Understanding the Link Between S-Adenosylmethionine Metabolism, Lipid Metabolism, and Stress-Responsive Gene Expression

Introduction

S-adenosylmethionine (SAM) is a critical metabolite in cellular metabolism, serving as a primary methyl donor for various biochemical reactions, including the methylation of histones, nucleic acids, and phospholipids. The metabolism of SAM is intricately linked to lipid metabolism and stress-responsive gene expression, impacting numerous physiological processes and disease states. This report delves into the biochemical pathways involving SAM, its role in lipid metabolism, and its influence on stress-responsive gene expression, providing a comprehensive understanding of these interconnections.

S-Adenosylmethionine: An Overview

SAM is synthesized from methionine and ATP by the enzyme methionine adenosyltransferase (MAT). This process is part of the one-carbon cycle (1CC), which integrates essential nutrients such as methionine, folate, and vitamin B12 to produce nucleotides, glutathione, and SAM (Godbole et al., 2023). SAM serves as a methyl donor in transmethylation reactions, transferring its methyl group to various substrates, including DNA, RNA, proteins, and lipids.

SAM and Lipid Metabolism

Phosphatidylcholine Synthesis

One of the critical roles of SAM in lipid metabolism is its involvement in the synthesis of phosphatidylcholine (PC), a major component of cell membranes. PC can be synthesized via two pathways: the CDP-choline pathway (Kennedy pathway) and the methylation of phosphatidylethanolamine (PE) via the PEMT pathway. In the PEMT pathway, SAM donates

methyl groups to PE to form PC, a process that consumes a significant portion of cellular SAM (EndocMetab).

Lipid Accumulation and Fatty Liver Disease

Reduced function of the one-carbon cycle (1CC) and subsequent SAM deficiency are strongly associated with metabolic disorders, particularly fatty liver disease. This condition is characterized by lipid accumulation and immune dysfunction (CellMetab). SAM deficiency may underlie liver pathology in alcohol-induced fatty liver disease (ALD), and nutritional limitations of 1CC function can accelerate injury in ALD models (Halsted et al., 2002).

Methylation and Lipid Metabolism Regulation

SAM-dependent methylation reactions are crucial for regulating lipid metabolism. For instance, the methylation of histones and DNA can influence the expression of genes involved in lipid metabolism. SAM levels govern the synthesis of PC, and reductions in PC can lead to lipid accumulation by activating the transcription factor SBP-1/SREBP-1, which regulates lipogenic gene expression (CellMetab).

SAM and Stress-Responsive Gene Expression

Epigenetic Regulation

SAM plays a pivotal role in epigenetic regulation through the methylation of histones and DNA. Histone methylation, particularly the trimethylation of histone H3 lysine 4 (H3K4me3), is a marker of active gene transcription. The availability of SAM can influence the extent of histone methylation, thereby affecting gene expression patterns during stress responses (Godbole et al., 2023).

Stress Responses in Caenorhabditis elegans

Studies in Caenorhabditis elegans have shown that SAM levels are critical for stress-responsive gene expression. For example, worms with reduced SAM levels exhibit altered responses to bacterial and toxic stress but respond normally to heat stress. This differential response is linked to the activity of specific histone methyltransferases, such as SET-2 and SET-16, which use SAM to modify histones (PLOSGen).

Innate Immunity

SAM levels also govern innate immunity through distinct methylation-dependent pathways. Low SAM levels are associated with lipid accumulation, tissue injury, and immune responses in fatty liver disease. The fluctuation of SAM impacts hepatic PC synthesis and may be linked to variations in DNA or histone methylation, influencing immune gene expression (CellMetab).

Molecular Mechanisms Linking SAM, Lipid Metabolism, and Stress Responses

Enzyme Specificity and SAM Provisioning

The specificity of SAM synthase enzymes towards target sequences establishes a layer of control over H3K4 trimethylation. Different SAM synthases, such as SAMS-1 and SAMS-4, contribute differently to the modification of H3K4me3, gene expression, and survival during stress. For instance, SAMS-4 enhances H3K4me3 in heat-shocked animals lacking SAMS-1, but SAMS-1 cannot compensate for SAMS-4, which is required for survival during heat stress (Godbole et al., 2023).

Impact on Gene Expression

The availability of SAM and its role in methylation reactions can significantly impact gene expression. In conditions of low SAM, there is a reduction in the methylation of histones and DNA, leading to altered gene expression patterns. This can affect the expression of genes involved in lipid metabolism, stress responses, and immune regulation (PLOSGen).

Nutritional Influences

Diets low in choline or methionine can affect the availability of SAM, thereby influencing methylation reactions and gene expression. This nutritional influence underscores the importance of dietary components in maintaining SAM levels and proper metabolic and stress-responsive functions (PLOSGen).

Conclusion

The metabolism of S-adenosylmethionine (SAM) is intricately linked to lipid metabolism and stress-responsive gene expression through its role as a methyl donor in various biochemical

reactions. SAM is crucial for the synthesis of phosphatidylcholine (PC), a major component of cell membranes, and its deficiency is associated with lipid accumulation and fatty liver disease. Additionally, SAM-dependent methylation reactions regulate gene expression, impacting stress responses and immune function. The specificity of SAM synthase enzymes and the availability of SAM are critical factors in these processes, highlighting the importance of SAM in maintaining cellular homeostasis and responding to metabolic and environmental challenges.

References

- Godbole et al., 2023
- CellMetab
- EndocMetab
- PLOSGen
- Halsted et al., 2002