Review of: "The role of pH in cancer biology and its impact on cellular repair, tumor markers, tumor stages, isoenzymes, and therapeutics"

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Review: The role of pH in cancer biology and its impact on cellular repair, tumor markers, tumor stages, isoenzymes, and therapeutics' by Maher Akl and Amr Ahmed

The article describes the impact of pH in carcinogenesis and development of cancer. However it should be noted that low pH also plays a significant role in severity and mortality of patients in many other pathological conditions (described below). So the question arises if net outcome in carcinogenesis is low pH or something else. However observations on high rate of glycolysis by tumor cells which were characterized by increased glucose uptake and excessive lactate production in the presence of oxygen (aerobic glycolysis) are universal (Waburg Effect). Lactate is the end product of glycolysis which under normal conditions occurs in inadequate supply of oxygen. Depending on pH, lactate is generated as the protonated acidic form (lactic acid) in a low pH environment or as sodium salt (sodium lactate) in a basic pH environment. Lactate is produced in the human body mostly from glucose. It serves as a key energy source, and a signaling molecule in normal human physiology.

Lactate is a foremost component of the inflammatory microenvironment. To fulfil their high energy and biosynthetic requirement, inflammatory cells switch their metabolism to glycolysis. Interestingly, metabolites that accumulate under glycolytic settings have been shown to enhance the inflammatory response by modifying intracellular signaling pathways, remodeling the epigenetic landscape, and controlling posttranscriptional and posttranslational modifications, among other things (1).

Lactate-induced metabolic acidosis

Under physiological pH 7.4, most lactate is deprotonated and present as lactate anion, a negatively charged, physiologically active form. Lactate is an essential oncometabolite that acts as a switch in cancer's metabolic reprogramming. The generation of significant amounts of lactate in cancer causes an acidification of extracellular microenvironment at pH 6.0 to 6.5. Angiogenesis and immunosuppression are aided by acidosis, which has been associated to a worse clinical outcome. Lactate levels above a certain threshold are linked to a poor prognosis for cancer. MCTs transport lactate and a hydrogen ion out of the cell together, causing the immediate environment to become acidic. The resulting drop in pH may aid cancer cell invasion and metastasis by destroying normal host cells, freeing up space for the tumour and maybe releasing nutrients that the tumour can ingest. Lactate, which is secreted by cancer cells, has also

been proposed as a source of nutrition for non-tumor stromal cells (1).

The lactate-induced acidosis hypothesis states that lactic acid is dissociated into lactate ions and hydrogen (H). Acidosis is produced as a result of this process. Therefore, lactate affects the immune system and acts as a signaling molecule, which can provide a “danger” signal for life. Several reports provide evidence that the serum lactate levels represent a chemical marker of severity of disease similar to LDH under inflammatory conditions. Both blood LDH and blood lactate have been suggested as risk factors for the mortality of patients in serious inflammatory diseases including cancer. Furthermore, Zhang et al. hypothesised the worldwide mechanism of histone lysine lactylation (Kla), which offers a novel avenue of chromatin structure for investigating carcinogenesis and promising therapeutic targets.

1. The Lactate and the Lactate Dehydrogenase in Inflammatory Diseases and Major Risk Factors in COVID-19 Patients. *Inflammation* *45*; 2091–2123 (2022)

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