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Understand the Fatty Acid Metabolic Reprogramming of Immune Cells in Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is a prevalent and challenging type of cancer worldwide. Recent research has focused intensively on understanding the molecular and pathological mechanisms of CRC because of the poor prognosis associated with its treatment. The tumor microenvironment (TME) is crucial in tumor progression and has been the subject of extensive investigation. Metabolic reprogramming has become a central focus in cancer research, with numerous studies emphasizing its importance in CRC. Specifically, the reprogramming of fatty acids has been found to alter the energy and nutrient composition within the tumor microenvironment, affecting the complex interaction between immune cells, especially macrophages and T cells, and associated immune factors. This disruption can influence the tumor's ability to evade immune surveillance. Our in-depth analysis highlights the role of lipid metabolism processes in shaping the immune microenvironment of colorectal cancer tumors, revealing the regulatory impact of fatty acid metabolism on CRC development. The potential impact of this research on improving CRC treatment is significant, underscoring the importance of contribution to this field.

Keywords: *Colorectal Cancer, G Protein-Coupled Receptors, Lysophosphatidic Acid, Phospholipids.*

Introduction

Cancer is the second leading cause of death worldwide, primarily as a noncommunicable disease. Besides, Colorectal cancer (CRC) is the third most prevalent malignant tumor, showing a high mortality rate and an expected 60% increase in cases by 2030 [1-3]. Prolonging human life expectancy in the 21st century poses a significant challenge. The tumor microenvironment (TME) changes are essential indicators of cancer progression [3]. Cancer cells have evolved unique metabolic characteristics to survive in an environment with limited nutrients and low oxygen levels. Otto Warburg first laid the groundwork for our

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understanding of cancer metabolism in the 1920s, observing that cancer cells preferentially convert glucose to lactate even in the presence of oxygen [4-6].

Further research into cancer metabolism has revealed the profound impact of nutrients such as glucose, amino acids, and lipids on cancer biology [7]. While glucose and amino acids have been extensively studied, lipids have presented challenges for isolation and analysis due to their hydrophobic and chemically unstable nature. This has led to technological limitations in studying lipid metabolism. However, recent advancements in lipidomics have revolutionized our ability to investigate lipid metabolism in cancer [8]. Lipids, a diverse group of molecules including fatty acids, cholesterol, and phospholipids, play crucial roles in energy provision, cell membrane formation, and intracellular signaling pathways. Fatty acids, in particular, have been closely linked to the onset and progression of cancer. *De novo* synthesis of fatty acids has been emphasized as a significant factor in cancer development, alongside the uptake and transport of fatty acids [4]. Alterations in essential enzymes involved in fatty acid metabolism are common in cancer and are often used as treatment indicators and targets [1, 4, 7, 9, 10].

Moreover, fatty acids have crucial roles in modulating the structural properties of cell membranes, influencing membrane fluidity and stiffness [8]. These implications affect the aggressiveness and metastatic potential of cancer cells. Lipid signaling molecules such as prostaglandins, leukotrienes, and other eicosanoids can also activate oncogenic pathways [4, 8]. This discussion will explore the recent advancements in understanding fatty acid metabolism in cancer, the impact of fatty acids on cancer cell membrane structure, and the functions of signaling lipids in cancer progression. Furthermore, we will delve into the promising future directions of therapeutic approaches that target fatty acid metabolism, offering new hope in the fight against cancer.

Impact of Fatty Acid Metabolism in the TME

Tumor cells can adapt to challenging conditions by adjusting their metabolic processes, enabling them to thrive in unfavorable environments [11]. These modifications in cellular metabolism play a crucial role in driving the proliferation, invasion, metastasis, and resistance to treatments observed in tumors [12]. Targeting the metabolism of tumor cells holds promise as an approach to enhance the effectiveness of cancer treatment or make tumors more responsive to drug interventions [13]. An illustrative instance of metabolic adaptation is the Warburg effect, which involves increased glucose consumption and its conversion to lactic acid by cancer cells, representing an early indication of metabolic reprogramming in these cells [10]. Both glucose and glutamine serve as primary sources of fuel and essential biochemical building blocks for sustaining cancerous cells [1, 14, 15].

Furthermore, lipid metabolism significantly contributes to cancer progression, as fatty acids provide energy and aid in forming cellular membranes and function as signaling molecules within the tumor microenvironment [4]. Cancer cells can acquire fatty acids through various mechanisms, including de novo synthesis, breakdown pathways, and uptake from external sources [16, 17]. The enzymatic conversion of acetyl-CoA by acetyl-CoA carboxylases and fatty acid synthase is a critical step in fatty acid biosynthesis, and the resulting products undergo further modifications to fulfill diverse cellular functions. Within the mitochondria, β-oxidation facilitates the breakdown of fatty acids to generate energy, supporting the metabolic demands of cancer cells. Specific transporters on the plasma membrane facilitate the uptake of fatty acids by cancer cells,

highlighting the significance of lipid metabolism in sustaining tumor growth and progression (Figure.1). Additionally, emerging research suggests that tumors can acquire fatty acids via exosome-mediated transport mechanisms, illuminating the intricate interplay between tumor cells and their microenvironment in promoting cancer development [12].

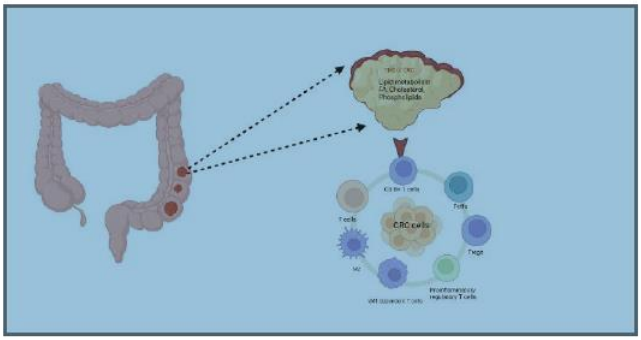

Figure 1. The Lipid Metabolisms on the TME of CRC

The Role of Lipid Metabolism in Immune Cell Function

Various factors influence the immune system's cellular function, including fatty acids, energy supply, and nutritional support [7]. The immune system has metabolic flexibility, allowing it to adapt to changes in the microenvironment. Different subsets of immune cells have distinct metabolic characteristics and utilize processes such as glycolysis, the citric acid cycle, and fatty acid oxidation to meet energy demands for growth and proliferation [12]. Fatty acids are critical in immune cell function and can impact T cell activity in antitumor immunity [4]. Fatty acid metabolism supports the survival and differentiation of CD8+ T cells in the tumor microenvironment [18]. Regulation of fatty acid anabolism can affect T cell differentiation and effector function [19]. Short-chain fatty acids also influence immune responses by inducing metabolic changes in T cells [20]. Fatty acid metabolism is crucial for T cells' activation, differentiation, and function. Different CD4+ T cell subsets exhibit distinct metabolic characteristics, and fatty acid metabolism can affect their activation and differentiation [21]. Treg cells rely on fatty acid oxidation for energy supply and metabolic signals [19, 22]. Targeting fatty acid metabolism in Treg cells is promising for enhancing antitumor immune responses [21]. Macrophages exhibit metabolic flexibility, with M1 macrophages relying on glycolysis and the pentose phosphate pathway, while M2 macrophages utilize oxidative phosphorylation and fatty acid oxidation [23]. Fatty acids can modulate macrophage polarization in the tumor microenvironment, impacting immune responses and tumor progression [9]. Overall, fatty acid metabolism plays a crucial role in immune cell function and can be targeted to enhance antitumor antitumor immunity.

Moreover, targeting lipid droplets in autophagy could be a potential direction for cancer therapy through nano-drug loading to affect macrophage fatty acid metabolism [9]. Metabolites in different macrophage states are crucial for signal transduction, as shown through experiments targeting TAMs and MGLL silencing in pancreatic cancer cells. TAM reprogramming from M2 to M1 increases tumor-killing factor production, exhibiting antitumor effects. Regulation of TAMs proves more effective than direct macrophage elimination for tumor growth control. Dendritic cells are crucial in initiating immune responses through TLR agonist activation in cDCs and pDCs. Fatty acid metabolism reprogramming influences DC

function, where high fatty acid accumulation impairs antigen presentation, hindering T-cell response. FABP5 regulates TLR signaling, affecting Treg production and tumor progression. TDEs deliver fatty acids, inducing lipid droplet production and immune dysfunction in DCs. Fatty acid modulation affects DC function and immunogenicity, highlighting potential targets for cancer immunotherapy. Modulating fatty acid synthesis and PGE2 inhibition can reverse tumor immune escape, which is promising for immunotherapy. In conclusion, targeting fatty acid metabolism in DCs holds promise for improving the immunosuppressive TME and enhancing antitumor immune responses.

The Impact of Lipid Metabolism on the Immune Microenvironment In CRC

Lipid metabolism is closely connected to cell proliferation and immune function, serving as a crucial energy source and an essential component of cell membranes [7, 8]. A high-fat diet can accelerate the advancement of colorectal cancer (CRC) by influencing gut bacteria, which in turn leads to changes in the CRC tumor environment [18]. This interaction can impede the infiltration and functioning of CD8+ T cells, promoting colorectal cancer growth by suppressing immune cell activity [24]. Overall, alterations in lipid metabolism are frequently observed in cancer and affect the immune environment and prognosis of CRC [1]. Disturbances in the metabolism of fatty acids, cholesterol, and phospholipids are linked explicitly to crucial aspects of CRC and impact its immune landscape [4]. The atypical behavior of different lipid categories in the modulation of lipid metabolism plays a critical role in CRC and its associated immune environment [1]. Disturbances in the metabolism of fatty acids also contribute to changes in the immune environment within CRC. Fatty acids are essential in biology and human nutrition, serving as a reliable energy source and effective anti-inflammatory and immunomodulatory agents [1]. Intracellular fat is primarily stored in structures known as lipid droplets (LDs), which accumulate in rapidly proliferating tumor cells, particularly in CRC, due to their high energy demands. LDs contribute to tumor progression by transferring to the LD membrane with the help of ATGL and HSL, releasing free fatty acids from stored triglycerides, which serve as a source of fatty acids for the polarization of tumor-associated macrophages (TAMs). This process promotes tumor growth by facilitating the M2-like polarization of TAMs [18, 25]. Additionally, Calreticulin (CRT), a versatile protein located in the endoplasmic reticulum, plays a multifaceted role in the development and progression of tumors by enhancing the maturation of dendritic cells (DCs).

Fatty Acid Metabolism in Colorectal Cancer

Lipid droplets, lipid-rich organelles, play a significant role in CRC progression. They can reduce the effectiveness of chemo-radiotherapy and disrupt the maturation and activation of dendritic cells, ultimately promoting tumor growth [18]. Additionally, lipid droplets can diminish the population of CD8+ T cells, enabling tumors to evade the immune system and hasten cancer progression. Understanding the signaling pathways related to the immune responses to lipid droplets and prostaglandins is crucial, as they play a vital role in CRC development and impact the TME by interacting with immune cell receptors. Prostaglandin E2 (PGE2) binding to prostaglandin E receptor 1 (EP1) boosts Fas ligand (FasL) production, compromising the function of CD8+ T cells and allowing cancer cells to evade detection. Fas protein levels are low in colorectal cancer, contributing to immune evasion within tumors. EP4 interacts with PGE2 to activate M2-type TAMs. The enzyme CPT1A, abundant in colorectal cancer, enhances fatty acid oxidation, supporting myeloid-derived suppressor cell function,

impairing T-cell immunity, and promoting tumor growth. Fatty acid oxidation upregulates PD-1 and carnitine palmitoyl transferase IA, inhibiting effector T-cell function and protecting cancer cells. Fatty acid metabolism is a significant process, and targeting various enzymes and pathways through a metabolic approach may be promising for treating colorectal cancer in the future. Prostaglandins and carnitine palmitoyl transferase, crucial in fatty acid metabolism, are relatively modifiable, offering potential targets for treatment. Literature has already discussed treatments focusing on these factors, and integrating these strategies into clinical practice could enhance effectiveness and patient outcomes. Recent studies have highlighted the significant influence of the gut microbiome on metabolic changes associated with colorectal cancer. The gut microbiome generates short-chain fatty acids (SCFAs) by breaking down dietary fiber and engaging in metabolic interactions among microbial species. These SCFAs regulate the gut microbiota, impact immune cell function and apoptosis, and inhibit tumor growth through GPR signaling pathways [18].

Cholesterol, a crucial component in cellular and systemic functions, undergoes metabolic changes in colorectal cancer, leading to increased production. This process depends on the expression of SREBP2 by the PI3K/AKT/mTOR axis [25, 26]. In colorectal cancer, cholesterol induces macrophage infiltration, leading to increased production of mitochondrial reactive oxygen species (ROS) and activation of NLRP3 inflammatory vesicles [26]. These vesicles release CCL5, facilitating immune evasion by colorectal cancer cells [27]. Cholesterol also influences T-cell proliferation, migratory dysfunction, and apoptosis by elevating PD-1 and 2B4 immune checkpoints on CD8+ T cells, which colorectal cancer cells exploit to evade T-cell immune surveillance [27]. Elevated deoxycholic acid (DCA) levels in colorectal cancer shape the tumor immune microenvironment by modulating EGFR, suppressing p53, and promoting proinflammatory differentiation in regulatory T cells [28]. Both cholesterol and DCA are specific targets in drug therapy, with the current use of statins and cholesterol uptake modifiers [29]. However, more potent drugs are needed to regulate the bile acid pathway in colorectal cancer.

Phospholipids in Colorectal Cancer Therapy

Phospholipids play a crucial role in mammalian cell biology, forming a barrier to control permeability and serving as fundamental components for lipid-mediated synthesis [1, 4, 10]. Phospholipids, a class of lipids that are significant components of all cell membranes, play a crucial role in modulating blood lipid cholesterol levels and supporting lipid metabolism [1]. They form a barrier to control permeability and serve as fundamental components for lipid-mediated synthesis [1, 4, 10]. Understanding the role of phospholipids in these processes is crucial for managing CRC [31]. There is an increasing interest in studying the impact of lysophosphatidic acid (LPA) on the progression of CRC. Researchers focus on how LPA affects cell pathways through G protein-coupled receptors. Studies show that AGPAT4 plays a significant role in regulating LPA levels in CRC cells. This regulation can stimulate M1-like macrophage-mediated activation of T-cells by upregulating IL1β and IL-6 levels through the p38/p65 signaling pathway, thus suppressing CRC development [30].

Additionally, researchers have looked into sphingomyelin-based nanovesicles loaded with camptothecin (called camptothesomes) and found that they can induce immunogenic cell death (ICD), reshaping the immunosuppressive environment of the TME and triggering T-cell-driven adaptive immune

responses against CRC [32]. Camptothesomes have also been shown to boost the effectiveness of PD-L1/PD-1 blockade by promoting a cytotoxic T-cell (CTL) response against CRC [24, 33]. The significant role of phospholipids in modulating blood lipid cholesterol levels, supporting lipid metabolism, and potentially inhibiting CRC metastasis underscores their potential as a promising therapeutic approach for managing CRC [1].

Summary and Future Perspectives

The body maintains its internal stability and function through fatty acid metabolic pathways. In cancer, these pathways undergo changes that impact the immune environment and cellular immune response of the tumor. In CRC, alterations in lipid metabolism led to cellular growth and proliferation changes influenced by shifts in metabolic profiles and the TME. This review delves into how fatty acid metabolic changes affect the immune environment of CRC patients and discusses their effects on various immune cell types. It highlights the crucial role of the immune microenvironment in CRC, aiming to captivate the audience's interest in this study area and the promising potential of therapeutic interventions. The accompanying review offers a foundational overview of the domain and novel research pathways for analyzing the immune microenvironment and associated treatments in colorectal cancer.

Conflict of Interest

None

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Sakthivel Muthu: Conceptualization, Prathapavarma Digala and Nallusamy Duraisamy:Writing-original draft, Nagaraj Subramani and Deepan Sundararaj: Writing-review and editing.

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