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Polarization State of Macrophages Under Lactate Action

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Abstract. As the most prevalent immunological population in the tumor microenvironment (TME), tumor associated macrophages (TAMs) are crucial to TME. Simultaneously, acidic environment is a prominent feature in TME. Recent studies have shown that macrophages undergo further division into two distinct types of TAMs, namely M1 and M2, respectively. They are induced by different inducing factors and play different roles in cancer and inflammation. Lactic acid strongly enhances the transformation of macrophages with M1 designation into macrophages with the M2 designation, as shown by the increased expression of M2 genes. This article analyzes EC lactate and obtains the results of its transportation in the form of MCT1 lactate transporter. There is also an epigenetic mechanism that promotes macrophage polarization. Using lactate as a target, MCT1 inhibitor AZD3965 can inhibit the expression of M2 macrophages. Because it only discusses lactic acid in acidic environments, it has limitations. This article provides reference for future research on lactate, and the specific mechanism of action of HIF-1 α in lactate environment has not been resolved. Future research can focus on this direction.

Keywords: lactic acid; M1 macrophages; M2 macrophages; mechanism of action.

1. Introduction

Macrophages are the predominant immune system cell type in the TME. Macrophages have the ability to undergo additional separation into two distinct kinds: macrophages of type M1 and macorphages of type M2.M1 and M2 macrophages are crucial in the development of tumors. M1 macrophages have conventionally been regarded as having anti-tumor properties, while M2 polarized macrophages are classified as TAMs. They have a significant role in promoting several cancer-related effects such as controlling the growth of blood vessels and lymphatic vessels, suppressing the immune system, inducing low oxygen levels, stimulating the proliferation of tumor cells, and facilitating their spread to other parts of the body. TME may influence the recruitment and polarization of macrophages, resulting in these pro-tumorigenic consequences.

The main characteristics of TME are overall hypoxia, acidification, interstitial hypertension, vascular high permeability, inflammatory reactivity, and immunosuppression. Among them, low pH is a significant feature. Lactic acid is both a bioactive chemical and a metabolic by-product. Lactate and macrophage polarization are tightly connected, as increasing amounts of evidence have demonstrated in recent years. According to a recent study [1], lactate is what propels TAM growth during the epithelial mesenchymal transition. Additionally, research has shown that lactic acid can stimulate M2 like macrophage polarization in HNSCC (human head and neck squamous cell cancer) [2]. At the same time, under the environment of gastric cancer, lactate helps macrophages to polarize into an M2-like state [3]. Tumor tissues create lactic acid, which stimulates the polarization of TAMs and therefore accelerates tumor development.

This article mainly discusses the effect of lactate on M2 macrophage polarization, further understanding the tumor promoting results related to lactate differentiated macrophages and the development of potential new therapeutic methods.

2. Organization of the Text

2.1. Macrophages

2.1.1. Macrophage Polarization

Macrophages originate from the bone marrow lineage and constitute the bulk of cells responsible for innate immunity. They also serve as crucial antigen-presenting cells that initiate adaptive immune responses. They are primarily found in many tissues and organs and play a crucial role in the body's innate immune response. Macrophages have the ability to develop into two distinct types: M1 macrophages and M2 macrophages. These types are distinguished based on the expression, secretion characteristics, and functions of several surface receptors. M1 macrophages exhibit a pro-inflammatory function and contribute to the suppression of tumors, while M2 macrophages have an anti-inflammatory function and promote tumor growth. Macrophage polarization denotes the unique activation state of macrophages at a given moment. However, since macrophages are malleable, their polarization state is not static and may be changed depending on the integration of multiple signals from other cells, tissues, and pathogens. This is because macrophages are able to change their properties. The polarization of macrophages is a complex process that extends beyond the basic categorization of the two types. The various subtypes really represent distinct positions along the range of macrophage divides, as seen in Figure 1.M1 macrophages and M2 macrophages maintain a dynamic equilibrium under normal physiological circumstances. In diseased circumstances, the shift of macrophage phenotype towards either M1 or M2 polarity might contribute to the advancement of several illnesses.

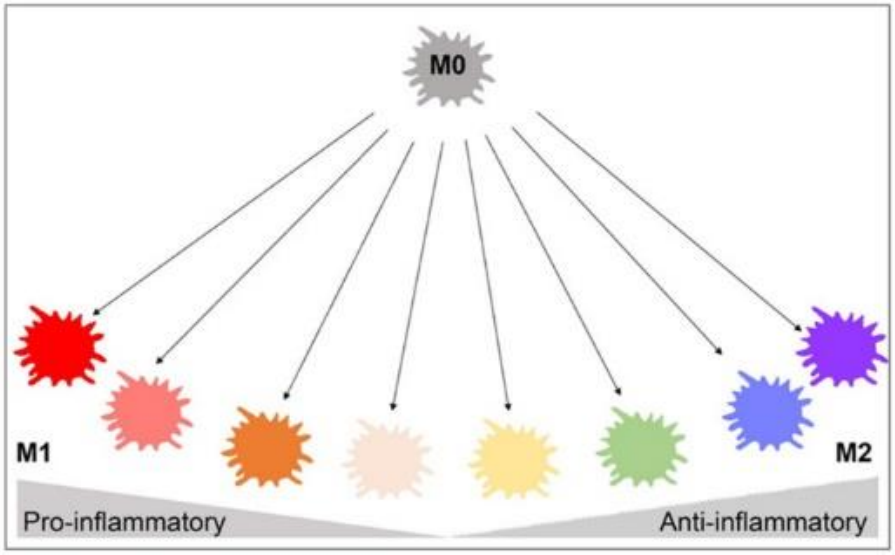


Fig. 1 Polarization Gradient of Macrophages [4].

2.1.2. M1 Macrophages: Classically Activated Macrophages

Interferon-γ (IFN-γ), Th-1 cells, or lipopolysaccharide (LPS) generated from pathogens may individually activate M1 macrophages [5]. One of its defining features is its ability to display a vast array of antigens and generate IL-12 and IL-23. They stimulate pro-inflammatory, antibacterial in nature, and anti-tumor actions [6]. The latest studies have discovered the metabolism-related features of m1/m2 macrophages, showing that alterations in the functional phenotypes of macrophages are predominantly influenced by the metabolism of macrophages [7].

2.1.3. M2 Macrophages

The following substances can trigger M2 macrophages: immune complexes, IL-4, IL-13, and IL-10. They have a limited capacity to display antigens. They control Th2 cells and increase the levels of arginase-1 (Arg-1), CD206, and CD163. TGF-β, IL-8, and VEGFA are further substances that M2 macrophages can create. These substances can encourage angiogenesis and lymph, both of which are

important for tissue and wound healing [8]. The three subtypes of M2 macrophages—M2a, M2b, and M2c—each of which performs a distinct function—may be further separated. M2a macrophages support tissue healing and cell proliferation and are activated by IL-4 or IL-13 [9]. Immune complex or LPS/IL-1 stimulation, which prevents the immediate inflammatory response, induces M2b macrophages. M2c macrophages are responsible for controlling immunity and reducing inflammation. They are activated by glucocorticoids, IL-10, or TGF-β [10]. The metabolism of lipids and iron in cells is also a major factor in the activation of M2 macrophages.

2.2. Lactic Acid

Lactate is mostly produced in the cytoplasm. Lactic acid is not considered a metabolic waste; rather, it serves as both a food and a signaling molecule with hormone-like properties. Lactic acid has several noteworthy attributes. It has a high energy content as a substrate. Additionally, it is a chemical that has the ability to influence epigenetics. It is a hormone that may dissolve in a liquid and can be detected by receptors located on the cell membrane. The lactate-induced signaling pathway is a crucial mechanism in humans [11]. The above procedures are aided by receptors or transporters. The physiological concentration of lactic acid is around 1.5-3 mmol. However, under normal physiological circumstances, this concentration may grow to 10 mmol in both blood and tissues. After intense exercise, the concentration of lactic acid can reach as high as 25 mmol. The concentration of lactic acid may reach around 10 mmol in inflammatory disorders such as atherosclerotic plaques or synovial fluid of rheumatoid arthritis. In cancer tissues, the concentration can even reach 20-40 mmol [12]. The presence of lactate significantly influences the behavior of macrophages that enter and persist inside the tumor, so further influencing the progression of the illness.

2.3. Lactic Acid's Effect on the Polarization of Macrophages

2.3.1. The Action of Lactate Is Mediated by HIF-1α (Hypoxia Inducible Factor 1)

It was shown that lactate was powerful enough to activate the M2 markers Fizz1, Mgl is a1, and Mgl is a2 when it was shown to increase Arg1 in bone marrow-derived macrophages [13]. Considering that HIF-1α is necessary for lactate to stimulate Arg1 in vitro, it was found that HIF-1α is also required for other M2 markers [13]. Following the injection of lung cancer tumor TAMs into HIF-1α defective macrophage mice and mice that were wild-type, the levels of M2 markers was examined. [13]. Compared with wild-type mice, the expression levels of Arg1, Fizz1, Mgl1 and Mgl2 in TAMs of HIF-1α deficient macrophage mice were lower [13]. The most common activators of macrophage M2 polarization are IL-4 and IL-13. After being activated with IL-4, macrophages derived from HIF1α null mice and wild-type mice were evaluated for gene expression [13]. Compared with wild-type macrophages, macrophages lacking HIF-1α had significantly weaker induction of Arg1, Fizz1 and Mgl2 [13]. Nevertheless, the increase in Mgl1 expression remained unchanged, suggesting that the presence of HIF-1α is necessary for a certain group of M2-related genes, independent of whether they are stimulated by IL-4 or lactate.

2.3.2. Mechanism of Lactic Acid on Macrophage Polarization

1)Lactate Produced by Endothelial Cells (ECs) Directs MCT1-Dependent Macrophage Functional Polarization:

As shown in Figure 2, MCT1 can control lactate uptake by macrophages [14]. Lactate produced by endothelial cells is absorbed by macrophages through MCT1 lactate transporter, thus ending up with the transformation of M1 macrophages into M2 macrophages as a consequence.MCT1 suspension mice were crossed with bone marrow cell specific LysM-Cre mice to generate mice lacking MCT1 in macrophages after 3 days of HLI, mct1DMac muscle had higher levels of macrophages, monocytes, and neutrophils, in addition, MCT1 depleted macrophages conveyed Relma as well as CD206 less [14]. This implies that lactate uptake dependent on MCT1 must be present for macrophage M2 functional polarization after muscle ischemia [14].

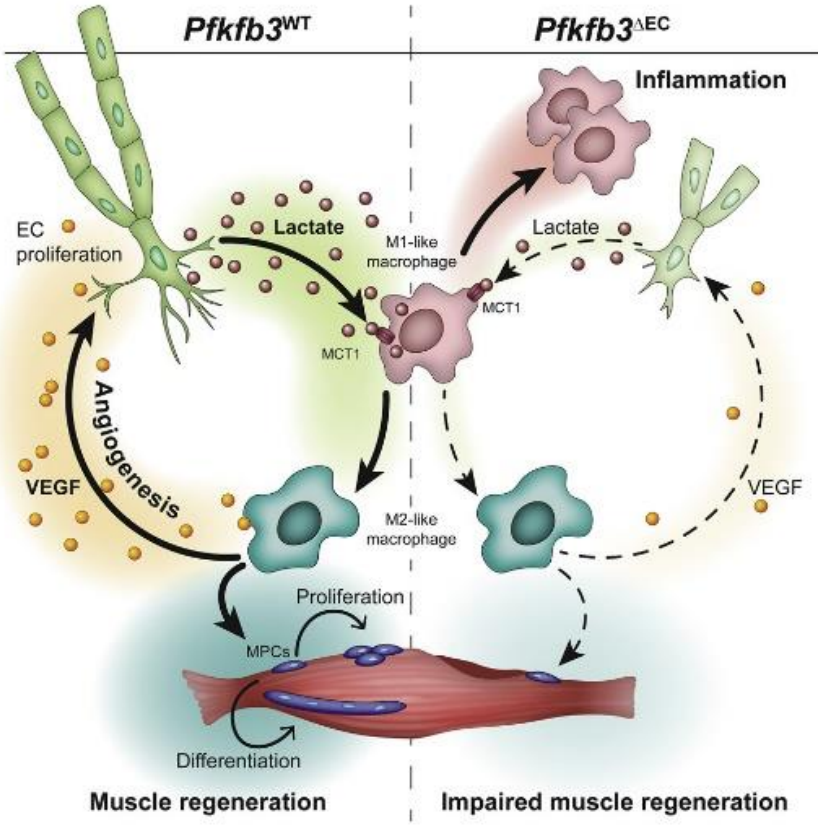


Fig. 2 Mechanism of Action of MCT1 Protein [14].

2) Through an Epigenetic Mechanism (Histone Lysine Lactation), Lactate Can Polarize Macrophages to a Behavior Similar to That of M2:

Studies have demonstrated that the histone Kla epigenetic process, which forms a covalent bond between the lysine residues of histones from macrophages and lactate entering the nucleus, can directly stimulate transcription of chromatin genes, help macrophages transition to a steady-state phenotype, and express genes similar to M2. The macrophage phenotype changes as a result of this process from one that is inflammatory to one that is anti-inflammatory [12]. Lactate induces histone lactation, as seen in Figure 3. M1 polarization is characterized by alterations in gene expression resulting from an intricate signaling cascade that is triggered by LPS and IFNγ and includes the production of lactic and histone Kla. In order to verify the roles of lactate and histone Kla in the control of gene expression, the levels of lactate were manipulated during M1 polarization as well and the impact on the expression of the arg1 gene belonging to the M2 class was examined [15]. Eliminating lactate dehydrogenase isoenzyme A was the initial step in reducing lactate levels (LDHA). Macrophages that lack LDHA show reduced lactate production and lower levels of global histone Kla during M1 polarization [15]. Removing LDHA from macrophages reduced histone Kla tagging on the Arg1 promoter and attenuated arg1 expression, but it had no effect on the production of pro-inflammatory cytokines [15]. When glycolysis inhibitors (2-DG, DCA, and GNE-140) were utilized to polarize macrophages to M1, similar results were seen. When M1 macrophages were exposed to exogenous lactate, there was a noticeable increase in intracellular lactate and histone Kla levels; also, there was an increase in Arg1 expression and the expression of Kla levels on the Arg1 promoter [15]. Even though exogenous lactate generation has no impact on the translation of early genes linked to inflammation, It has the potential to enhance the activation of additional M2 genes, such as VEGFA, while undergoing M1 polarization [15]. Results therefore confirmed the hypothesis that lactate and histone Kla favorably affect M2-like gene generation through the polarization of macrophages with M1 status [15].

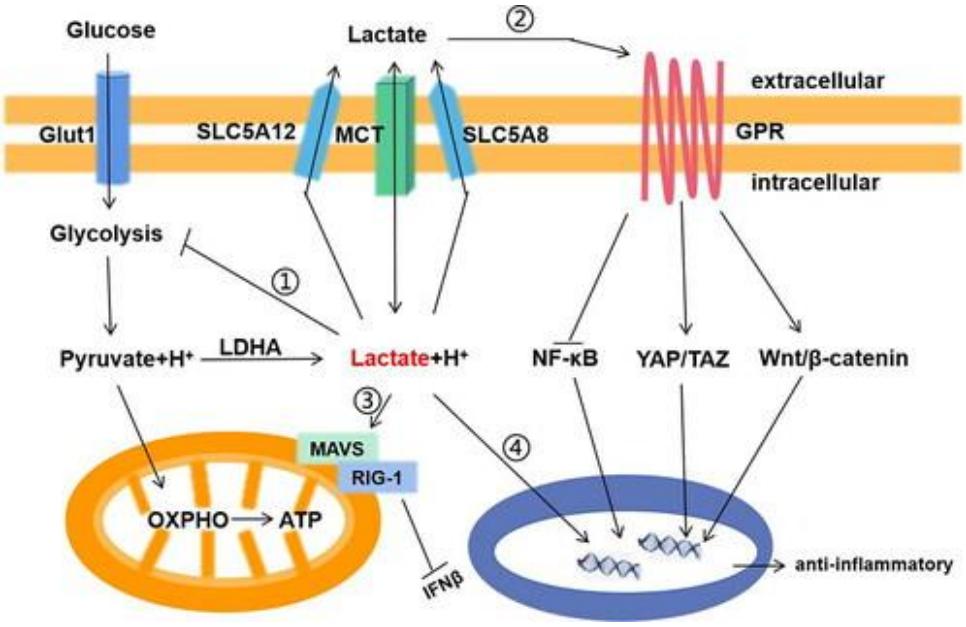
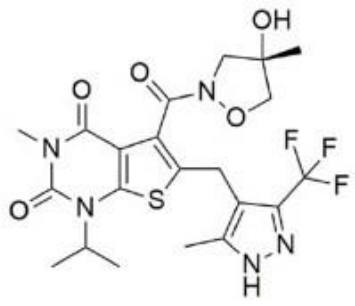


Fig. 3 Lactate-Mediated Histone Modification and M2 Gene Activation [15].

2.3.3. Potential Drug Targets of Macrophage Polarization Controlled by Lactate during Malignant Tumor Progression

In agreement with studies, lactate near the location of the tumor can enhance angiogenesis of the tumor, polarize M2 macrophages, and advance the tumor. Research into lactate, its signaling pathways, and TAMs has emerged as a promising new avenue for the management of malignant tumors in recent years. For instance, AZD3965, an inhibitor of carboxylate transporter 1 (MCT1). According to clinical research, AZD3965 is useful in the treatment of cancers related to small cell lung cancer (SCLC), breast cancer, gastric cancer, and Burkitt lymphoma. An oral bioavailable MCT1 selective inhibitor called AZD3965, a derivative of pyrrolidine pyrimidine, has completed a phase I clinical study in the UK for the treatment of lymphomas and advanced solid tumors [16] (Figure 4). The trial's secondary end measures included establishing the drug's pharmacokinetic properties in plasma and objective tumor response, while the primary goal was to ascertain the biological activity and safe dose of AZD3965 for assessment in upcoming phase II clinical trials. Although AZD3965 was usually well tolerated, the initial batch of findings indicated that it exhibited dose-limiting toxicity beyond 20 mg (oral) in the treatment of advanced solid tumors, as seen by increased cardiac troponin and electroretinogram alterations [16]. Since MCT4 appears to establish a compensatory mechanism that can withstand MCT1 blocking, there is evidence suggesting that MCT4 serves an important part in the resistance to AZD3965 therapy. Further deliberation is needed in this particular domain.



AZD3965

Fig. 4 AZD3965 Molecular Structure Formula [16].

3. Conclusion

In addition to being a byproduct of glycolysis, lactic acid also plays a role in M2 macrophage polarization. This article focuses on the important role of lactate in promoting the differentiation of M1 macrophages into M2 macrophages to adapt to TME and HIF-1α in M2 gene through various ways. Outlined in brief the distinct roles that two distinct phenotypes of macrophages play in inflammatory and neoplastic environments. This means that taking lactate as a target can effectively treat life-threatening diseases and hinder the progress of tumors. If it has the ability to control the polarization state of macrophages, it may become an effective cancer therapeutic target. In this paper, the factors inducing M1 macrophages to differentiate into M2 macrophages are only limited to the acidic environment, so other characteristics in TME can be studied in the future. There are still many aspects that can be understood and solved in the regulation of macrophages in the TME, such as other forms of epigenetic mechanisms and various inducers of M2 macrophage polarization. Secondly, it is worth exploring the effects of other metabolites such as ketone bodies, fatty acids, amino acids, etc. on macrophage polarization and tumor development.

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