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A reversible Warburg effect is induced by Theileria parasites to transform host leukocytes

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Notable characteristics of growing tumor cells are their increased glycolytic rate and their decreased oxidative respiration, irrespective of oxygen availability. This key hallmark of cancers is known as the "Warburg effect".[1] In the emerging field linking glucose metabolism and cancer progression, there is much debate about the causal role of the Warburg effect. It is unclear whether the Warburg effect is merely a secondary side effect of cancer transformation, or whether it is a direct initiator of tumorigenesis or essential for maintenance. Resolving this conundrum is an important research and clinical need, sparking intense investigation into the molecular features of the Warburg effect.

To contribute to this debate, we exploited a unique model for cancer transformation: bovine leukocytes infected and transformed by the eukaryotic intracellular parasite Theileria. We studied the metabolic relationship between host and parasite cells. Theileria parasites of the Apicomplexa phylum infect bovine leukocytes and turn them into invasive, cancer-like cells in a lymphoproliferative disease.[2,3] Theileria parasites residing in the host cell cytoplasm manipulate and functionally rewire the host cell.[4] We hypothesized that the intimate host-parasite relationship might disrupt host cell metabolism and contribute to the cancer-like phenotypes. We recently described an ingenious mechanism by which the intracellular parasite induces a Warburg-like effect in infected host cells, associated with a shift from oxidative phosphorylation to aerobic glycolysis.[5] We observed that the parasite inside the host leukocyte induces, directly or indirectly, elevated production of reactive oxygen species (ROS). This increase in oxidative stress is associated with stabilization and activation of the hypoxia-inducible factor 1 α (HIF1α) that plays a pivotal role in the establishment/maintenance of the Warburg effect in diverse cancers.[6]

We speculate that the major shift in cellular glucose demands could be the consequence of increased nutrient requirements of the intracellular parasite. Indeed, the shift in host glucose metabolism could constitute an efficient way of providing critical nutrients (for example, for nucleotide and lipid synthesis pathways) that are required for Theileria proliferation and maintenance within the host cell. Thus, the metabolite requirements of the intracellular parasite might inadvertently lead to metabolic reprogramming of the host cell. Our recent findings also suggest that Theileria may secrete proteins into host compartments, which can rewire glucose metabolism through HIF1α regulation, thereby directly targeting actors of metabolic homeostasis (unpublished data).

An intriguing particularity of the Theileria model is its reversibility. Elimination of the parasite, using the specific theilericidal drug Buparvaquone, inhibits the transformation process and abolishes the Warburg effect. The reversal of the Warburg effect is associated with inactivation of HIF1α, loss of expression of the key HIF1-regulated glycolytic enzymes, and subsequent reversion of the transformed phenotypes. These results suggest that the Warburg effect directly contributes to the establishment or maintenance of the transformed phenotype, constituting the first step to tumor development in Theileria-infected leukocyte cells. In support of this conclusion, we showed that inhibition of cell glycolysis (using the 2-Deoxy-D-glucose, a non-metabolizable glucose analog) in Theileria-infected leukocytes also reverted the transformed phenotype, and inactivation of HIF1α, using pharmacological or genetic tools, caused reversion of the Warburg effect and inhibition of the transformed phenotype in our model. We further showed that the oxidative stress generated by the presence of the parasite in the host cytoplasm is required for chronic HIF1α activation. Treatment with antioxidants could also reverse the transformation. Hence, our study revealed that targeting three pathways linked to glucose metabolism rewiring (namely glycolysis, HIF1α signaling, and ROS production) was sufficient to revert the Warburg effect and the transformed phenotypes of infected leukocytes. Hence, the study of how infectious agents hijack the host cell machinery in parasite-host interactions can still teach us much about tumorigenesis.[2,5,7]

This direct correlation between the parasite-induced Warburg effect and the tumor-initiating phenotype (and its reversibility) is relevant to therapeutic approaches for cancer. Targeting the main actors of the establishment and/or maintenance of the Warburg effect is an effective strategy to selectively kill cancer cells. Significant efforts are being made to engineer inhibitors of glycolysis, antioxidants, and inhibitors of the HIF1α factor, each of which offers promising therapeutic opportunities to treat cancer.[8] Combining strategies that target these three pathways might reverse the Warburg effect, with clear clinical benefits to cancer patients.

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