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Lactate on the crossroads of immune system and cancer: A new hypothesis

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ABSTRACT

The hypothesis account for the site specific/organ specific role of lactate production as a metabolic precursor as well as potent immuno-suppressive molecule. Known sites of lactate production elucidate the evolutionary role of lactate as an important player in regulating immune function and cancer cells exploit the lactate for their survival as a metabolic precursor. The hypothesis provided new insight about how cancer cells shift towards anaerobic respiration and how efficiently cellular metabolism and immune system is coupled to maintain homeostasis in blood stream, muscles and immune privilege organ(eye).

Keywords**:** *(anaerobic respiration, homeostasis, immuno-suppressive molecule, Lactate, metabolic precursor)*

I. INTRODUCTION AND ANALYSIS

Lactate is produced by lactate dehydrogenase (LDH) and is equilibrated via diffusion by monocarboxylate transporters (MCTs) across the plasma membrane. Lactate is produced during anaerobic glycolysis and has important role of helping in synthesis of metabolic precursors. Lactate is not a metabolic waste product that is produced during hypoxic conditions that is contrary to earlier notion where lactate was considered as metabolic waste [1, 2]. Lactate is produced by lactate dehydrogenase (LDH) and is equilibrated via diffusion by monocarboxylate transporters (MCTs) across the plasma membrane[3]. Lactate is produced during anaerobic glycolysis and has important role of helping in synthesis of metabolic precursors. The metabolism of cancer cells need to shift towards the anabolic state to help the proliferation of highly demanding cancerous cells. Thus cancer cells shift their metabolic state towards generation of lactate and hence other metabolic precursors. Lactate is known to favor the growth and proliferation of cancer tissues by providing the precursors and via signaling the survival of cancer tissues by modulating immune response[4]. The destructive wrath of immune system is avoided by cancer tissues by producing lactate to neutralize the immunological response. The decrease in PH by lactate suppresses T-cell function and other immune cell functions[5]**,** interestingly in cancerous tissues, T-cell function can be restored by buffering the pH to normal physiological range[6]. Lactate modifies the cancer tissue environment by causing immunosuppression so that cancer cells can survive the immune system attack. Cancer cells have fewer mitochondria than normal cells to avoid the apoptotic mechanism of cell death and to enhance the lactate production for sustained production of metabolites to be used in anabolism. Cancer is outcome of failure of multiple genes or some crucial genes having important role in regulating cell

growth and survival. Downregulation and upregulation of some crucial genes in cancer cells may modulate normal microtubule dynamics. Microtubules are responsible for distributing the mitochondria to daughter cells[7]. Thus, suppression of microtubule dynamics may cause heterogeneity in cancer cell in terms of mitochondrial number. Thus, some cells possess more and other cells have less mitochondria. The cells having less mitochondria/mutated mitochondrial genes gain adaptive advantage to survive the hypoxic conditions prevailing in cancer tissues. The less number of mitochondria/dysfunctional mitochondria divert the metabolism of the cells towards more lactate production and thus better chances of survival in demanding situation. It might be a crucial mechanism how a cancer cell overtakes its metabolism to perfectly suit the hypoxic conditions and to produce more and more lactate to ensure anabolic state. Lactate also act as a signaling molecule which causes the stabilization of hypoxia inducible factor-1α (HIF-1α), and also increases the expression of vascular endothelial growth factor (VEGF) that promotes angiogenesis a mechanism aimed to provide cancerous tissues with ample nutrients to maintain their anabolic demands[1].

Lactate molecule being an important precursor in glycolytic pathway has other accessory and important functions to perform in our system. Earlier lactate was considered as a waste product of hypoxic condition. We must ponder why lactate is produced during hypoxic state? During strenuous exercise there is lactate production which may be our defense system to regulate the immune system at the site of probable leakage of immune cells towards body tissues. Thus, lactate might be an important player to prevent the autoimmune response during normal exercise or due to day to day strenuous jobs. Athletes have a problem in maintaining normal immune functioning due to bulk production of lactate, which causes immunosuppression. The limitation of Warburg effect was being though that some normal stromal fibroblasts produce lactate. In reality, if we look at the locations of stromal fibroblasts they are best suited to prevent the injury mediated infiltration of immune cells and their subsequent reactions towards self tissues. Similarly, eye is an immunopreveleged organ. Nature has made eye an immunoprevileged organ, keeping in view the delicate functions of eye involving focusing the objects and things in the outside world. Thus focal distance is an important player in clear vision and nature cannot afford tweaking with the focal length by regular day to day infections and inflamations. Thus, nature has kept eye as an immune-previleged organ[8]. Muller cells in eye produce a lots of lactate [9], which might be also a defense mechanism to fight the infiltrating T-cells and render them ineffective in causing autoimmuno response. Excessive exercise in some trained athlete leads to overtraining syndrome which is characterized by compromised immune function that makes athletes susceptible to various infections[10]. Thus, a link can be found between physical pressure on muscle tissues and switching of the immune system for preventing initiate of any autoimmune reaction cascade. Our body has developed lactate generation mechanism to evade any predator by providing continuous energy to burn glucose. Strenuous exercise causes muscle damage thus exposing muscle tissues to our blood circulation that may be a causative factor of autoimmune disease like Fibromyalgia, Polymyalgia Rheumatica [11].

Another site where lactate is produced in our body are red blood cells[12]. Thus, there should be some natural function of lactate generation in the RBCs. We can propose activation threshold optimization mechanism induction by RBC lactate. RBCs possess remarkable metabolism of producing lactate from glycose by

glycolysis. RBCS and WBCs are circulating in the blood. T-cells and B-cells are produced in thymus and bone marrow and then circulate between blood and lymphatic system. According, to the clonal selection theory and subsequent data in the field[13-15], our body has capacity of generating antibodies which can react to any antigen in the universe. Our circulatory system is composed of naïve/effector/memory T and B cells. Nave and memory B-cells/T-cells had to be stimulated by proper and relievant antigenic stimulus to prevent activation of naïve autoimmune T/B cells. Thus, in our system there is activation threshold beyond which a T/B cell can be activated. To maintain the systemic regulation on T/B cell activation, lactate produced from proximal/adjacent RBCs helps in increasing the activation threshold of naïve/memory T/B cells to reserve and commet them for appropriate antigenic/pathogenic response and to prevent autoimmunity. Nature has developed the strategy to separate lymphatic system from circulatory system. Lymph nodes are primary sites of exposure of naïve or memory B/T-cells to antigen/pathogenic challenge[16, 17]. The absence of RBCs and thus lactate exposure to B/T cells in the lymphatic system promotes better incitation of immunological response to antigens, as it is important to curb the pathogenic infection. Once a T/B cells is activated by pathogenic epitopes, it will proliferate quickly to make its clones. During infextion when additional effector B/T cells move into blood stream, the ratio of RBCs to WBCs is altered. Thus, upon infection the decrease in RBC to WBC ratio would reduce the lactate production, in addition to this production of interleukins/growth factors by activated B/T cells may promote the activation of some naïve T/B cells thus may create autoimmune disease problems. To maintain the balance in such a crucial and demanding situation nature has adapted an alternative strategy where in the number of lactate producing cells increase i,e activated T/B cells shift towards lactate production[18, 19] which elevates the activation threshold of other naïve T/B cells. Another reason for shift in metabolism by T/B cells towards lactate production is to sustain enhanced growth and proliferation of activated T/B cells. It is the same strategy which cancer cells adopt to maintain anabolic state. The shift in metabolism towards lactate production in activated T/B cells may also help us in explaining original antigenic sin where in body responses immediately to antigen to which it was exposed earlier but cannot generate the antibodies towards new dominant epitopes present on the same pathogen or its new strain[20]. It can be due to significant increase in lactate producing activated T/B cells from earlier antigen to which our system reacts promptly owing to the presence of memory T/B cells against that epitope. This increase in lactate production due to profuse proliferation of memory T/B cells might be increasing the activation threshold for naïve B/T cells to be activated by new dominant epitopes present on pathogenic organism/virus.

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