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The Mechanistic and Clinical Significance of Low - Density Lipoprotein in Head and Neck Squamous Cell Carcinoma

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Abstract: Low-density lipoprotein (LDL) plays a pivotal role in the pathogenesis of head and neck squamous cell carcinoma (HNSCC). This review systematically examines the mechanistic roles and clinical implications of LDL in HNSCC. The structural characteristics, biosynthesis, metabolic pathways of LDL, and its interplay with cholesterol homeostasis constitute the foundation for its involvement in HNSCC progression. Within the tumor microenvironment (TME), LDL modulates tumor progression through regulation of inflammatory responses and oxidative stress, while critically influencing key biological behaviors of HNSCC cells, including proliferation, apoptosis, invasion, and migration. The expression levels of LDL and its associated factors demonstrate significant correlations with HNSCC patient prognosis, highlighting their potential utility as biomarkers for outcome prediction. Furthermore, LDL-related signaling pathways exhibit considerable therapeutic potential, though challenges such as adverse effects and inter-individual heterogeneity must be addressed when targeting LDL for treatment. Future investigations should prioritize elucidating the complex LDL-HNSCC interplay, leveraging advanced biotechnological approaches to uncover novel mechanisms, thereby establishing a robust theoretical foundation for early prevention and personalized therapeutic strategies in HNSCC.

Keywords: Low-Density Lipoprotein; Head and Neck Squamous Cell Carcinoma; Mechanism; Clinical Significance; Biomarker.

1. Introduction

HNSCC, a prevalent malignant tumor, exhibits a persistently increasing global incidence. In recent years, the role of LDL in tumor biology has emerged as a critical research focus. LDL serves not only as the primary carrier of cholesterol metabolism but also exerts critical regulatory functions in cancer cell biological behaviors, oxidative stress, and inflammatory responses[1] . Clinical evidence indicates a significant association between elevated LDL expression levels and favorable prognosis in HNSCC patients. Specifically, high levels of low-density lipoprotein cholesterol (LDL-C) are recognized as a protective factor against HNSCC progression, whereas elevated apolipoprotein B (Apo B) levels correlate with poorer survival rates[2, 3] .

LDL plays a crucial role in the biological behaviors of HNSCC and in the tumor microenvironment during the tumorigenesis and development process. Oxidized Low - Density Lipoprotein (oxLDL) is regarded as an important factor promoting tumor development. OxLDL promotes the proliferation and migration of tumor cells by activating multiple signaling pathways. For example, in HNSCC, oxLDL can bind to tumor cells through receptors such as CD36 and Lectin - like Oxidized Low - Density Lipoprotein Receptor - 1 (Lox-1), inducing cell migration and invasion[4] . The effects of LDL and its oxidation products on HNSCC are not limited to cancer cell proliferation and migration but also involve the regulation of the tumor microenvironment. It has been found that Oxidized Low - Density Lipoprotein Receptor 1 (OLR1) is specifically enriched on Tumor - Associated Macrophages (TAMs), affecting the infiltration of immune cells in the tumor microenvironment and further promoting tumor progression, resulting in a poor prognostic survival period for patients[5]. Therefore, understanding the mechanism of action of LDL in HNSCC will provide important clues for the early diagnosis, disease monitoring, and development of new therapies for this cancer.

LDL and its related molecules may also emerge as novel targets in the treatment of HNSCC. Quercetin inhibits the elevation of cholesterol and LDL levels in cisplatin - resistant CAL27 cells by regulating the AGR2/AKT/SREBP2 axis, enhancing the chemosensitivity of cancer cells to cisplatin and thus augmenting the anti - cancer effect[6] . In other cancers, drugs that target the LDL receptor or its downstream signaling pathways may improve the prognosis of cancer patients[7]. Overall, the mechanism of action and clinical significance of LDL in head and neck squamous cell carcinoma, the therapeutic strategies for interfering with LDL and its related molecules, and how the combination of these approaches with existing anti - cancer therapies can produce synergistic effects are worthy of further in - depth research. This is expected to provide new ideas and methods for the treatment of HNSCC.

2. Biological Characteristics of LDL

LDL is mainly responsible for transporting cholesterol from the liver to peripheral tissues. Its biological characteristics, including structure, function, synthesis, and its relationship with cholesterol metabolism, play important roles in the pathogenesis of various diseases[8]. LDL presents as spherical particles, and its structure is mainly composed of three parts: a core, a lipid membrane, and a protein coat. The core consists of cholesterol esters and triglycerides, the lipid

membrane contains phospholipids and free cholesterol, and the coat is mainly composed of apolipoprotein B100. The synthesis of LDL mainly depends on the cholesterol synthesis and transport processes in the liver[9]. The metabolic process of LDL involves, first, the endocytosis mediated by the binding of the LDL receptor (LDLR) on the cell membrane surface to apolipoprotein B100. After being taken up by cells, LDL is further transported to lysosomes and degraded into free cholesterol, fatty acids, amino acids, etc., which are then released and participate in the construction of cell membranes and the synthesis of hormones[10]. Therefore, a deep understanding of the biological characteristics of LDL and its role in cholesterol metabolism is of great significance for revealing the pathogenesis of HNSCC.

3. LDL and the Tumor Microenvironment

The TME is a complex local environment composed of various biomolecules that play crucial roles in the occurrence and development of cancer[11]. Abnormal metabolism of LDL is closely associated with the onset and progression of multiple types of tumors. LDL not only influences the biological behaviors of tumor cells but also affects the tumorigenesis and development by regulating various biological processes in the TME, such as the inflammatory response and oxidative stress[12, 13].

3.1. Regulatory Role of LDL in Inflammatory Responses

Inflammatory processes are closely associated with HNSCC progression, where LDL and its related components play pivotal roles in modulating inflammatory cascades within the TME. Evidence indicates that elevated LDL levels correlate with upregulated expression of tumor-associated inflammatory mediators, which may facilitate neoplastic proliferation and metastatic dissemination. Notably, oxidized low-density lipoprotein receptor 1 (OLR1) has been implicated in reprogramming TAMs toward an M2-polarized phenotype within HNSCC TME. These immunosuppressive M2-TAMs compromise immune surveillance mechanisms, thereby contributing to unfavorable clinical outcomes[5]. Furthermore, endoplasmic reticulum stress in HNSCC induces lectin-type oxidized LOX-1 overexpression on neutrophils, conferring immunosuppressive properties that may elevate risks of premalignant transformation and diminish survival rates[14]. Collectively, targeting LDL-mediated inflammatory signaling emerges as a promising therapeutic strategy for HNSCC intervention.

3.2. Impact of Oxidative Stress on Tumor Progression

Oxidative stress represents a critical determinant in the TME, where oxLDL exert substantial pathophysiological effects. Elevated oxLDL levels exhibit strong correlations with aggravated pathological features in HNSCC patients. Notably, clinical investigations have demonstrated significantly increased plasma oxLDL concentrations in HNSCC cohorts, showing positive associations with advanced tumor staging and disease severity[5]. Mechanistically, oxidative stress drives oral carcinogenesis, as evidenced by marked alterations in oxidative stress-related biomarkers within serum and saliva samples from HNSCC patients[15, 16]. Therapeutic interventions targeting oxidized LDL, such as antioxidant administration, have shown efficacy in suppressing angiogenic effects and inducing apoptosis in HNSCC xenograft models[17].

Collectively, LDL and its derivatives critically influence HNSCC progression and prognosis through dual regulatory mechanisms: modulating inflammatory responses and amplifying oxidative stress within the TME. Elucidating the precise molecular interplay between LDL metabolism and tumor evolution may enable the development of targeted therapies, potentially offering novel therapeutic avenues for HNSCC patients.

4. Impact of LDL on Biological Behaviors of HNSCC

LDL plays a crucial role in modulating key biological processes in HNSCC, including cellular proliferation, apoptosis, invasion, and migration. Mechanistically, LDL not only provides energy and biosynthetic precursors for cancer cells but also regulates cell signaling pathways to promote tumor proliferation. Additionally, LDL and its related components significantly influence the invasive and migratory capacities of HNSCC cells. These findings underscore the importance of LDL in HNSCC research. In-depth investigation into the underlying mechanisms may provide novel therapeutic strategies and potential targets for HNSCC treatment.

4.1. Role of LDL in HNSCC Cell Proliferation and Apoptosis

In human papillomavirus (HPV)-positive HNSCC patients, genomic deletions of low-density lipoprotein receptor-related protein 1B (LRP1B) are significantly enriched in post-chemoradiotherapy recurrence samples. Studies demonstrate that LRP1B knockdown in HPV-positive cancer cells promotes tumor cell proliferation, enhances clonogenic potential, and increases therapeutic resistance to chemoradiation[18]. Further investigations confirm that LRP1B expression levels modulate the proliferative capacity of HNSCC cells[19]. Notably, HNSCC cells with endothelial-like characteristics internalize LDL to store cellular energy, thereby facilitating tumor proliferation and angiogenesis[20]. Luciferase reporter assays reveal that miR-139-3p regulates HNSCC cell proliferation through OLR1 modulation[21]. Pharmacological inhibition of LDL oxidation via antioxidants induces apoptosis in murine HNSCC cell lines, demonstrating therapeutic potential[17]. These findings collectively indicate that LDL contributes to HNSCC proliferation not only by supplying metabolic substrates but also through direct regulation of oncogenic signaling pathways.

4.2. Impact of LDL on HNSCC Invasion and Metastasis

LDL and its associated components critically regulate invasive and metastatic processes in HNSCC. Genomic analyses reveal that recurrent copy number variations affecting LRP1B occur frequently in HNSCC patients, with six specific genetic alterations identified to enhance tumor cell migration and invasion[19]. Experimental evidence demonstrates that LRP1B knockout in HPV-positive oropharyngeal squamous cell carcinoma models significantly increases cellular invasiveness and metastatic potential[18]. Furthermore, endothelial-like HNSCC cells internalize LDL

to accumulate energy reserves, thereby augmenting migratory and invasive capacities that accelerate disease progression[20]. Integrated analysis of The Cancer Genome Atlas (TCGA) data and luciferase reporter assays confirms that downregulated miR-139 expression directly modulates OLR1 activity, mechanistically influencing HNSCC cell invasion dynamics[21]. Notably, oxL DL upregulates CD36 expression in HNSCC cell lines, enhancing lipid uptake through the CD36/β-catenin signaling axis to suppress malignant cell migration[4]. These collective findings establish LDL-associated pathways as pivotal regulators of HNSCC metastasis, highlighting their potential as therapeutic targets.

5. Clinical Applications of LDL in Prognostic Assessment and Treatment Strategies for HNSCC

Overall, LDL and its associated factors are intimately linked to the prognosis of HNSCC. Their levels are potentially valuable as biomarkers for evaluating the survival status and metastasis risk of patients. In terms of treatment, whether it is regulating cholesterol metabolism to reduce drug resistance or inhibiting LDL oxidation to control tumor progression, the significant potential of LDL and its associated pathways as therapeutic targets has been demonstrated. Despite the fact that clinical trials are still in the early stages, research experiences from other cancers can provide new directions for HNSCC treatment. In the future, in - depth research on the mechanism of LDL in HNSCC is expected to further optimize clinical treatment plans. This may involve exploring more effective ways to intervene in LDL - related pathways, and developing personalized treatment strategies based on the characteristics of individual patients. By doing so, it is hoped that the prognosis of HNSCC patients can be improved, ultimately bringing more benefits to patients suffering from this disease.

5.1. The Association between LDL Levels and the Prognosis of HNSCC

A multitude of studies have demonstrated that there is a strong connection between the expression levels of LDL and its associated factors and the prognosis of HNSCC. For example, HNSCC patients with higher in - vivo LDL levels exhibit an overall survival rate that is above the average. In another research, elevated levels of LDL-C have been verified to be associated with more favorable progression - free survival and disease - specific survival. However, when Apo B, which is closely related to LDL, shows high expression, it turns into a risk factor influencing the prognosis[2, 3]. Moreover, LRP1B polymorphism has been found to be associated with an increased risk of lymph node metastasis in patients with oral cancer complicated by diabetes mellitus[22]. The above - mentioned research findings strongly suggest that LDL and its related factors hold potential value as biomarkers for the prognostic assessment of HNSCC. They are expected to offer novel strategies for clinical treatment.

5.2. The Potential of LDL as a Therapeutic Target for HNSCC

LDL and its related factors are of great significance in the clinical research of HNSCC and have the potential to serve as therapeutic targets. It has been found that quercetin can inhibit cholesterol metabolism by suppressing the AGR2/AKT/SREBP2 signaling pathway, thereby reducing the expression levels of LDL and other related factors and alleviating the cisplatin resistance of oral squamous cell carcinoma[6]. OxL DL can promote the migration of HNSCC, while the application of antioxidants to inhibit the oxidation of LDL can effectively reduce tumor development[4, 17]. Although current clinical trials targeting LDL for the treatment of HNSCC are still in the preliminary stage, in other cancer fields, therapeutic strategies that interfere with cholesterol metabolism have been extensively studied. Moreover, the synergistic effects generated when these methods are used in combination with existing anti - cancer therapies have brought new opportunities for cancer treatment[7]. Therefore, LDL and its related pathways are highly potential targets for the treatment of HNSCC patients and are likely to open up new paths for the clinical treatment of HNSCC.

6. Conclusion

In summary, LDL and its related factors play a crucial role in multiple aspects of HNSCC, including tumorigenesis, development, prognosis, and treatment. From the perspective of biological characteristics, the unique structure, synthesis and metabolic mechanisms of LDL, as well as its close relationship with cholesterol metabolism, lay the foundation for its functions in HNSCC. In the TME, LDL significantly affects tumor progression and prognosis by regulating the inflammatory response and oxidative stress. Regarding the biological behaviors of HNSCC, LDL not only plays a key role in cell proliferation and apoptosis, providing energy and raw materials for biosynthesis to cancer cells and regulating cell signaling pathways to promote tumor growth, but also exerts an important influence on cell invasion and migration. Its related factors are closely associated with the invasive and metastatic abilities of cancer cells. Furthermore, the levels of LDL and its related factors are closely related to the prognosis of HNSCC and can be used as potential biomarkers for prognostic assessment. Meanwhile, they show great potential in treatment strategies, offering novel ideas and directions for clinical treatment. The research on LDL in HNSCC not only provides new insights into tumor biology but also offers new directions for clinical applications. It is anticipated that through multidisciplinary cooperation, in - depth research in this field can be promoted, thereby laying a more solid theoretical foundation for the early prevention and personalized treatment of HNSCC.

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