Immunome Research
ISSN: 1745-7580
OPEN ACCESS Freely available online
Commentary

The Role of Cholesterol Absorption in Modulating the Immune Response in Colorectal Cancer

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DESCRIPTION

Colorectal Cancer (CRC) is a major cause of cancer-related illness and death globally. Despite advancements in treatment strategies, the prognosis for CRC patients remains poor, particularly in advanced stages. The complexity of the immune response in CRC, specifically the role of immune cells in shaping tumor progression, has garnered significant attention in recent years. A growing body of research has identified the metabolic alterations occurring in tumor cells, including altered cholesterol metabolism, as key factors in modulating the immune environment and influencing tumor immunity. Among these, the absorption and accumulation of cholesterol in colorectal cancer cells have been shown to trigger immunosuppressive signaling pathways, which play a key role in inhibiting effective antitumor immunity, particularly by inactivating memory $CD8^+$ T cells.

Cholesterol metabolism in colorectal cancer

Cholesterol is an essential lipid that serves as a building block for cell membranes, hormones, and bile acids. In cancer cells, alterations in lipid metabolism are common, as these cells require increased lipid biosynthesis to support their rapid proliferation and survival. In CRC, increased cholesterol uptake via the Low-Density Lipoprotein Receptor (LDLR) and other transport mechanisms facilitates the accumulation of cholesterol in tumor cells. This altered cholesterol metabolism is not only important for cancer cell growth and invasion but also for modulating the surrounding tumor microenvironment, which plays a pivotal role in immune evasion.

Immunosuppressive signaling induced by cholesterol in CRC

The immunosuppressive microenvironment in colorectal cancer is a critical factor that enables tumor cells to evade detection and destruction by the immune system. One of the most important immune components that are affected by this altered metabolism is the memory $CD8^+$ T cell. Memory $CD8^+$ T cells are integral to the body's ability to set up a strong and efficient immune response against cancer cells upon re-exposure to tumor antigens. However, in CRC, the tumor cells can impair the function of these cells through various mechanisms, with cholesterol accumulation being a significant contributor.

Cholesterol, through its interaction with cell surface receptors and lipid rafts, activates several downstream signaling pathways that modulate the immune response. In CRC cells, the accumulation of cholesterol activates the activation of key immunosuppressive molecules, such as (PD-L1) Programmed cell Death Ligand 1, which binds to PD-1 receptors on immune cells, including $CD8^+$ T cells, leading to their exhaustion and anergy. This interaction dampens the cytotoxic function of memory $CD8^+$ T cells, rendering them ineffective in recognizing and destroying tumor cells.

Moreover, elevated cholesterol levels in CRC cells can promote the secretion of cytokines such as TGF-β and IL-10, which further contribute to the immunosuppressive tumor microenvironment. These cytokines inhibit the activation and proliferation of effector T cells, while also inducing the differentiation of regulatory T cells (Tregs), which are known for their suppressive effects on antitumor immune responses.

Inactivation of memory $CD8^+$ t cells

Memory $CD8^+$ T cells are necessary for the long-term surveillance of tumors and have been shown to play a role in preventing relapse after cancer treatment. However, the immunosuppressive signals induced by cholesterol-rich CRC cells can lead to the dysfunction of these memory T cells. The accumulation of cholesterol disrupts the signaling pathways necessary for the maintenance and activation of memory $CD8^+$ T cells. Specifically, the engagement of the PD-1/PD-L1 axis and the release of immunosuppressive cytokines, such as TGF-β, lead to the exhaustion of memory T cells. These exhausted T cells exhibit reduced cytotoxic activity, impaired proliferation and limited cytokine production, rendering them incapable of mounting an effective immune response. In addition to the

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Received: 21-Nov-2024, Manuscript No. IMR-24-36057; **Editor assigned:** 25-Nov-2024, PreQC No. IMR-24-36057 (PQ); **Reviewed:** 10-Dec-2024, QC No. IMR-24-36057; **Revised:** 18-Dec-2024, Manuscript No. IMR-24-36057 (R); **Published:** 25-Dec-2024, DOI: 10.35248/1745-7580.24.20.287

Citation: Williams M (2024). The Role of Cholesterol Absorption in Modulating the Immune Response in Colorectal Cancer. Immunome Res. 20:287.

direct effects on memory T cells, cholesterol-induced changes in the tumor microenvironment also contribute to the recruitment and activation of Myeloid-Derived Suppressor Cells (MDSCs) and Tregs. These cells further dampen the ability of memory $CD8^+$ T cells to respond to tumor-associated antigens, perpetuating an immunosuppressive loop that allows the tumor to grow unchecked.

Potential therapeutic implications

Understanding the role of cholesterol absorption and metabolism in CRC cells provides a novel avenue for therapeutic intervention. Targeting cholesterol metabolism in CRC cells, either through the inhibition of LDLR or other cholesterol transporters, could potentially reduce the cholesterol accumulation in tumor cells and restore immune function. In addition, therapies that block the PD-1/PD-L1 interaction or modulate the cytokine environment could help reinvigorate exhausted memory $CD8^+$ T cells, improving the effectiveness of immunotherapy.

Recent studies have highlighted the potential of combining cholesterol-lowering agents, such as statins, with immune checkpoint inhibitors to enhance the antitumor immune response. Statins have been shown to reduce cholesterol levels in tumor cells, thereby limiting the immunosuppressive signaling that leads to T cell dysfunction. By combining statins with immune checkpoint inhibitors, it may be possible to reverse the immune evasion mechanisms in CRC and improve the therapeutic outcomes of immunotherapy.

Cholesterol absorption and accumulation in colorectal cancer cells play a critical role in creating an immunosuppressive microenvironment that impairs the function of memory $CD8^+$ T cells. The activation of immunosuppressive signaling pathways, such as the PD-1/PD-L1 axis and the secretion of immunosuppressive cytokines, leads to the exhaustion of memory T cells, lowering the immune system's ability to mount an effective response against the tumor. Targeting cholesterol metabolism and the immunosuppressive pathways it activates offers potential therapeutic strategies to enhance the effectiveness of immunotherapy in CRC and improve patient outcomes.