

## Parasitic Metabolic Pathway of Oral Cancer Cells: The Reverse Warburg Effect

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Cancer cells require a high input of energy to compensate for its rapid proliferation. Various theories have been put forth to comprehend the high energy source feeding the tumor cells. Otto Warburg in 1924 proposed that the tumor cells produce more adenosine triphosphate (ATP) molecules by non-oxidative glycolysis (Warburg effect/metabolism) to meet its high energy demand and due to its lack of functional mitochondria.<sup>1</sup> Warburg's theory had several drawbacks: Oxidative phosphorylation is proven to produce more ATP molecules than non-oxidative glycolysis. Furthermore, the mitochondrial units in most tumor cells were found to be functional. In spite of the criticism, Warburg's theory prevailed as several studies have shown that progressive tumors accumulate higher levels of pyruvate and lactate (metabolic products of non-oxidative glycolysis). In addition, the tumor cells with Warburg metabolism avoid exposure to free oxygen radicals and produce antioxidant to resist oxidative stress. Although the literature remains divided as to the exact reason for Warburg metabolism, it is established as one of the survival tools for tumor cells against therapeutic agents.<sup>2</sup>

Recent studies have demonstrated Warburg effect in the cells of tumor microenvironment other than the tumor cells. The role of tumor microenvironment in the initiation and progression of oral cancer is well-established. Tumor microenvironment consists of tumor associated inflammatory cells, fibroblast, lymphatic, and vascular endothelial cells. Among these, the myofibroblast (MF) has proven to have a significant impact on tumor aggressiveness. The tumor cells release transforming growth factor- $\beta$  (TGF- $\beta$ ) which in turn leads to the differentiation of fibroblast to MF. Under physiological conditions, caveolin 1 (Cav-1) inhibits TGF- $\beta$ , preventing MF differentiation.<sup>3,4</sup>

Pavlidis *et al.* demonstrated that the breast tumor associated fibroblast (TAF)/MF generate energy through Warburg effect (non-oxidative glycolysis). They proposed a modified energy pathway in which the TAF/MF, transfer the generated energy to the associated tumor cells. The tumor cells in turn generate ATP molecules from the TAF/MF generated pyruvate/lactate metabolites through oxidative phosphorylation. Thus, the tumor cells exhibit a parasitic metabolic pathway by gaining its metabolic source from the TAF/MF. This phenomenon was termed as reverse Warburg effect. The molecules involved in the pathway include: TGF- $\beta$ , Cav-1, lactate dehydrogenase that converts lactate to pyruvate which in turn enters the tricarboxylic acid cycle and monocarboxylate transporters (MCT4) and MCT1. MCT4 is responsible for the export of metabolites from the TAF/MF. MCT1 aids in the uptake of the metabolites into the tumor cells.<sup>3,5</sup>

Jensen *et al.* in a recent study examined the role of reverse Warburg effect on oral squamous cell carcinoma (OSCC) specimens. They studied the expression of MCT1, MCT4, Cav-1, glucose transporter 1,  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), TOMM20, and KI-67 in their respective epithelial and connective tissue compartments. The results showed that OSCC specimens were positive for the MCT in both connective tissue and epithelial cells highlighting the energy transportation from the TAF/MF to the tumor cells. However, there was no correlation between MF ( $\alpha$ -SMA) and MCT4, thus questioning the role of MF in reverse Warburg metabolism. In addition, there was also a lack of correlation between MF ( $\alpha$ -SMA) and Cav-1, which controverts the mechanism of MF formation in tumor associated stroma.<sup>6</sup>

To conclude, several malignant entities including OSCC have shown an increased resistance to anti-angiogenic drugs. These tumor cells rely on non-oxidative metabolites from TAF/MF to survive. Thus, regimens targeting tumor angiogenesis and inhibiting the reverse Warburg effect could improve the overall patient survival and provide better therapeutic outcomes.

## References

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