Cancer generated lactic acid: Novel therapeutic approach

Aerobic glycolysis or Warburg effect[1] and increased degradation of glutamine collectively known as reprogrammed energy metabolism are considered as a key metabolic hallmark of cancer.[2] Normal cell metabolize glucose to pyruvate via glycolysis and to carbon dioxide for oxidative phosphorylation under aerobic conditions. In anaerobic conditions, relatively more pyruvate is converted to lactate with less being shifted to mitochondria. On the other hand, cancerous cells even in the presence of oxygen convert glucose to lactate by an altered energy metabolic pathway less efficient than oxidative phosphorylation.[2] This along with increased degradation of glutamine leads to metabolic acidosis with pH of the solid cancers as low as 6.0–6.5.[3-5]

Many speculations have been proposed for the existence of aerobic glycolysis in cancer cells. One states that this mechanism could provide a proliferative advantage to cancer cells[6,7] by incomplete utilization of glucose and so providing intermediates to be redirected for biosynthesis of biomolecules for essential cellular components. Other states the lactic acid generation may lead to acid resistant phenotypes, and therefore, the unrestricted proliferation of cancer cells.[6] Otto Warburg proposed the presence of aerobic glycolysis due to some mitochondrial defect[8] although some cancers are reported to revert to oxidative phosphorylation by inhibition of lactic acid generation[9] thus proposing that mitochondrial defect may be partially responsible for it. The altered energy metabolism can also be an adaption for survival in episodes of hypoxic and normoxic conditions as hypoxic cells are considered to be the main utilizers of glucose converting it into lactate.[6,10] Furthermore, the increased degradation of glutamine also provides glutamine and aspartate, the intermediates for nucleic acid synthesis and an alternative energy source whenever the glucose is not available.[11,12] The altered energy metabolism may also promote proliferation of angiogenic endothelial cells, thus leading to the synthesis of more vascular bodies.[13]

Earlier lactic acid was thought to be mere metabolic product,[14] but studies have shown that it imparts a regulatory predictive role in the proliferation of cancerous cells, metastasis of cancer and patient survival.[15] Cancer generated lactic acid induced acidosis impede the function of normal immune cells,[16] loss of T-cell function of human, and murine tumor-infiltrating lymphocytes[4] and so suppressing the anti-cancer immune response. Another study has shown cancer cells may enhance their survival by inhibiting the anti-cancer immune response through actively maintaining a slightly acidic micro-environment by altering their energy metabolism by controlling their lactic acid production.[17]

Normalizing cancer generated lactic acid and resultant acidification and focusing on altered metabolic pathway may lead to cancer inhibition. Considering this hypothesis that regulation of lactic acid production may lead to a positive effect on control of cancerous growth, studies are on progress to find the inhibitors of aerobic glycolysis. Several small molecules have emerged that exhibit promising anticancer activity *in vitro* and *in vivo*, as single agent or in combination with other therapeutic modalities. The glycolytic inhibitors are particularly effective against cancer cells with mitochondrial defects or under hypoxic conditions, which are frequently associated with cellular resistance to conventional anti-cancer drugs and radiation therapy.[18] One recent study has shown the antiglycolytic activity of 3-bromopyruvate on rat mammary tumor cells implanted in rats[19] or dichloroacetate as inhibitors of cancer-cell-specific aerobic glycolysis.[20] The careful planning of therapeutic dose of these anti-cancer inhibitors is necessary as normal cells also derive their energy from it. Other pathways leading to inhibition of generation of lactic acid production are also on trial. Four major types of pH regulator have been identified to be up-regulated in tumor cells, the proton pump, the sodium-proton exchanger family, the bicarbonate transporter family, and the monocarboxylate transporter family (MCT).[21] The bicarbonate administration has been shown to increase the pH of tumors, reduce the formation of spontaneous metastases in mouse models of metastatic breast cancer, and reduce the rate of lymph node involvement.[22] Histone acetylation has also been reported to regulate intracellular pH. As pH decreases, histones are globally deacetylated by histone deacetylases, and the released acetate anions are coexported with protons out of the cell by MCTs, preventing further reductions in pH.[23] All these strategies (inhibition of lactic acid generation, normalization of pH in cancer cells) can be useful for the control of cancer in combination with immunotherapeutic approaches.[24] Inhibition of lactic acid generation of cancers may lead to inhibition of proliferation of cancerous cell by dual pathway via energy depletion, and by reduction of their immunosuppressive activity in the tumor micro-environment. This could be effective for the therapy of almost all of the cancers with promising patient survival.

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