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Review Article

Cholesterol metabolism reprogramming in multiple myeloma: examining its specificity and impact on the immune microenvironment

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Abstract: Multiple myeloma (MM) represents a malignancy within the hematological system, in which the reprogramming of cholesterol metabolism plays a pivotal role in its pathogenesis. This review focuses on the specificity of cholesterol metabolism abnormalities in the diagnosis of MM and their implications for the immune microenvironment, aiming to provide new perspectives for both diagnosis and treatment of MM. The expression changes of cholesterol metabolism-related genes (CMGs), such as ANXA2 and CHKA, closely correlate with the prognosis of MM. These CMGs are linked not only to clinical parameters, including the number of transplants and the International Staging System, but also to tumor incidence, progression, and treatment resistance. Consequently, they offer new biological markers for both the prognosis assessment and therapeutic strategies for MM. In terms of the immune microenvironment, reprogramming of cholesterol metabolism significantly influences tumor-infiltrating immune cells (TIICs), including T lymphocytes, B lymphocytes, tumor-associated macrophages (TAMs), dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs). Moreover, the cholesterol metabolite 25-hydroxycholesterol (25-HC) enhances the activity of immunosuppressive macrophages by modulating lysosomal AMPK activation and metabolic reprogramming, thus presenting a new metabolic target for tumor immunotherapy. The regulatory effects of cholesterol metabolism on MDSCs are also noteworthy; these cells promote tumor progression by inhibiting T-cell responses. High-fat diets and obesity can induce the accumulation of MDSCs, where molecules involved in the cholesterol metabolic pathway, such as the synthase CYP27A1 for 27-hydroxycholesterol (27-HC), have been associated with poor prognoses in ovarian cancer. Genetic knockout of this enzyme significantly inhibits tumor progression. Regarding the diagnostic specificity of cholesterol metabolism abnormalities, these changes present novel biomarkers for the early diagnosis and therapeutic monitoring of MM. Analyzing the correlation between immune cell proportions in the tumor microenvironment and lipid metabolism genes has unveiled potential links between cholesterol metabolism and immune responses, paving the way for precision medicine in MM. Thus, the reprogramming of cholesterol metabolism in MM offers a multidimensional and interdisciplinary research avenue. Future studies need to delve deeper into the specific mechanisms through which cholesterol metabolism contributes to MM development and leverage these findings to formulate new therapeutic strategies, ultimately improving outcomes for MM patients.

Keywords: Multiple myeloma, cholesterol metabolism reprogramming, immune microenvironment, diagnostic specificity

Introduction

Multiple myeloma (MM) is a malignant tumor originating from plasma cells in the bone marrow, characterized by the unrestricted proliferation of clonal plasma cells. This leads to a series of serious clinical manifestations, including skeletal lesions, anemia, hypercalcemia, and renal impairment [1]. According to the Global Burden of Disease 2016 (GBD 2016), there were approximately 16,500 new cases of MM and around 10,300 deaths in China in 2016, with age-standardized incidence and mortality rates of 1.03 and 0.67 per 100,000, respectively [2]. The incidence of MM is showing an upward trend worldwide, with around 160,000 new cases reported globally in 2020. In China, while the overall incidence remains relatively low, it is on the rise due to the aging population, potentially influenced by various

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factors, including genetics, environmental conditions, and lifestyle choices [3]. The pathogenesis of MM is complex, involving intricate interactions across multiple levels such as genetics, epigenetics, metabolic disturbances, and the immune microenvironment [4, 5]. Recent research has increasingly highlighted the significant role of metabolic disorders in the pathogenesis of MM.

Cholesterol metabolism plays a critical role in tumor biology, with its aberrant activation closely linked to tumor initiation, progression, recurrence, and metastasis [6-8]. In multiple myeloma (MM), the reprogramming of cholesterol metabolism not only directly influences the biological behavior of tumor cells but also may regulate the activity of immune cells within the tumor microenvironment, although this area of research is still in its early stages [9]. Cholesterol is an essential lipid component of cell membranes and lipid rafts, as well as a precursor for bile acids, steroids, and steroid hormones, making it vital for the survival and growth of mammals [10]. Dysregulation of cholesterol levels can lead to cardiovascular diseases, neurodegenerative disorders, and cancer, posing a significant threat to human health [8, 11, 12]. In tumor cells, the abnormal activation of cholesterol metabolism can promote cell proliferation and survival through various mechanisms [13, 14]. Studies have indicated that the expression of the key enzyme in the cholesterol synthesis pathway, 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), is upregulated in tumor cells, thus facilitating cholesterol synthesis [15]. Furthermore, the accumulation of cholesterol derivatives, such as oxidized cholesterol, within the tumor microenvironment can impact signaling pathways and metabolic activities of tumor cells, further driving tumor progression [16]. In multiple myeloma, the metabolic characteristics of tumor cells exhibit unique reprogramming, including alterations in cholesterol metabolism. These metabolic changes occur not only within the tumor cells themselves but also in the tumor microenvironment [17]. Recently, studies have suggested a potential correlation between the proportion of immune cells in the tumor microenvironment and lipid metabolism-related genes, indicating a direct link between cholesterol metabolism and immune responses [18]. Collectively, this evidence suggests that the reprogramming of cholesterol metabolism in multiple myeloma may significantly affect tumor immune recognition and evasion.

Multiple Myeloma (MM) is a hematological malignancy characterized by the malignant proliferation of monoclonal plasma cells in the bone marrow. The significance of the immune microenvironment in the progression of MM has garnered increasing attention, as it not only provides a refuge for MM cells to survive and proliferate but also promotes immune evasion and disease progression through various mechanisms. The cellular components of the immune microenvironment - including tumor-associated macrophages, myeloid-derived suppressor cells, osteoclasts, regulatory T cells, dendritic cells, and natural killer cells - collectively contribute to the establishment of an immunosuppressive milieu [19-21]. Under the influence of MM cells, these immune cells become functionally impaired, resulting in a loss of immune surveillance and cytotoxicity against malignant MM cells. Rather than targeting MM cells, these immune components may inadvertently support and sustain their growth and survival, potentially leading to the development of drug resistance and frequent relapse of the disease. Additionally, the non-cellular elements of the immune microenvironment, such as cytokines and metabolic byproducts, also play a crucial role in the immune evasion mechanisms employed by MM. Research has demonstrated that MM cells can secrete pro-inflammatory factors like IL-8, which facilitates the chemotaxis and migration of MM cells, thereby influencing disease progression [22]. Furthermore, the high expression of PD-L1 on MM cells enables binding to PD-1 on T cells, which inhibits T cell activation through the PD-1/PD-L1 signaling pathway, thereby promoting tumor immune escape [23].

In recent years, research has unveiled that cholesterol metabolism reprogramming not only directly influences the biological behavior of tumor cells but also modulates the anti-tumor activity of immune cells within the tumor microenvironment, subsequently affecting tumor immune recognition and evasion [24]. In multiple myeloma (MM), aberrant activation of cholesterol metabolism is closely linked to disease progression and prognosis. A study by Na Zhao et al. demonstrated a significant correlation between the expression of cholesterol metabolism-related genes (CMGs) and the prognosis

of MM patients. By constructing a prognostic model based on CMGs, it effectively predicts survival outcomes for individuals with MM [18]. Cholesterol metabolism exerts a substantial impact on various immune cell types within the immune microenvironment. Myeloid-derived suppressor cells (MDSCs) accumulate in tumors and promote tumor progression through the overexpression of specific molecules involved in the cholesterol metabolic pathway, such as the synthesis enzyme CYP27A1 for 27-HC [25, 26]. Additionally, the reprogramming of cholesterol metabolism in tumor-associated macrophages (TAMs) and dendritic cells (DCs) is also intricately associated with tumor immunity [27, 28]. Furthermore, ApoE binds to LRP8 on MDSCs, enhancing anti-tumor immunity [29], while in acute myeloid leukemia, ApoE directly binds to LILRB4 on tumor cells, facilitating immune escape [30]. T lymphocytes play a central role in anti-tumor immunity, and cholesterol, along with its derivatives, serves as a significant regulator of T lymphocyte function. Research indicates that pharmacological inhibition of ACAT1 activity in $CD8^+$ T cells can elevate cholesterol content in the cell membrane, thereby promoting $CD8^+$ T cell activation and enhancing their cytotoxic effect on tumors [31]. Moreover, cholesterol metabolism is associated with the production of IL-10 by regulatory B cells, as cholesterol metabolism drives the function of these cells by supplying GGPP [32].

This review aims to explore the specificity of cholesterol metabolism reprogramming in MM and its impact on the immune microenvironment. It will analyze the advancements in the research concerning the interactions between cholesterol metabolism and various immune cells within the immune microenvironment, as well as discuss the implications of these findings for the clinical treatment of MM patients. A deeper understanding of the mechanisms through which cholesterol metabolism operates in MM could provide new perspectives and strategies for precision therapy, underscoring its significant clinical relevance.

The role of cholesterol metabolism in multiple myeloma

Cholesterol metabolism in normal bone marrow-derived plasma cells

The cholesterol metabolism process in normal bone marrow-derived plasma cells is a complex and tightly regulated procedure involving multiple molecular mechanisms and genetic targets. Cholesterol synthesis within plasma cells primarily occurs through the mevalonate pathway. Initially, acetyl-CoA in the cytoplasm is catalyzed by acetoacetyl-CoA thiolase to generate acetoacetyl-CoA, which then combines with another molecule of acetyl-CoA under the action of 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS) to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). Subsequently, HMG-CoA reductase (HMGCR) reduces HMG-CoA to mevalonate, which is the first rate-limiting step in cholesterol synthesis [33]. Mevalonate undergoes a series of phosphorylation and decarboxylation reactions, ultimately generating squalene. Squalene is then converted to 2,3-oxidosqualene under the catalysis of squalene epoxidase (SQLE), followed by the generation of lanosterol and, through a series of complex reactions, the final production of cholesterol [34]. In addition, plasma cells can also obtain cholesterol by taking up lipoproteins from the blood. The low-density lipoprotein receptor (LDLR) plays a key role in the uptake of low-density lipoprotein (LDL) particles by plasma cells. LDLR specifically recognizes and binds to LDL particles, internalizing them into the cell. Within the cell, LDL particles are degraded, releasing free cholesterol for cellular use [35].

This metabolic process is primarily regulated by the SREBP pathway and the LXR pathway. In normal bone marrow-derived plasma cells, when intracellular cholesterol levels are low, SREBP-2 translocates from the endoplasmic reticulum to the Golgi apparatus, where it is cleaved and activated. The activated SREBP-2 enters the nucleus and binds to the promoter regions of cholesterol synthesis-related genes, such as HMGCR and HMGCS, promoting the expression of these genes and thereby increasing cholesterol synthesis. At the same time, SREBP-2 also upregulates the expression of LDLR, enhancing cellular uptake of LDL [36]. LXR can form heterodimers with retinoid X receptor (RXR) and bind to the LXRE elements of cholesterol metabolism-related genes, regulating their expression. In normal plasma cells, LXR maintains cholesterol homeostasis by regulating the expression of genes involved in cholesterol synthesis and uptake [37].

Cholesterol is an essential component of cell membranes, regulating membrane fluidity and stability, thereby ensuring the normal physio-

logical functions of plasma cells. Moreover, cholesterol metabolites, such as 27-hydroxycholesterol, can act as signaling molecules, participating in intracellular signaling processes and influencing the proliferation, differentiation, and immune function of plasma cells [38]. Additionally, cholesterol serves as a precursor to steroid hormones. Within plasma cells, cholesterol can be converted into biologically active steroid hormones, which participate in physiological regulation of the body [39].

Alterations in cholesterol metabolism pathways in MM

The role of cholesterol metabolism in multiple myeloma (MM) is gaining increased recognition. Research indicates that the cholesterol metabolic pathways in MM patients exhibit significant alterations that are closely linked to disease progression and prognosis [40]. Often, MM patients experience hypocholesterolemia, which may result from the elevated uptake of low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) by MM cells. This uptake is accompanied by the overexpression of LDL receptors and associated proteins, as well as the inhibition of cholesterol conversion to bile acids within the cells [41]. Moreover, LDL-c enhances the survival of MM cells through its anti-apoptotic effects, rendering exogenous cholesterol a critical factor for the survival of these cells [42]. Within the cholesterol metabolism pathway, the mevalonate (MVA) signaling pathway plays a pivotal role in the survival of MM cells with the t(4;14) translocation [43]. HMG-CoA reductase, the rate-limiting enzyme in the MVA signaling pathway, is a target for statin medications, which preferentially induce apoptosis in t(4;14) translocated MM cells by inhibiting the MVA pathway [44]. Additionally, cholesterol metabolites such as 25-hydroxycholesterol (25-HC) can influence the immunosuppressive function of macrophages by modulating their metabolic reprogramming, offering new targets for tumor immunotherapy aimed at macrophages [45]. The findings outlined above highlight the significant role of altered cholesterol metabolism pathways in the pathogenesis of MM and suggest the potential for these pathways to serve as therapeutic targets. By modulating cholesterol metabolism, it may be possible not only to directly impact the biological behavior of MM cells but also to alter the functionality of immune cells within the tumor microenvironment, thereby providing novel avenues for immunotherapy in MM.

The relationship between cholesterol metabolism and the biological behavior of MM cells

The significance of cholesterol metabolism in multiple myeloma (MM) is increasingly recognized, particularly concerning its close association with the biological behaviors of MM cells. Cholesterol serves as a critical component of cellular membranes and plays a vital role in cell signaling and recognition, significantly influencing cellular growth, differentiation, and apoptosis [46]. In the context of MM, the aberrant activation of cholesterol metabolism may facilitate tumor cell proliferation and survival. Research indicates that MM cells may enhance their uptake of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) by upregulating the expression of low-density lipoprotein receptors (LDL-R) and associated proteins, leading to elevated intracellular cholesterol levels [47]. Additionally, MM cells might contribute to hypocholesterolemia by inhibiting the conversion of cholesterol to bile acids and reducing dietary cholesterol absorption, creating a metabolic environment conducive to their survival and proliferation [48]. Another crucial aspect of disrupted cholesterol metabolism in MM is its impact on the fluidity of cellular membranes. Changes in the cholesterol composition within cell membranes may influence membrane fluidity and structure, thereby affecting cellular functional characteristics. Studies have shown a close relationship between drug resistance in tumor cells and factors such as membrane fluidity, lipid composition, and the presence of cholesterol and unsaturated fatty acid chains [49]. In vitro studies demonstrate that drugs that decrease membrane fluidity may exert anti-tumor effects on MM cells resistant to proteasome inhibitors [50]. Furthermore, abnormalities in cholesterol metabolism may also affect the metabolic reprogramming of MM cells. These cells may upregulate the expression of HMG-CoA reductase, a key enzyme in the cholesterol synthesis pathway, thereby promoting cholesterol production [51]. This metabolic reprogramming likely provides MM cells with increased bioenergy and biochemical precursors, further supporting their rapid proliferation. Current research on cholesterol metabo-

Table 1. Contradictions in cholesterol metabolism research in tumors

Research Perspective	Research Conclusion	Source
High cholesterol intake is associated with cancer	A high-cholesterol diet is associated with a high incidence of certain cancers	[52]
	High cholesterol levels may promote the proliferation and survival of tumor cells	[53]
Low cholesterol levels may increase cancer risk	Low cholesterol levels are associated with a high risk of certain cancers	[54]
	Low cholesterol levels may affect the normal function of the immune system, thereby increasing the risk of cancer	[55]
The correlation between blood cholesterol levels and cancer incidence	Blood cholesterol levels are positively correlated with the incidence of certain cancers	[56]
	There is no significant correlation between blood cholesterol levels and the incidence of certain cancers	[57]
The correlation between ACAT1 expression and cancer incidence	High expression of ACAT1 may be associated with a high risk of certain cancers	[58]
	There is no significant correlation between ACAT1 expression levels and the incidence of certain cancers	[59]
The correlation between SREBP2 expression and cancer incidence	High expression of SREBP2 may promote the development of certain cancers	[60]
	There is no significant correlation between SREBP2 expression levels and the incidence of certain cancers	[61]

lism in tumors presents certain contradictions, which are detailed in **Table 1**.

The impact of abnormal cholesterol metabolism on the progression of MM

Abnormal cholesterol metabolism plays a crucial role in the progression of MM. Research indicates that patients with MM often present with hypocholesterolemia, which may be linked to increased utilization of cholesterol by tumor cells [48]. Specifically, MM cells can enhance their cholesterol uptake by upregulating the expression of low-density lipoprotein receptors (LDL-R) and associated proteins, as well as inhibiting the conversion of cholesterol to bile acids. Additionally, exogenous cholesterol is vital for the survival of MM cells; LDL-C promotes cell viability through anti-apoptotic mechanisms [42]. The alterations in cholesterol metabolism not only directly influence the biological behaviors of MM cells but also regulate the anti-tumor activity of immune cells within the tumor microenvironment. Notably, reprogramming of cholesterol metabolism affects the functionality of various immune components, including myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), dendritic cells (DCs), and T cells [28, 62, 63]. During CAR-T cell therapy, changes in serum lipid levels and nutritional status in patients have also been associated with abnormalities in cholesterol metabolism, with decreased serum lipid levels potentially linked to cytokine release syndrome (CRS) [64]. Furthermore, specific cholesterol metabolism-related genes (CMGs) have been found to correlate with overall survival in MM, and constructed prognostic features can effectively predict outcomes and inform targeted therapies [18]. It is evident that abnormal cholesterol metabolism may indirectly promote the progression of MM by affecting the functionality of immune cells and altering the tumor microenvironment. Discrepancies in cholesterol metabolism between multiple myeloma cancer cells and normal cells are illustrated in **Figure 1**.

Impact of cholesterol metabolism reprogramming on the immune microenvironment in MM

Interaction between cholesterol metabolism and tumor-infiltrating immune cells (TIICs)

The reprogramming of cholesterol metabolism has gained increasing attention in its effects on tumor-infiltrating immune cells (TIICs) in multiple myeloma (MM). Studies indicate that MM cells enhance cholesterol uptake by upregulating the expression of low-density lipoprotein (LDL) receptors and associated proteins while simultaneously inhibiting the conversion of cholesterol into bile acids, thereby increasing intracellular cholesterol levels [47]. This metabolic reprogramming not only influences the biological behavior of MM cells but also significantly impacts the immune microenvironment, particularly the TIICs.

Within the TIICs, myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) represent two critical populations involved in immune suppression [62, 65]. MDSCs expand during cancer, inflammation,

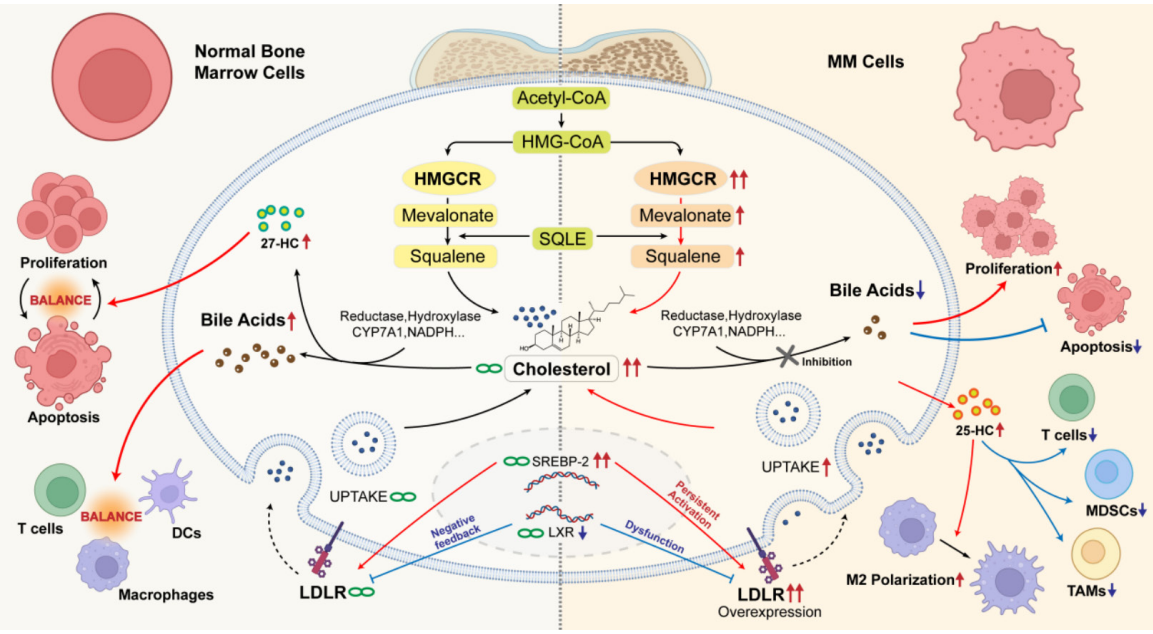

Figure 1. The discrepancies in cholesterol metabolism between multiple myeloma cancer cells and normal cells.

injury, and infection; they contribute to the rapid growth and spontaneous metastasis of primary tumors by suppressing the activation of $CD8^+$ T cells [66]. Molecules involved in cholesterol metabolism, such as the synthase CYP27A1 responsible for the production of 27-Hydroxycholesterol (27-HC), are positively correlated with poor prognosis in ovarian cancer. Notably, gene knockout of CYP27A1 in mouse models significantly inhibits tumor development, an effect that can be mitigated by the exogenous addition of 27-HC. This compound enhances the differentiation of M-MDSCs and increases their abundance within tumors, thereby promoting tumor progression [26]. TAMs produce 27-HC locally within breast tissue, while the high methylation of the CYP27B1 promoter in breast cancer cells further impedes the degradation of 27-HC, leading to its accumulation in tumor tissues. Elevated levels of 27-HC not only promote the proliferation of breast cancer cells but also induce macrophages to secrete a range of chemokines that facilitate the recruitment of monocytes and their differentiation into M2 phenotype macrophages. The interaction between 27-HC and M2 macrophages further exacerbates the progression of breast cancer [67]. Moreover, abnormal cholesterol metabolism influences dendritic cells (DCs) and T lymphocytes within the TIICs [28, 68]. Specifically, 27-HC can induce the differentiation of monocytes into mature DCs that express various surface molecules, such as CCR7, which impairs their migration to lymphoid organs and diminishes their anti-tumor activities. Consequently, this leads to tumor escape from immune surveillance [69].

The role of cholesterol metabolism in myeloid-derived suppressor cells (MDSCs)

Cholesterol metabolism plays a crucial role within the immune microenvironment of multiple myeloma (MM), particularly in the context of myeloid-derived suppressor cells (MDSCs). These cells are significant immunosuppressive components in the tumor microenvironment, aiding tumor cells in evading immune surveillance by inhibiting the function of immune cells such as T cells and natural killer (NK) cells. In the context of MM, the quantity and activity of MDSCs are closely associated with disease progression.

Research has demonstrated that cholesterol metabolism is instrumental in the immunosuppressive functions of MDSCs. Cholesterol metabolites, notably 27-hydroxycholesterol (27-HC), have been shown to promote the differentiation of monocyte-derived MDSCs (M-MDSCs) and increase their abundance within the tumor, thereby facilitating tumor advance-

ment. Furthermore, 27-HC contributes to the establishment of an immunosuppressive microenvironment by acting on MDSCs, thereby promoting the progression of breast cancer [70]. This suggests that cholesterol metabolism influences not only the differentiation and maturation of MDSCs but may also regulate their immunosuppressive activities. Abnormal activation of cholesterol metabolism in MDSCs could be linked to tumor immune escape. Studies indicate that a high-fat diet and obesity can induce the accumulation of MDSCs in tumor-bearing mice. These MDSCs promote rapid primary tumor growth and spontaneous metastasis by inhibiting the activation of $CD8^+$ T cells [66]. These findings underscore the significance of cholesterol metabolism in MDSC functionality and indicate that targeting cholesterol metabolism may represent a promising therapeutic strategy to modulate MDSC activity and enhance anti-tumor immune responses.

The relationship between cholesterol metabolism and tumor-associated macrophages (TAMs)

Cholesterol metabolism is a critical factor in the immune microenvironment of multiple myeloma (MM), particularly with regard to tumor-associated macrophages (TAMs). TAMs are vital immune regulatory cells that contribute to tumor progression by promoting the proliferation, survival, and immune evasion of tumor cells. The aberrant activation of cholesterol metabolism plays a significant role in the immunosuppressive functions of TAMs.

Research indicates that TAMs are the predominant local source of 27-hydroxycholesterol (27-HC) in breast tissue. The hypermethylation of the CYP27B1 promoter in breast cancer cells further impairs the degradation of 27-HC, leading to its accumulation within the tumor tissue. Elevated levels of 27-HC not only promote the proliferation of estrogen receptor (ER)-dependent breast cancer cells but also stimulate macrophages to secrete various chemokines, such as CCL2, CCL3, and CCL4, which facilitate the recruitment and M2 polarization of monocytes. The interaction between 27-HC and M2-type TAMs subsequently enhances the progression of breast cancer [71]. Additionally, cholesterol metabolites can influence tumor malignancy by modulating the functions of TAMs. Specifically, increased membrane cholesterol efflux leads to the polarization of TAMs towards an immunosuppressive M2-like phenotype that promotes tumor progression [72].

The impact of cholesterol metabolism on dendritic cell (DC) function

Cholesterol metabolism plays a crucial role in the function of dendritic cells (DCs), particularly within the immune microenvironment of multiple myeloma (MM). Studies have shown that cholesterol and its metabolic derivatives can significantly influence the differentiation and maturation of DCs. Notably, 27-hydroxycholesterol (27-HC) is capable of inducing the differentiation of monocytes into mature DCs, which then express various surface markers such as MHC-II, CCR7, CD40, and CD80, ultimately enhancing immune responses [73]. Moreover, cyclosporine A has been shown to affect the differentiation of monocytes induced by 27-HC, downregulating DC-specific markers and thereby inhibiting their maturation and function [74]. Further investigations indicate that the absence of ApoE leads to cholesterol accumulation in the cell membranes of DCs. This accumulation enhances the clustering of MHC-II molecules on the DC membrane, thereby improving their antigen-presenting capabilities and promoting $CD4^+$ T cell-mediated immune responses [75]. These findings suggest that by modulating cholesterol metabolism in DCs, it is possible to enhance their antigen-presenting function and subsequently activate T cells, playing a vital role in anti-tumor immunity. In the tumor microenvironment, aberrant activation of cholesterol metabolism may influence tumor immune evasion by affecting DC functionality. Specifically, liver X receptor (LXR) agonists can restore cholesterol efflux by upregulating ABCA1 and ABCG1, thereby triggering apoptosis in tumor cells [76]. Collectively, these results indicate that the regulation of cholesterol metabolism not only impacts the functionality of DCs but may also have direct effects on tumor cell survival.

Regulatory role of cholesterol metabolism in T lymphocytes

Cholesterol metabolism plays a pivotal regulatory role in T lymphocytes within the immune microenvironment of multiple myeloma (MM). T lymphocytes, particularly $CD8^+$ cytotoxic T cells, are essential for effective anti-tumor immunity.

Table 2. Impact of cholesterol metabolism reprogramming on the immune microenvironment in MM

Immune Cell Type	Impact of Cholesterol Metabolism	Specific Effects and Related Research
Tumor Infiltrating Immune Cells (TIICs)	Cholesterol metabolism reprogramming affects TIICs	MM cells increase cholesterol uptake, inhibit conversion to bile acids, affecting TIICs, especially MDSCs and TAMs
Myeloid-Derived Suppressor Cells (MDSCs)	Cholesterol metabolism promotes MDSCs differentiation and abundance	27-HC promotes differentiation of M-MDSCs, increases tumoral M-MDSCs abundance, forms an immunosuppressive environment
Tumor-Associated Macrophages (TAMs)	Cholesterol metabolism interaction with TAMs promotes tumor progression	TAMs produce 27-HC, hypermethylation of CYP27B1 promoter in breast cancer cells reduces 27-HC degradation, promotes breast cancer progression
Dendritic Cells (DCs)	Cholesterol metabolism affects DCs differentiation and maturation	27-HC induces monocytes to differentiate into mature DCs, ApoE deficiency enhances DCs antigen presentation capacity
T Lymphocytes	Abnormal activation of cholesterol metabolism affects T cell function	Accumulation of 27-HC may negatively impact T cell function, increased ACAT1 activity leads to cholesterol accumulation within cells, inhibiting T cell activation and proliferation

However, in the tumor microenvironment associated with MM, T cells frequently exhibit functional impairments and exhaustion, which is closely linked to dysregulated cholesterol metabolism. The accumulation of 27-hydroxycholesterol (27-HC) in the tumor microenvironment can adversely affect T cell functionality. Aberrant activation of cholesterol metabolism can disrupt T cell signaling, proliferation, and survival, thereby diminishing their anti-tumor activities [77]. In the context of MM, there is an increase in the activity of acyl-CoA:cholesterol acyltransferase 1 (ACAT1) in T cells, leading to the accumulation of cholesterol within the cells. This accumulation can inhibit T cell activation and proliferation. Conversely, inhibiting ACAT1 results in elevated cholesterol levels on the plasma membrane, which enhances T cell signaling and cytotoxic functions [78]. Moreover, abnormal activation of cholesterol metabolism may impact T cell metabolic reprogramming, further influencing their anti-tumor capabilities [79]. This intricate relationship highlights the significance of cholesterol metabolism in modulating T cell responses, suggesting potential therapeutic avenues for improving anti-tumor immunity in MM. The impact of cholesterol metabolism reprogramming on the immune microenvironment in MM was shown in **Table 2**.

Applications of cholesterol metabolism reprogramming in the diagnostic specificity of MM

The value of cholesterol metabolism biomarkers in the diagnosis of MM

Cholesterol metabolism biomarkers hold significant diagnostic value in multiple myeloma (MM). Research has demonstrated that patients with MM often exhibit dyslipidemia, particularly alterations in cholesterol levels, which may be related to the utilization and metabolism of lipids by tumor cells. One study indicated that untreated MM patients had lower serum levels of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) compared to healthy controls, with serum TC levels negatively correlated with plasma total protein (TP) levels and positively correlated with albumin (Alb) levels [80]. Furthermore, following treatment, responders showed a notable increase in serum TC and HDL-C levels, suggesting that changes in lipid profiles may reflect disease status and treatment efficacy in MM [81, 82].

The abnormal activation of cholesterol metabolism may also be associated with the proliferation and survival of MM cells. In MM cells, the activity of rate-limiting enzymes in the cholesterol synthesis pathway, such as HMG-CoA reductase (HMGCR) and squalene monooxygenase, may be elevated, leading to increased cholesterol synthesis [83]. Additionally, the expression of LDL receptors and associated proteins may be upregulated to enhance cholesterol uptake. These metabolic alterations in cholesterol not only offer potential biomarkers for diagnosing MM but also provide crucial information for monitoring the disease and assessing treatment responses. In clinical practice, measuring cholesterol levels and related metabolic products in serum can offer vital clues for the early diagnosis of MM. These biomarkers assist clinicians in more accurately evaluating the disease status of MM patients,

thereby enabling the development of more effective treatment strategies. Hence, cholesterol metabolism biomarkers have promising applications in the specificity of MM testing.

The potential of cholesterol metabolism pathways as prognostic and predictive biomarkers in MM

The cholesterol metabolism pathway is increasingly recognized for its potential as a prognostic and predictive biomarker in multiple myeloma (MM). Abnormal activation of cholesterol metabolism is closely linked to the progression of MM and may serve as a valuable marker for prognosis and prediction. Notably, fluctuations in low-density lipoprotein cholesterol (LDL-C) levels have been correlated with outcomes in MM patients. In MM cells, the activity of the rate-limiting enzyme in the cholesterol synthesis pathway, 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), may be elevated, leading to increased cholesterol synthesis. Additionally, there may be an upregulation of LDL receptors and associated proteins to enhance cholesterol uptake. These alterations in cholesterol metabolism not only provide potential biomarkers for the diagnosis of MM but also yield critical insights for monitoring disease progression and evaluating treatment responses.

Specific biomarkers within the cholesterol metabolism pathway, such as ApoE and ABCG1, have been found to play roles in regulating immune cell activity and tumor progression [84, 85]. The absence of ApoE results in cholesterol accumulation on dendritic cell (DC) membranes, which enhances the aggregation of MHC-II molecules, thereby improving antigen presentation and promoting $CD4^+$ T cell-mediated immune responses [75]. Moreover, changes in the expression of ABCG1, a cholesterol transporter, have been closely associated with tumor immunity. These findings suggest that modulation of cholesterol metabolism in immune cells may bolster their antitumor capabilities, offering a new perspective and potential therapeutic strategies for tumor immunotherapy. Within the context of MM, the aberrant activation of cholesterol metabolism pathways may impact immune cell function, thereby influencing disease progression. Research has shown that the accumulation of 27-hydroxycholesterol (27-HC) may adversely affect T cell functionality, while modulation of cholesterol metabolism has the potential to alter T cell immune activation, thus enhancing antitumor immune responses [86]. These discoveries underscore the significance of cholesterol metabolism in MM and highlight the prospect of targeted interventions within these pathways as novel therapeutic strategies for MM. By regulating the cholesterol metabolism of both MM cells and immune cells, there is potential to alter their biological behavior, offering new biomarkers for prognosis and prediction in this challenging disease.

Cholesterol metabolism biomarkers hold significant value in the diagnosis of multiple myeloma (MM), yet they possess both advantages and limitations. Biomarkers such as serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels can reflect disease status and therapeutic response in MM patients. Studies have demonstrated that patients who respond positively to treatment exhibit marked increases in serum TC and HDL-C levels post-therapy, suggesting these markers may serve as valuable tools for monitoring disease progression and treatment efficacy [87]. Furthermore, measuring serum cholesterol levels and associated metabolites can provide critical insights for early diagnosis of MM, enabling clinicians to more accurately assess disease status and devise more effective treatment strategies [88]. However, dysregulation of cholesterol metabolism is not exclusive to MM and may also occur in other conditions, such as cardiovascular disease and diabetes. This lack of specificity may limit the diagnostic utility of these biomarkers in MM [89]. Additionally, cholesterol levels can be influenced by external factors, including diet, medications (e.g., statins), and physiological variations, which may introduce variability in test results and compromise diagnostic accuracy [90]. At present, no standardized guidelines exist for the dynamic monitoring and interpretation of cholesterol metabolism biomarkers in MM, potentially leading to inconsistencies in clinical application [87]. In summary, while cholesterol metabolism biomarkers hold considerable promise for the diagnosis and monitoring of MM, their non-specificity and susceptibility to external influences present challenges for clinical utility. Future research should focus on optimizing the use of these biomark-

ers to enhance their specificity and accuracy in MM diagnosis, thereby maximizing their translational potential in clinical practice.

The role of cholesterol metabolism reprogramming in personalized treatment of MM

Cholesterol metabolism reprogramming has shown significant potential in the personalized treatment of multiple myeloma (MM). Research indicates that cholesterol metabolism not only directly influences the biological behavior of tumor cells but also plays a critical role in modulating the antitumor activity of immune cells within the tumor microenvironment [90]. The alterations in cholesterol metabolism thus present promising targets for personalized therapy in MM.

Abnormal activation of cholesterol metabolism may affect immune cell functionality, thereby impacting disease progression. Studies have demonstrated that the accumulation of 27-hydroxycholesterol (27-HC) can have detrimental effects on T cell functionality, and that modulation of cholesterol metabolism can reshape T cell immune activation, subsequently enhancing antitumor immune responses [91]. In dendritic cells (DCs), dysregulated cholesterol metabolism may interfere with their differentiation and maturation, affecting their antitumor capabilities. Interestingly, it has been shown that 27-HC can induce the differentiation of monocytes into mature DCs while promoting the expression of various surface molecules, including MHC-II, CCR7, CD40, and CD80, thereby facilitating immune responses [73]. Furthermore, cholesterol metabolism reprogramming may influence the progression of malignancy by regulating the function of tumor-associated macrophages (TAMs). Research has revealed that the efflux of cholesterol promotes the polarization of TAMs toward an immunosuppressive, pro-tumor M2-like phenotype. TAMs are a major source of 27-HC generated locally within breast tissue, and hypermethylation of the CYP27B1 promoter in breast cancer cells further impedes the degradation of 27-HC, leading to its accumulation in tumor tissues. Elevated levels of 27-HC not only stimulate the proliferation of estrogen receptor (ER)-dependent breast cancer cells but also induce macrophages to secrete various chemokines, such as CCL2, CCL3, and CCL4, promoting the recruitment and differentiation of monocytes into M2-type macrophages [71]. The interaction between 27-HC and M2-type TAMs further drives the progression of breast cancer. These findings underscore the significant potential of cholesterol metabolism in the personalized treatment of MM. By modulating the cholesterol metabolism pathways within immune cells, there is an opportunity to alter their immunological activation capabilities, thus offering novel strategies for effectively treating MM.

Influence of cholesterol metabolism on immunotherapy in MM

The role of cholesterol metabolism intervention in immunotherapy for MM

The significance of cholesterol metabolism in the context of immunotherapy for multiple myeloma (MM) has garnered increasing attention. Research has demonstrated that cholesterol metabolism not only directly influences the biological behavior of tumor cells but also modulates the antitumor activity of immune cells within the tumor microenvironment. In the context of MM, alterations in cholesterol metabolism may impact the functions and activities of T cells, thereby affecting the efficacy of immunotherapy.

Notably, the cholesterol metabolic programs in T cells significantly differ from those in non-proliferative bone marrow cells within the tumor microenvironment [68]. Upon antigen stimulation, lymphocytes enhance both the biosynthesis and uptake of cholesterol to support clonal expansion. In contrast, non-proliferative bone marrow cells downregulate cholesterol biosynthesis while upregulating cholesterol uptake in response to interferon stimulation, facilitating their involvement in inflammatory processes [92]. Furthermore, tumor-infiltrating lymphocytes (TILs) exhibit a state of cholesterol deficiency, whereas immunosuppressive bone marrow cells and tumor cells display abundant cholesterol levels, effectively depleting the available cholesterol in their environment [93]. This deficiency in cholesterol profoundly impacts the proliferation and survival of $CD8^+$ cytotoxic T cells, as low cholesterol levels inhibit T cell proliferation and induce autophagy-mediated apoptosis, particularly in cytotoxic T cells [94]. Additionally, research has shown that deleting LXRβ in CAR-T cells via CRISPR-Cas9 gene editing enhances their anti-

tumor functionality against solid tumors without causing uncontrolled proliferation or prolonged retention post-transfer [95]. This finding indicates that modulating cholesterol metabolism may bolster the antitumor activity of CAR-T cells, offering a novel strategy for immunotherapy in MM. Moreover, abnormal activation of cholesterol metabolism can influence disease progression by affecting immune cell functionality. Specifically, the accumulation of 27-hydroxycholesterol (27-HC) may negatively impact T cell function, whereas regulating cholesterol metabolism could enhance T cell immune activation, thereby improving antitumor immune responses [75].

Cholesterol metabolism modulators as potential therapeutics for MM

Recent studies have demonstrated that cholesterol metabolism modulators, such as statins, can significantly influence the metabolism of multiple myeloma (MM) cells, thereby inhibiting tumor cell growth. Statins exert their effects by inhibiting HMG-CoA reductase, leading to a reduction in cholesterol biosynthesis. This alteration impacts the integrity of cell membranes and disrupts cellular signaling pathways, ultimately inducing apoptosis in MM cells [44]. In the realm of immunotherapy, the application of cholesterol metabolism modulators presents a novel approach to treating MM. One promising strategy involves the modulation of cholesterol metabolism in dendritic cells (DCs), which can enhance their antigen presentation capabilities and stimulate robust antitumor immune responses. Research conducted by Shen Qi's group has utilized a gelation reaction between graphene oxide (GO) and metformin hydrochloride (MET) to load metabolic nanointervention agents into a multifunctional hydrogel system. This innovative approach allows for precise and sustained immunometabolic intervention in DCs, significantly improving therapeutic outcomes [96]. Furthermore, cholesterol metabolism modulators may also influence the function of tumor-associated macrophages (TAMs), thereby affecting the tumor immune microenvironment. It has been shown that the cholesterol metabolite 25-hydroxycholesterol (25-HC) accumulates in the lysosomes of macrophages and competes with cholesterol for binding to the lysosomal localization signaling protein GPR155. This interaction inhibits mTORC1 activation, thereby enhancing the immunosuppressive functions of TAMs [97]. These findings suggest that by modulating cholesterol metabolism, one can alter the phenotype of TAMs, which may subsequently enhance antitumor immune responses.

The combined application of cholesterol metabolism modulators and immune checkpoint inhibitors

Cholesterol metabolism plays a crucial role in the immunotherapy of multiple myeloma (MM), particularly in conjunction with immune checkpoint inhibitors. Cholesterol-lowering agents, such as statins, have been shown to inhibit HMG-CoA reductase, leading to a decrease in cholesterol biosynthesis and subsequently influencing the proliferation of MM cells. Furthermore, metabolic products of cholesterol, such as 27-hydroxycholesterol (27-HC), accumulate within the tumor microenvironment and can adversely affect T cell functionality. Modulating cholesterol metabolism may modify the immune activation functions of T cells, thereby enhancing antitumor immune responses [98].

In the realm of immunotherapy, the effects of cholesterol metabolism modulators extend beyond direct interference with tumor cells. A research team at the Chinese Academy of Sciences' Center for Excellence in Molecular Cell Science has identified cholesterol 25-hydroxylase (CH25H) as a novel metabolic target for tumor immunotherapy. In the tumor microenvironment, tumor-associated macrophages (TAMs) are induced to express CH25H, resulting in the accumulation of 25-HC, which promotes the expression of Arg1 among TAMs, thereby facilitating tumor progression. Knocking out CH25H in macrophages has been shown to convert cold tumors into hot tumors by increasing the number of T cells and enhancing their cytotoxicity within the microenvironment. This intervention has been found to synergize with anti-PD-1 therapy, leading to improved antitumor efficacy [97].

Additionally, research conducted by Yang Wei, Ding Yanqing, and Zhang Zhenhai has demonstrated that the tumor microenvironment can inhibit the expression of low-density lipoprotein receptor (LDLR) in $CD8^+$ T cells through the core regulatory factor PCSK9 involved in cholesterol

Table 3. Therapeutic mechanisms of cholesterol metabolism modulating agents in MM

Drug Name	Combination Therapy Effects	Impact on the Immune Microenvironment	Reference
Statins	High-dose statins can inhibit the survival of multiple myeloma cells and enhance therapeutic effects when combined with chemotherapeutic drugs	Statins may enhance the efficacy of immunotherapy by modulating immune cells (e.g., $CD8^+$ T cells) in the tumor microenvironment	[87]
Ezetimibe	When combined with statins, it further lowers cholesterol levels and enhances antitumor effects	-	[100]
Statins Combined with Immune Checkpoint Inhibitors	-	Statins may enhance the efficacy of immunotherapy by reducing cholesterol levels in the tumor microenvironment and increasing $CD8^+$ T cell infiltration	[101]

metabolism. This suppression impairs the antitumor activity of $CD8^+$ T cells [99]. Information regarding the use of cholesterol-lowering medications, either alone or in combination with other chemotherapeutic agents, in cancer treatment can be found in **Table 3**.

These findings support the notion that PCSK9 may serve as a new target in tumor immunotherapy, underscoring the significance of developing novel inhibitors or monoclonal antibodies based on PCSK9 for clinical oncological treatment. Collectively, these advances suggest that the combination of cholesterol metabolism modulators with immune checkpoint inhibitors may offer novel strategies for the immunotherapy of MM. By modulating cholesterol metabolism, it may be possible to enhance the antitumor activity of immune cells, thereby improving the overall effectiveness of immunotherapy. These insights provide new perspectives and potential therapeutic strategies for addressing MM.

Future research directions

The specific examination of cholesterol metabolism reprogramming in multiple myeloma (MM) and its impact on the immune microenvironment has emerged as a focal point in current research. Future investigations are anticipated to delve deeper into the molecular mechanisms underlying the interactions between cholesterol metabolism and the MM microenvironment, as well as the potential applications of cholesterol metabolism reprogramming in the early diagnosis and treatment of MM. Furthermore, new strategies for cholesterol metabolism intervention in MM immunotherapy will also be a significant area of focus.

Cholesterol metabolism not only directly influences the biological behavior of MM cells but also modulates the antitumor activity of immune cells within the tumor microenvironment. Research has shown that the cholesterol metabolite, 25-hydroxycholesterol (25-HC), accumulates in the lysosomes of macrophages, where it competes with cholesterol for binding to the lysosomal signaling protein GPR155. This interaction inhibits mTORC1 activation, promoting macrophages to produce higher levels of Arg1 and anti-inflammatory factors [97]. This indicates that the regulation of cholesterol metabolism could alter the functionality of immune cells, subsequently affecting the progression of MM. Additionally, the abnormal activation of cholesterol metabolism may influence disease progression through its effects on immune cell functionality. The accumulation of 27-hydroxycholesterol (27-HC), in particular, may adversely affect T cell functions, while the modulation of cholesterol metabolism has the potential to enhance T cell immune activation, thereby strengthening antitumor immune responses. These findings provide new biomarkers and therapeutic targets for the early diagnosis and treatment of MM [86]. Cholesterol metabolism modulators, such as statins, have been found to reduce cholesterol biosynthesis by inhibiting HMG-CoA reductase, which can subsequently impact MM cell growth [44]. Moreover, these modulators may also affect the functionality of tumor-associated macrophages (TAMs), thereby influencing the immunological landscape of tumors. Studies have highlighted the roles of cholesterol oxidase CH25H and oxidized sterol 25-HC in tumor immunotherapy, revealing novel metabolic targets for macrophage-focused cancer immunotherapy [45].

In summary, the reprogramming of cholesterol metabolism in MM and its effects on the immune microenvironment are multifaceted, encompassing exploration of molecular mecha-

nisms, applications for early diagnosis and treatment, as well as the development of new immunotherapeutic strategies. These research directions are poised to provide fresh perspectives and potential treatment strategies for MM.

Conclusion

Significant advancements have been made in understanding cholesterol metabolism reprogramming in multiple myeloma (MM), particularly regarding its impact on the immune microenvironment and its potential challenges and applications in MM therapy. Research indicates that cholesterol metabolism not only directly influences the biological behavior of tumor cells but also plays a crucial role in modulating the anti-tumor activity of immune cells within the tumor microenvironment. One key metabolite, 25-hydroxycholesterol (25-HC), has been shown to accumulate in macrophage lysosomes, where it competes with cholesterol for binding to the lysosomal signaling protein GPR155, effectively inhibiting the activation of mTORC1. This action promotes the production of Arginase 1 (Arg1) and anti-inflammatory factors by macrophages, thereby influencing tumor progression. Moreover, the effects of cholesterol metabolism on the immune microenvironment of MM are multifaceted. Dysregulated cholesterol metabolism may activate immune cells, affecting disease progression. Notably, studies have demonstrated that the accumulation of 27-hydroxycholesterol (27-HC) can negatively impact T-cell functionality, while modulation of cholesterol metabolism can enhance T-cell immune activation, thereby strengthening anti-tumor immune responses. Additionally, cholesterol-lowering agents such as statins have been discovered to inhibit HMG-CoA reductase, reducing cholesterol biosynthesis, which can subsequently affect the proliferation of MM cells. These insights highlight the intricate relationship between cholesterol metabolism and immune modulation in the context of multiple myeloma, suggesting promising avenues for future research and therapeutic strategies.

The potential and challenges of cholesterol metabolism intervention in the treatment of MM coexist. The application of cholesterol metabolic regulators offers new perspectives for MM therapy. For instance, by modulating the cholesterol metabolism of dendritic cells (DCs), it is possible to enhance their antigen-presenting capability and activate effective anti-tumor immune responses. Research from the team led by Shen Qi demonstrates that by utilizing a gelation reaction between graphene oxide (GO) and metformin hydrochloride (MET), they successfully loaded metabolic nanointervention agents onto a multifunctional hydrogel system. This approach allows for precise and sustained immune metabolic intervention in DCs, significantly improving treatment outcomes. However, the role of cholesterol metabolism within the tumor microenvironment is complex, and the effects of cholesterol on immune cells are not strictly tumor-promoting or tumor-suppressing. Numerous questions remain unresolved. For example, the functions of exogenous and endogenous cholesterol may differ; exogenous cholesterol often disrupts the membrane signaling pathways of tumor-infiltrating immune cells (TIICs), impairing their normal antigen-presenting and cytotoxic functions. Meanwhile, deficiencies of intracellular and membrane cholesterol can affect proper localization and the formation of signaling microdomains such as lipid rafts. The relationship between cholesterol metabolism and tumor immunity is characterized by complexity and diversity. The differences and commonalities in how cholesterol metabolism reprogramming within the tumor microenvironment affects immune cell activity, as well as the specific regulatory mechanisms, remain areas that require further investigation. Targeted interventions in cholesterol metabolic pathways in immune cells hold promise as a novel strategy for leveraging cholesterol metabolism in tumor immunotherapy.

Disclosure of conflict of interest

None.

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