



REVIEW ARTICLE

Aerobic glycolysis and high level of lactate in cancer metabolism and microenvironment



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Abstract Metabolic abnormalities is a hallmark of cancer. About 100 years ago, Nobel laureate Otto Heinrich Warburg first described high rate of glycolysis in cancer cells. Recently more and more novel opinions about cancer metabolism supplement to this hypothesis, consist of glucose uptake, lactic acid generation and secretion, acidification of the microenvironment and cancer immune evasion. Here we briefly review metabolic pathways generating lactate, and discuss the function of higher lactic acid in cancer microenvironments.

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Introduction

Tumor consists of multiple cell types, the surrounding microenvironment support cancer cells growth, migration, invasion, and metastasis. Different cancer cells coevolve through paracrine and exosomes communication.^{1,2} Metabolic products of cancer cells also influence itself, other type cancer cells and immune cells in same microenvironment.

Metabolic abnormalities is a hallmark of cancer. Growing papers about the metabolism of cancer cells hint that aerobic glycolysis inhibitors and other new medications targeting metabolic enzyme have great potential to block cancer progress. According Warburg's hypothesis, cancer cells choose aerobic glycolysis as main mode of glucose metabolism instead of more efficient oxidative phosphorylation. Dysfunction of mitochondria, loss of tumor suppressors, the

hypoxic microenvironment, and oncogene-driven metabolic reprogramming are initiating events of abnormal energy metabolism of cancer cells.³ In over 70% of human cancers, glycolytic genes are ubiquitously overexpressed.^{4,5}

Aerobic glycolysis only produces 2 ATP molecules per glucose molecule, it means cancer cells need uptake more glucose molecules from microenvironment to meet energy requirements, and secretes more lactic acids to microenvironment for the maintenance of cellular environment homeostasis. So, cancer metabolism and microenvironment have close interactions and relationships. In the current paper, the relationship between cancer metabolism and cancer microenvironment are discussed and analyzed.

Overexpressed glucose transporters

Uptake of glucose from microenvironment into cytoplasm occurs by facilitated the transport of glucose over a plasma membrane through glucose transporter/solute carrier

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(GLUT/SLC2A) family. GLUT family includes 14 membrane-bound proteins, named from GLUT1 to GLUT14.

Glucose uptake is a rate-limiting step in aerobic glycolysis in cancer cells. Under the condition of hypoxia, cancer cells frequently over-express GLUTs, especially GLUT1 and GLUT3. Tumor hypoxia microenvironment cause hypoxia-inducible factors (HIFs) containing HIF-1 α and HIF-1 β subunits overexpressed. HIF-1 has been proved to activate several signal pathways in cancer cells. GLUT1 levels have been shown to increase with changes at both the mRNA and protein levels in hypoxic conditions. HIF-1 recognized as oxygen sensing up-regulate GLUT1 expression. An enhancer element lying 5' to the *Glut-1* gene could be activated by hypoxia, and found a distinct cis-acting sequences as a HIF-1 binding site to increase GLUT1 expression.⁶

Hypoxia microenvironment also lead to activation of NF- κ B and hypoxia-inducible-1 α (HIF-1 α) pathways in cancer-associated fibroblasts (CAF). Basal-like CAFs secrete hepatocyte growth factor (HGF) which bind to c-met on cancer cell membrane, then upregulate glucose transporter expression.⁷

Both GLUT1 ($K_m = 6.9$ mM) and GLUT3 ($K_m = 1.8$ mM) have a high affinity for glucose.⁸ So cancer cells can efficiently plunder glucose, reduce glucose concentration in tumor microenvironment,⁹ subsequently influence the function of infiltrated immune cells.

Lactic acid biosynthesis and secretion

The Warburg effect present that cancer cells enhance aerobic glycolysis to generate energy and supply intermediate for macromolecule biosynthetic, including ribose-5-phosphate, glycine for nucleotide, or glycerol for lipid. Enhanced aerobic glycolysis do not mean aerobic oxidation and the tricarboxylic acid (TCA) cycle has been 100% blocked. Recent investigations has reported that the function of mitochondria in most cancers is intact.^{10,11} Cancer cells also partly generate ATP by consume pyruvate and other TCA cycle intermediate. So, Warburg effect is essentially a consequence of an imbalance between maximum rates of glycolysis and pyruvate oxidation.¹²

In aerobic glycolysis, pyruvate is converted to lactic acid by lactic acid dehydrogenase-A (LDHA). The accumulation of lactic acids in cancer cells promotes lactic acid transport by the proton-linked monocarboxylate transporter (MCT), particularly MCT1¹³ and MCT4.^{14,15} These MCTs are found overexpressed to accelerate lactic acid secretion from cytoplasm to extracellular fluid. It makes pH dropped to 6.6 within the tumor microenvironment.¹⁶ The acidification of the microenvironment was mainly caused by lactic acid which secreted from cancer cells.¹⁷ Inhibitors of MCT1 such as α -cyano-4-OH-cinnamate (CHC) or lonidamine effectively inhibit the tumor growth *in vivo* studies,^{18,19} and increase sensitivity to radiation therapy. It means that lactic acid exported from cancer cytoplasm to remove excess carbon and maintain NADPH⁺ store is very important to tumor growth. And MCT1, MCT4 are potential therapeutic targets for cancer.

Lactic acid activates vascular endothelial growth factor (VEGF),^{20,21} transforming growth factor beta (TGF beta),²² interleukin-1 (IL-1) and HIF-1 even in normoxic oxidative

tumor cells. As described earlier, HIF-1 is a key regulator during glucose metabolism shift. So higher lactic acid can feed back to enhance glycolysis in cancer cells, cause a vicious circle. Higher VEGF further induces tumor angiogenesis, by stimulating endothelial cell migration and the recruitment of circulating vascular progenitor cells and vascular morphogenesis.

Energy waste and re-used

Tumor consists of a serial distinct subpopulation of cells. Cancer cells in hypoxic environment consume high levels glucose, using aerobic glycolysis as altered energy metabolism pathway, secrete high levels lactic acid out of cytoplasm. Cancer cell near blood vessels with plenty oxygen supplement, preferentially utilizes the lactic acid as their main energy source. So, Lactic acid is not a waste, it is re-used as energy vehicles, transfer energy among different cancer sub-populations.

Three models of lactic acid re-used in cancer microenvironment have been described: the "reverse Warburg effect", metabolic symbiosis, and vascular endothelial cell shuttling. "Reverse Warburg effect" means cancer cells secrete hydrogen peroxide to create a "pseudo-hypoxic" environment to activates HIF-1 α , glycolysis, and MCT4 expression of stromal cells. The metabolism of glycoses of stromal cells shifts to aerobic glycolysis, and secrete lactic acid to microenvironment, in turn, the novel generated lactic acid are uptake by cancer as energy substrate. Metabolic symbiosis describe that lactic acid worked as a medium to transfer energy from highly glycolytic, hypoxic cancer cells to more oxidative cancer cells.

Acidification of the microenvironment and cancer immune evasion

The anti-cancer immune response has been known to be mediated by effector T-cells, which dependent on helper cells and cytokines in micro-environment. The tumor immunity also is influenced by the environmental pH, an acidic pH in microenvironment can markedly weaken response of immune cells.²³ Modulation of microenvironment acidity towards physiological values reverses the anergy of tumor-infiltrating T lymphocytes.²⁴

Aerobic glycolysis also is a mainly method which activated T cell generate energy.²⁵ During T cell activation, T cells increase glucose uptake and glycolytic rate, by up-regulating glycolytic enzymes, which generate more lactic acid to secrete into microenvironment. Lower pH and higher lactic acid concentration caused by tumor cells inhibit lactic acid secretion from T cell, and cause T cell be asphyxiated, then reduce proliferation and cytokine production by 95%.²⁶ These effects are mediated by decreased MAPKs p38 and JNK/c-Jun phosphorylation of T cells.

Lactic acid also inhibits the innate immune through down-regulating the expression of LPS induced genes, delayed LPS-induced phosphorylation of AKT and the degradation of IKB. Pre-incubation with lactic acid following LPS stimulation significantly reduced TNF, IL-6

MCP-1, MIP-1a secretion. It means that higher lactic concentration might be play as a suppressive role.

Summary

Cancer cells have significant heterogeneity in glucose metabolism. Most cancer cells rely largely on aerobic glycolysis as it accounts for 56–63% of their ATP budget. So, cancer cells plunder more glucose from microenvironment and secrete more lactic acid to meet requirement of energy and material metabolism. This characteristic of cancer cells cause lower glucose concentration and higher acidity in tumor microenvironment, subsequently suppress infiltrated immune cells, contribute to tumor immune evasion. Development novel drugs which target glucose intake, aerobic glycolysis, or lactic acid secretion of cancer cells might engender double effects: inhibition of tumor cells and recovering immune response.

Conflict of interest

The author has none to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.gendis.2017.02.003>.

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