Mansoura, Egypt
² Department of Biochemistry and Clinical Biochemistry, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt

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*Correspondence to: Ahmed S Ibrahim, Biochemistry Department, Mansoura University, Mansoura 35516, Egypt; ahmedsalahibrahim@yahoo.com

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March has been officially dedicated as National Colorectal Cancer (CRC) Awareness Month. This is important, as CRC incidence is now dramatically increasing in many developing countries that are undergoing major economic transition[1]. The uptrend in CRC rates has been attributed to the adoption of Western lifestyle and dietary habits, including increased intake of meat, fat and total calories, alcohol consumption, cigarette smoking, and decreased physical activity[1]. Almost a third of all CRC patients already have metastatic disease at diagnosis and nearly 50% of all diagnosed CRC will subsequently develop metastasis with mostly fatal prognosis[2].

Endothelial cells (ECs) are vital components present in the CRC microenvironment that are essential for tumor angiogenesis and metastasis[3]. Therefore, the current option for patients with metastatic CRC involves combination chemotherapy consisting of fluorouracil, irinotecan, and oxaliplatin plus vascular endothelial growth factor (VEGF) inhibitors. There are four agents being used to block VEGF signaling to improve the survival of patients with metastatic CRC: bevacizumab, ramucirumab, regorafenib, and aflibercept. Unfortunately, the overall impact of such agents in prolonging survival has been limited in the long term due to the emergence of resistance[4].

Resistance to anti-VEGF therapies has been attributed to the ability of CRC to induce angiogenesis in different ways. CRC changes the way it communicates with ECs in order to escape therapies that inhibit angiogenesis. A better understanding of this phenomenon will change the paradigm in CRC therapy. Through a wide variety of cell-to-cell communication means including soluble factors, vesicles, the changing of pH, and microRNA, CRC cells recruit ECs towards the tumor metabolic environment by switching the ECs from quiescent to angiogenic phenotype[5–8]. Regardless of the type of angiogenic stimuli, ECs adapt their metabolism to the rising bioenergetic demands of the angiogenic switch. Yet, the precise role of EC metabolism in CRC metastasis remains incompletely understood. Studies in EC derived from other organs have shown that ECs in quiescent state get most of their energy from glycolysis despite their immediate proximity to oxygen[9]. However, when ECs are activated for migration or proliferation, they exhibit characteristics of the Warburg effect like in CRC cells whereby the ECs double their glycolytic flux and decrease their oxidative phosphorylation[10,11]. Beside Warburg effect, fatty acid (FA) metabolism is another important metabolic pathway that takes place in the mitochondria and contributes to the altered behavior of tumor ECs. De novo lipid synthesis is required to generate bioactive lipids for cell signaling and membrane expansion during the rapid EC growth[12]. Following angiogenic stimulation such as VEGF, ECs
increase the expression of their primary glucose transporter (GLUT-1), which is a facilitated diffusion carrier protein, allowing ECs to take up glucose independently from insulin and utilize it as a carbon source for glycolysis and fatty acid synthesis as well\textsuperscript{9,13,14}. Hence, targeting the convergence of angiogenic signals on endothelial metabolism would be an effective alternative to anti-VEGF in metastatic CRC therapy.

Drugs targeting the Warburg effect are under pre-clinical and clinical investigations\textsuperscript{15–19}. These include GLUT1-targeted therapeutic agents such as small chemical entities, as well as GLUT1-mediated target drug delivery for anticancer agents such as fluorine-substituted platinum(II)-sugar conjugates. WZB117 and STF-31 have been shown as novel small molecules with highest affinities for sugar transport inhibition that are able to efficiently block tumor growth when used in mouse models without significant adverse events in treated animals\textsuperscript{20,21}. Additionally, fluorine-substituted series of glucose-, mannose- and galactose-conjugated platinum(II) complexes have been designed and synthesized to leverage GLUT1-mediated specific drug uptake, utilizing the metabolic disparity between normal and malignant cells\textsuperscript{22}. The results showed that sugar-conjugated platinum(II) complexes are recognized by the glucose recognition binding site of GLUT1 with desirable profiles for platinum-based drug design\textsuperscript{23}.

Very recently, strategies of inhibiting the de novo synthesis of fatty acids as well as GLUT1-mediated drug design have been tested successfully in colon cancer xenograft model and in vitro model of human colon carcinoma\textsuperscript{22,24}. If this trend is confirmed also in tumor vasculature, the inhibition of the Warburg phenotype in ECs in combination with inhibiting FA synthesis would become a valid strategy for overcoming the acquired resistance to anti-VEGF that has thwarted clinical success in CRC treatment.

**Conflict of interest**

The authors declare no potential conflict of interest with respect to the research, authorship and/or publication of this article.

**References**


