THE ROLE OF SCAVENGER RECEPTORS IN ATHEROSCLEROSIS: BIOCHEMICAL MECHANISMS AND IMPLICATIONS

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Annotation: *Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of lipids, immune cells, and fibrous elements in the arterial walls. This condition significantly contributes to cardiovascular diseases, including heart attacks and strokes. Among the various cellular components involved in atherosclerosis, scavenger receptors play a pivotal role in the disease's biochemical mechanisms. This article explores the functions of scavenger receptors in atherosclerosis, their contributions to lipid metabolism, inflammation, and potential therapeutic implications.*

Key words: *Atherosclerosis, lipids, scavenger receptors, cardiovascular diseases, low-density lipoprotein (LDL), Nuclear Factor-kappa B (NF-кВ)*

ATEROSKLEROZDA SEKVENJER RETSEPTORLARINING ROLI: BIOKIMYOVIY MEXANIZMLAR VA OQIBATLARI

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Annotatsiya: *Ateroskleroz surunkali yallig'lanish kasalligi bo'lib, arterial devorlarda lipidlar, immun hujayralar va tolali elementlarning to'planishi bilan tavsiflanadi. Bu holat yurak-qon tomir kasalliklariga, shu jumladan yurak xuruji va qon tomirlariga sezilarli hissa qo'shadi. Ateroskleroz bilan bog'liq bo'lgan turli xil hujayrali komponentlar orasida tozalovchi retseptorlari kasallikning biokimyoviy mexanizmlarida hal qiluvchi rol o'ynaydi. Ushbu maqola aterosklerozda tozalash retseptorlarining funktsiyalarini, ularning lipid metabolizmiga, yallig'lanishga qo'shgan hissasini va potentsial terapevtik oqibatlarini o'rganadi.*

Kalit so'zlar: *Ateroskleroz, lipidlar, sekvenjer retseptorlari, yurak-qon tomir kasalliklari, past zichlikdagi lipoproteinlar (LDL), noklear kappa omili B (NF-kB)*

РОЛЬ РЕЦЕПТОРОВ-МУСОРЩИКОВ ПРИ АТЕРОСКЛЕРОЗЕ: БИОХИМИЧЕСКИЕ МЕХАНИЗМЫ И ПОСЛЕДСТВИЯ

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Аннотация: *Атеросклероз — хроническое воспалительное заболевание, характеризующееся накоплением липидов, иммунных клеток и фиброзных элементов в стенках артерий. Это состояние вносит значительный вклад в сердечно-сосудистые заболевания, включая инфаркты и инсульты. Среди различных клеточных компонентов, участвующих в атеросклерозе, рецепторы-мусорщики играют ключевую роль в биохимических механизмах заболевания. В этой статье рассматриваются функции рецепторов-мусорщиков при атеросклерозе, их вклад в липидный обмен, воспаление и потенциальные терапевтические последствия.*

Ключевые слова: *атеросклероз, липиды, рецепторы-мусорщики, сердечно-сосудистые заболевания, липопротеины низкой плотности (ЛПНП), ядерный фактор каппа В (NF-кВ)*

Scavenger receptors are a diverse group of membrane proteins primarily expressed on macrophages, endothelial cells, and smooth muscle cells. They are classified into several families, with Class A and Class B scavenger receptors being the most studied in the context of atherosclerosis. These receptors are known for their ability to bind and internalize modified forms of low-density lipoprotein (LDL), such as oxidized LDL (oxLDL), as well as other ligands, including apoptotic cells and various pathogens

Key Types of Scavenger Receptors

Class A Scavenger Receptors (SR-A):

These receptors are primarily involved in the recognition and uptake of oxLDL. Their expression on macrophages increases in response to inflammatory stimuli, facilitating foam cell formation—an early event in atherosclerotic plaque development.

Class B Scavenger Receptors (SR-B): The most notable member, SR-BI, plays a crucial role in cholesterol homeostasis by mediating the selective uptake of cholesteryl esters from high-density lipoproteins (HDL). This function can have protective effects against atherosclerosis.

Other Receptors: Other scavenger receptors, such as CD36 and LOX-1, also participate in the uptake of modified lipoproteins and contribute to inflammatory responses.

Scavenger Receptors and Lipid Metabolism

The interaction between scavenger receptors and modified LDL is central to the development of atherosclerosis. When macrophages internalize oxLDL through SR-A and CD36, they undergo a transformation into foam cells. This process is characterized by:

Cholesterol Accumulation: Foam cells accumulate excess lipids, leading to the formation of fatty streaks in the arterial walls.

Inflammatory Cytokine Production: The uptake of oxLDL activates signaling pathways that promote the release of pro-inflammatory cytokines, perpetuating the inflammatory cycle. This cycle not only contributes to plaque formation but also enhances the recruitment of additional immune cells to the site of inflammation, exacerbating the atherosclerotic process.

Inflammation and Scavenger Receptors

The role of scavenger receptors extends beyond lipid uptake; they are also critical mediators of inflammation in atherosclerosis. Upon binding oxLDL, scavenger receptors trigger various intracellular signaling pathways that lead to:

Nuclear Factor-kappa B (NF-κB) Activation: This transcription factor promotes the expression of adhesion molecules and inflammatory cytokines, further amplifying the inflammatory response.

Macrophage Activation: The continuous activation of macrophages leads to the release of reactive oxygen species (ROS) and other inflammatory mediators, contributing to endothelial dysfunction and plaque instability.

Therapeutic Implications

Given their central role in the development and progression of atherosclerosis, scavenger receptors represent promising therapeutic targets. Modulating their activity could offer new strategies for preventing and treating cardiovascular diseases. Here are some potential approaches:

1. Inhibitors of Scavenger Receptor Activity

Blocking OxLDL Uptake: Developing small molecules or monoclonal antibodies that inhibit the binding of oxidized LDL to scavenger receptors, particularly SR-A and CD36, could reduce foam cell formation. By limiting the internalization of oxLDL, these inhibitors may help mitigate plaque development and inflammation.

Competitive Inhibitors: Compounds that mimic the ligands of scavenger receptors could be designed to competitively inhibit the binding of harmful ligands, thereby reducing the inflammatory response associated with atherosclerosis.

2. Enhancing Protective Scavenger Receptor Functions

Promoting SR-BI Activity: Enhancing the activity of SR-BI, which facilitates the selective uptake of cholesteryl esters from HDL, could improve cholesterol efflux from foam cells. This may help to stabilize plaques and promote reverse cholesterol transport, potentially reducing cardiovascular risk.

Gene Therapy Approaches: Utilizing gene therapy to upregulate the expression of beneficial scavenger receptors like SR-BI in macrophages or endothelial cells could bolster their protective effects against atherosclerosis.

3. Modulating Inflammatory Responses

Targeting Downstream Signaling Pathways: Inhibiting signaling pathways activated by scavenger receptors, such as NF-κB, could reduce inflammation in atherosclerotic lesions. This approach may involve using specific inhibitors that block key molecules in these signaling cascades, thereby mitigating the inflammatory response.

Anti-Inflammatory Agents: Combining scavenger receptor-targeting therapies with anti-inflammatory agents might provide a synergistic effect, helping to address both lipid accumulation and the inflammatory component of atherosclerosis.

4. Lifestyle and Dietary Interventions

Dietary Modulation: Diets rich in antioxidants may help reduce oxidative stress and subsequent oxLDL formation, indirectly lowering the activation of scavenger receptors. Encouraging a diet high in fruits, vegetables, and healthy fats could support cardiovascular health.

Exercise: Regular physical activity has been shown to improve lipid profiles and enhance HDL function, potentially promoting the beneficial actions of scavenger receptors involved in lipid metabolism.

5. Biomarker Development

The identification and validation of biomarkers associated with scavenger receptors hold significant promise for enhancing the understanding, diagnosis, and management of atherosclerosis. Here are some key areas where biomarker development can be particularly impactful:

1. Scavenger Receptor Expression Levels

Tissue and Blood Biomarkers: Measuring the expression levels of specific scavenger receptors (e.g., SR-A, SR-BI, CD36) in atherosclerotic lesions or peripheral blood mononuclear cells can provide insights into the inflammatory status and progression of atherosclerosis. Elevated levels of these receptors might correlate with increased foam cell formation and plaque instability.

Gene Expression Profiling: Utilizing techniques such as quantitative PCR or RNA sequencing to analyze scavenger receptor gene expression in vascular tissues or circulating immune cells can help identify patterns associated with disease severity. Changes in expression profiles may serve as indicators of atherosclerosis progression or response to treatment.

2. Oxidized LDL (oxLDL) Levels

Direct Measurement: The concentration of oxLDL in the bloodstream can serve as a potential biomarker for atherosclerosis. Elevated levels of oxLDL are associated

with increased scavenger receptor activity, particularly in macrophages, leading to foam cell formation.

OxLDL-Scavenger Receptor Complex: Developing assays to detect complexes formed between oxLDL and scavenger receptors may provide a more direct measure of receptor activity and engagement, offering insight into the inflammatory processes in atherosclerotic lesions.

3. Inflammatory Cytokine Profiles

Cytokine Panels: Since scavenger receptor activation often leads to the release of pro-inflammatory cytokines (e.g., TNF-α, IL-6), measuring the levels of these cytokines in circulation could serve as a proxy for scavenger receptor-mediated inflammation. High levels of specific cytokines may indicate a heightened inflammatory state in atherosclerosis.

Cytokine Receptor Interaction: Investigating the interplay between scavenger receptors and inflammatory cytokine signaling could lead to the development of more nuanced biomarkers that reflect the inflammatory microenvironment in atherosclerotic plaques.

4. MicroRNAs and Other Non-Coding RNAs

Regulatory RNAs: MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) that regulate scavenger receptor expression and activity could be explored as potential biomarkers. For example, specific miRNAs may target scavenger receptor genes and could be implicated in atherosclerosis progression. Profiling these RNA species in circulation may offer a novel approach to assess cardiovascular risk.

5. Integration of Omics Technologies

Multi-Omics Approaches: Combining genomics, proteomics, and metabolomics to study scavenger receptors in the context of atherosclerosis could yield comprehensive biomarker signatures. For instance, integrating lipidomic profiles with scavenger receptor activity data may provide insights into the lipid environment influencing receptor engagement and disease outcomes.

Biomarker Panels: Developing multi-biomarker panels that include scavenger receptor levels, oxLDL, inflammatory cytokines, and other relevant markers could improve diagnostic accuracy and risk stratification for atherosclerosis.

6. Clinical Implications and Applications

Risk Stratification: Biomarkers derived from scavenger receptor activity could aid in the early identification of individuals at high risk for atherosclerosis, enabling more targeted preventative measures.

Monitoring Treatment Efficacy: Tracking changes in scavenger receptor-related biomarkers during treatment could help assess the effectiveness of therapeutic interventions, allowing for personalized adjustments to treatment plans.

Guiding Clinical Decision-Making: Incorporating scavenger receptor biomarker profiles into clinical practice could provide healthcare providers with valuable

information to make informed decisions regarding patient management and lifestyle interventions.

Conclusion

The role of scavenger receptors in atherosclerosis is complex and multifaceted, encompassing critical functions in lipid metabolism, inflammatory processes, and cellular signaling. As integral components of the immune response to lipid accumulation, these receptors contribute significantly to the formation of foam cells, plaque development, and the progression of atherosclerotic disease. Understanding the biochemical mechanisms by which scavenger receptors operate not only elucidates their contribution to atherosclerosis but also highlights their potential as therapeutic targets. Interventions aimed at modulating scavenger receptor activity—whether through pharmacological agents, gene therapies, or lifestyle modifications—could provide innovative strategies for managing and preventing cardiovascular diseases. Moreover, ongoing research into the signaling pathways and molecular interactions associated with scavenger receptors may reveal additional therapeutic targets and lead to the development of novel anti-atherosclerotic strategies. As our understanding of these receptors deepens, it may pave the way for innovative treatments that not only address the symptoms of atherosclerosis but also tackle its underlying mechanisms.

In summary, scavenger receptors represent a vital link in the intricate web of biochemical processes that drive atherosclerosis. Continued exploration of their roles offers hope for advancing therapeutic interventions and improving cardiovascular health outcomes. As we refine our understanding of these mechanisms, we move closer to developing effective strategies to combat one of the leading causes of morbidity and mortality worldwide. The future of atherosclerosis management will undoubtedly benefit from a deeper appreciation of scavenger receptors and their multifaceted roles in cardiovascular disease.

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