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Recent Advances in Lipid Metabolism and Regulations: A Review

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Abstract

Lipid metabolism is a highly intricate and tightly regulated process essential for cellular function, energy homeostasis, and metabolic balance. It encompasses lipid synthesis (lipogenesis), storage, breakdown (lipolysis and β-oxidation), and transport, all of which are orchestrated by complex regulatory networks involving enzymes, transcription factors, hormones, and environmental influences. Dysregulation of lipid metabolism is implicated in various metabolic disorders, including obesity, diabetes, cardiovascular disease, and metabolic syndrome. Recent advances in lipidomics, molecular biology, and metabolic engineering have significantly expanded our understanding of lipid metabolism, revealing novel regulatory mechanisms and therapeutic targets. The discovery of non-coding RNAs (e.g., microRNAs and long non-coding RNAs) as modulators of lipid homeostasis has provided new insights into gene regulation, while research on gut microbiome interactions has highlighted the role of microbial metabolites in lipid metabolism. Key metabolic pathways, such as fatty acid synthesis, triglyceride metabolism, cholesterol biosynthesis, and ketogenesis, are controlled by pivotal regulatory elements, including peroxisome proliferator-activated receptors (PPARs), sterol regulatory

element-binding proteins (SREBPs), and AMP-activated protein kinase (AMPK). Additionally, cholesterol biosynthesis, transport, and excretion are modulated through intricate feedback mechanisms involving the liver, lipoproteins, and sterol regulatory networks. This review explores the latest advancements in lipid metabolism, including lipidomics applications, regulatory mechanisms, and emerging therapeutic strategies for metabolic disorders. A deeper understanding of lipid metabolic pathways and their regulation will pave the way for novel precision medicine approaches in managing lipid-related diseases and optimizing metabolic health.

Keywords: Lipid Metabolism, Regulatory Mechanisms, Metabolic Disorders, Lipidomics, Therapeutic Targets

Introduction

Lipid metabolism is a highly intricate and tightly regulated process that governs the synthesis, storage, and degradation of lipids—essential biomolecules with diverse physiological functions (Vanherle *et al.*, 2025). Lipids serve as fundamental components of biological membranes (Variyam *et al.*, 2025), crucial energy reservoirs, and precursors for a wide range of signaling molecules (Kundu and Halder, 2024), including steroid hormones, eicosanoids, and second messengers involved in cellular communication (Ali and Szabó, 2023). The homeostatic regulation of lipid metabolism is vital for maintaining cellular function and overall metabolic balance, and its dysregulation is a hallmark of numerous pathological conditions, including cardiovascular disease, obesity, diabetes, and metabolic syndrome (Zhang *et al.*, 2022).

The complexity of lipid metabolism stems from the intricate interplay of metabolic pathways that involve lipid synthesis (lipogenesis), storage (in lipid droplets and adipose tissue), and breakdown (lipolysis and β-oxidation) (Xu et al., 2024; Vanherle et al., 2025). These processes are coordinated by a sophisticated network of enzymes, transport proteins, and regulatory molecules that respond dynamically to cellular and systemic energy demands (Ghosh et al., 2025). Key metabolic pathways such as fatty acid synthesis, triglyceride metabolism, cholesterol biosynthesis, and phospholipid remodeling are tightly controlled by hormonal and transcriptional regulators, including peroxisome proliferator-activated receptors (PPARs), sterol regulatory element-binding proteins (SREBPs), and the AMP-activated protein kinase (AMPK) pathway (Brown and Goldstein, 2021).

In recent years, major advances in lipidomics, metabolic engineering, and molecular biology have transformed our understanding of lipid metabolism and its regulatory mechanisms. The discovery of novel lipid-modifying enzymes, the elucidation of lipid–protein interactions, and insights into lipid-mediated signaling pathways have opened new avenues for therapeutic interventions. The role of non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), in modulating lipid metabolism has also gained significant attention, offering potential targets for precision medicine approaches (Chen *et al.*, 2023).

Moreover, emerging research highlights the profound influence of the gut microbiome on lipid metabolism. Microbial metabolites, including short-chain fatty acids (SCFAs) and bile acid derivatives, are now recognized as key modulators of lipid homeostasis, linking dietary factors and host metabolic health (Wang *et al.*, 2022). The interplay between host genetics, microbiota composition, and lipid metabolism underscores the potential of microbiome-targeted therapies in managing metabolic disorders.

This review aims to explore recent advances in lipid metabolism and its regulatory mechanisms, focusing on novel therapeutic strategies, lipidomics applications, and the implications of these findings for metabolic disease management. By synthesizing current knowledge, we aim to provide a comprehensive understanding of the evolving landscape of lipid metabolism research and its translational potential in biomedical sciences.

Key Metabolic Processes in Lipid Metabolism

Lipid metabolism encompasses several key processes: dietary lipid breakdown and absorption, fatty acid synthesis (lipogenesis), triglyceride breakdown (lipolysis), fatty acid oxidation, ketone body formation (ketogenesis), and cholesterol/lipoprotein metabolism (Bays *et al.,* 2024).

Lipogenesis (Fatty Acid and Triglyceride Synthesis)

Primarily occurring in the liver and adipose tissue, lipogenesis is the process of synthesizing fatty acids and triglycerides for energy storage (Boren et al., 2022). De novo fatty acid synthesis converts excess carbohydrates into fatty acids, starting with acetyl-CoA and culminating in palmitic acid production (Paiva et al., 2021). This process is tightly regulated by hormones like insulin (stimulates) and glucagon/epinephrine (inhibit).

Insulin upregulates key enzymes and transcription factors like Sterol regulatory element binding protein 1 (SREBP-1), while glucagon activates AMP-activated protein kinase (AMPK), which inactivates Acetyl-CoA carboxylase (ACC), a crucial enzyme in fatty acid synthesis. The newly synthesized fatty acids are then esterified with glycerol to form triglycerides, the primary storage form of fat, stored in lipid droplets within adipose tissue (Yoon *et al.,* 2021).

Lipolysis (Fat Breakdown and Mobilization)

Primarily in adipose tissue, lipolysis breaks down stored triglycerides into free fatty acids and glycerol (Mallick et al 2024). This process is crucial for energy homeostasis, especially during fasting or increased energy demand. Enzymes like Adipose triglyceride lipase (ATGL), Hormone-sensitive lipase (HSL), and Monoacylglycerol lipase (MGL) sequentially hydrolyze triglycerides into fatty acids and glycerol. Lipolysis is hormonally regulated: catecholamines (epinephrine, norepinephrine) stimulate it via β-adrenergic receptors and Protein Kinase A (PKA) activation, while insulin suppresses it by activating Phosphodiesterase 3B (PDE3B) and degrading cAMP (Folestad and Falkevall, 2024). Glucocorticoids can enhance lipolysis under stress. Released fatty acids are transported to tissues for energy production via β-oxidation, while glycerol is used for gluconeogenesis in the liver.

Fatty Acid β-Oxidation

This is the primary pathway for fatty acid degradation, generating energy by sequentially removing two-carbon units from fatty acyl-CoA. Long-chain fatty acids are transported into the mitochondrial matrix via the carnitine shuttle system, involving Carnitine Palmitoyltransferase I and Carnitine Palmitoyltransferase II (CPT-I and CPT-II) (Nie *et al.,* 2024). β-oxidation proceeds through four steps: activation, oxidation, hydration, and thiolysis, producing FADH2, NADH, and acetyl-CoA. The complete oxidation of palmitic acid yields significantly more ATP than glucose metabolism (Mihajlovic and Vinken, 2022). Very long-chain fatty acids undergo initial degradation in peroxisomes.

Ketogenesis and Ketone Body Utilization

In the liver, during prolonged fasting, carbohydrate restriction, or uncontrolled diabetes, fatty acids are converted into ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone).

Ketogenesis is regulated by insulin (inhibits) and glucagon (stimulates) (Mihajlovic and Vinken, 2022). Insulin suppresses lipolysis and promotes glucose uptake, while glucagon stimulates lipolysis and increases acetyl-CoA production. Ketone bodies serve as an alternative energy source, particularly for the brain during glucose scarcity (Folestad and Falkevall, 2024). They are transported across the blood-brain barrier and utilized by cells through a series of enzymatic reactions, ultimately producing ATP in the TCA cycle.

Cholesterol and Lipoprotein Metabolism

Cholesterol, essential for cell membranes, steroid hormones, bile acids, and vitamin D synthesis, is synthesized primarily in the liver via the HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase pathway. This pathway is tightly regulated by cholesterol levels and hormones (Alves *et al.,* 2021). Cholesterol is transported through the bloodstream by lipoproteins: LDL (transports cholesterol to tissues, "bad cholesterol"), HDL (removes excess cholesterol from tissues, "good cholesterol"), VLDL (transports triglycerides), and chylomicrons (Singh *et al.,* 2023; Kontush, 2024). Maintaining a balance among these lipoproteins is crucial for cardiovascular health. Reverse cholesterol transport, mediated by HDL, removes excess cholesterol from tissues and returns it to the liver for excretion.

Table 1: Summary of Lipid Metabolism

Process	Key Pathways	Major Enzymes/Regulators	Function
Lipid Synthesis (Lipogenesis)	Fatty Acid Synthesis, Triglyceride Synthesis	Acetyl-CoA Carboxylase (ACC), Fatty Acid Synthase (FAS), SREBP-1c	Converts excess carbohydrates into fatty acids and stores energy as triglycerides
Lipid Storage	Adipogenesis, Lipid Droplet Formation	Peroxisome Proliferator-Activated Receptors (PPARγ), Adipose Triglyceride Lipase (ATGL)	Stores lipids in adipose tissue for energy reserves
Lipid Breakdown (Lipolysis)	Triglyceride Hydrolysis	Hormone-Sensitive Lipase (HSL), Adipose Triglyceride Lipase (ATGL)	Releases fatty acids from stored triglycerides for energy use
Fatty Acid Oxidation (β-Oxidation)	Mitochondrial and Peroxisomal β-Oxidation	Carnitine Palmitoyltransferase (CPT1, CPT2), Acyl-CoA Dehydrogenases	Converts fatty acids into ATP in mitochondria and

Process	Key Pathways	Major Enzymes/Regulators	Function
			peroxisomes
Cholesterol Metabolism	Cholesterol Biosynthesis, Transport, and Excretion	HMG-CoA Reductase, LDL Receptor, PCSK9, ABC Transporters	Maintains cholesterol homeostasis, regulates bile acid synthesis
Lipid Transport	Lipoprotein Metabolism (Chylomicrons, VLDL, LDL, HDL)	Apolipoproteins (ApoA, ApoB, ApoC), Lipoprotein Lipase (LPL), Lecithin-Cholesterol Acyltransferase (LCAT)	Facilitates lipid movement through the bloodstream
Phospholipid Metabolism	Glycerophospholipid & Sphingolipid Synthesis	Phospholipase A2, CDP-Choline Pathway Enzymes	Regulates membrane composition and cell signaling
Ketogenesis	Ketone Body Production	HMG-CoA Synthase, HMG-CoA Lyase	Provides an alternative energy source during fasting or low-carb states

Regulation of Lipid Metabolism

Lipid metabolism is tightly regulated through a complex interplay of enzymes, cofactors, transcription factors, hormones, and environmental factors. Key enzymes such as fatty acid synthase (FASN) and stearoyl-CoA desaturase-1 (SCD1) drive lipid synthesis and modification (Li et al., 2024; Sun et al., 2024), while essential cofactors, including acetyl-CoA, NADPH, and ATP, provide the necessary biochemical energy for these processes (Castelli et al., 2021; Yoon et al., 2021). Transcription factors, such as sterol regulatory element-binding proteins (SREBPs), peroxisome proliferator-activated receptors (PPARs), and carbohydrate-responsive element-binding protein (ChREBP), play pivotal roles in lipid homeostasis by regulating fatty acid and cholesterol metabolism (Bravo-Ruiz et al., 2021; Ramatchandirin et al., 2023).

Hormonal regulation further fine-tunes lipid metabolism. Insulin promotes lipid synthesis, glucagon activates lipolysis, cortisol enhances lipid breakdown, and thyroid hormones influence both lipid synthesis and oxidation (Aldhalemi and Lahhob, 2024).

SREBPs primarily regulate cholesterol and fatty acid synthesis, while PPARs control fatty acid oxidation and lipid storage. ChREBP serves as a key link between carbohydrate intake and lipid synthesis, ensuring metabolic adaptation to dietary changes (Bravo-Ruiz et al., 2021; Ramatchandirin et al., 2023). Additionally, environmental and dietary factors significantly impact lipid metabolism. The composition of dietary macronutrients, particularly the balance between carbohydrates and polyunsaturated fatty acids, influences lipid synthesis and storage. Moreover, exposure to endocrine-disrupting compounds can alter lipid regulatory pathways, further affecting metabolic homeostasis (Turchini et al., 2022).

Regulation of Cholesterol Biosynthesis

The liver is the central organ for cholesterol synthesis, with 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase serving as the rate-limiting enzyme in this pathway (Wang et al., 2023). Cholesterol biosynthesis is regulated at multiple levels, including transcriptional, post-translational, and epigenetic mechanisms. At the transcriptional level, sterol regulatory element-binding proteins (SREBPs) play a key role in modulating HMG-CoA reductase expression. When intracellular cholesterol levels are low, SREBPs activate the transcription of the *HMGCR* gene, increasing cholesterol synthesis (Singh et al., 2023; Bravo-Ruiz et al., 2021; Ramatchandirin et al., 2023). Conversely, high cholesterol levels suppress *HMGCR* transcription to maintain lipid homeostasis.

Post-translational regulation further refines cholesterol synthesis by targeting HMG-CoA reductase for degradation. The enzyme undergoes ubiquitination and is degraded via the endoplasmic reticulum-associated degradation (ERAD) pathway, allowing for rapid adjustments to cholesterol levels in response to cellular needs (Jo and DeBose-Boyd, 2022; Liu et al., 2022). Recent advances have highlighted the role of non-coding RNAs, particularly microRNAs (miRNAs), in modulating cholesterol biosynthesis. miRNAs can regulate *HMGCR* expression by targeting its mRNA, adding an additional layer of post-transcriptional control (Nemeth et al., 2024; Tabrez et al., 2024).

Epigenetic modifications also contribute to cholesterol regulation. DNA methylation and histone modifications influence the transcriptional activity of HMGCR, affecting its expression in response to metabolic signals (Duddu et al., 2025; Rai and Rai, 2024). These discoveries open new avenues for therapeutic interventions aimed at fine-tuning

cholesterol biosynthesis, offering potential strategies for managing dyslipidemia and other metabolic disorders.

Lipoprotein Metabolism and Cholesterol Transport

Cholesterol, being hydrophobic, is transported in the bloodstream by lipoproteins (Bhale *et al.,* 2024): low-density lipoproteins (LDL), high-density lipoproteins (HDL), and very-low-density lipoproteins (VLDL) (Zhou *et al.,* 2024). LDL particles deliver cholesterol from the liver to peripheral tissues. This uptake is mediated by the LDL receptor (LDLR) on cell surfaces (Babakr, 2024). The number of LDLRs on a cell's surface dictates how much cholesterol it can absorb. A key regulator of LDLR levels is proprotein convertase subtilisin/kexin type 9 (PCSK9) (Lamia *et al.,* 2024). PCSK9 binds to the LDLR, promoting its degradation and reducing cholesterol uptake. The discovery of PCSK9's role has led to the development of PCSK9 inhibitors, a class of drugs that effectively lower LDL cholesterol levels and significantly reduce CVD risk (Lamia *et al.,* 2024).

HDL particles, in contrast, play a crucial role in reverse cholesterol transport (Zhou *et al.,* 2024). HDL picks up excess cholesterol from peripheral cells, including macrophages in arterial walls (a key step in atherosclerosis development), and transports it back to the liver for excretion in bile (Zhou *et al.,* 2024). It's now understood that HDL *functionality*, rather than simply HDL cholesterol levels, is a better predictor of cardiovascular risk (Madaudo *et al.,* 2024). Research is focused on identifying novel HDL-associated proteins, such as apolipoprotein M (ApoM) (Bhale *et al.,* 2024; Frances *et al.,* 2024) and its ligand sphingosine-1-phosphate (S1P) (Del Gaudio *et al.,* 2024), which may represent targets for enhancing cholesterol efflux capacity and improving HDL function.

Lipid Metabolism in Health and Disease

Dysregulation of lipid metabolism plays a significant role in the development of various metabolic disorders. One major consequence is obesity and metabolic syndrome, where excessive fat accumulation and ectopic fat deposition contribute to insulin resistance, chronic inflammation, and metabolic dysfunction (Janssen, 2024). These disruptions increase the risk of developing conditions such as type 2 diabetes and cardiovascular diseases.

Abnormal lipid levels, known as dyslipidemia, are another critical outcome of impaired lipid metabolism (Kaze *et al.,* 2021). Elevated low-density lipoprotein (LDL), reduced high-density lipoprotein (HDL), and high triglyceride levels contribute to atherosclerosis (Vekic *et al.,* 2022; Balling *et al.,* 2023), a key factor in cardiovascular diseases (CVDs). These imbalances promote plaque formation in blood vessels, increasing the likelihood of heart attacks and strokes.

Fatty liver diseases, including non-alcoholic fatty liver disease (NAFLD) and its more severe form, non-alcoholic steatohepatitis (NASH), are also linked to lipid metabolism disorders (Bence and Birnbaum, 2021). Excessive hepatic fat accumulation, often associated with insulin resistance, leads to inflammation and oxidative stress, which can progress to liver fibrosis and cirrhosis.

In diabetes mellitus, insulin resistance and altered lipid metabolism contribute to diabetic dyslipidemia, a condition characterized by elevated triglycerides, reduced HDL cholesterol, and increased small, dense LDL particles (Thambiah and Lai, 2021). These abnormalities significantly heighten the risk of cardiovascular complications in diabetic individuals.

Also, genetic disorders affecting lipid metabolism can result in severe metabolic conditions. Mutations in specific genes disrupt lipid processing pathways, leading to diseases such as Gaucher disease, Tay-Sachs disease, and familial hypercholesterolemia (Masood *et al.,* 2024). These inherited disorders often involve lipid accumulation in tissues, causing progressive organ damage and severe clinical symptoms.

New Frontiers in Lipid Metabolism

Lipid metabolism research is advancing rapidly, driven by cutting-edge technologies and new scientific insights. One significant area of progress is lipidomics and metabolic profiling (Gątarek and Kałużna-Czaplińska, 2024). Advances in mass spectrometry (MS) (Titkare *et al.,* 2024) and nuclear magnetic resonance (NMR) spectroscopy (Yilmaz *et al.,* 2025) enable comprehensive lipid analysis, facilitating the identification of biomarkers for metabolic disorders. These developments pave the way for personalized treatment strategies tailored to an individual's lipid profile.

The gut microbiota has also emerged as a crucial factor in lipid metabolism. The composition and function of gut microbes influence lipid absorption, storage, and overall metabolic health (Jia *et al.,* 2024). Dysbiosis, or microbial imbalance, is increasingly linked to metabolic disorders such as obesity and diabetes (Fan and Pedersen, 2021). As a result, microbiome-based therapies, including probiotics, prebiotics, and fecal microbiota transplantation, are gaining attention as potential interventions.

In therapeutics, novel drug targets are being explored to regulate lipid metabolism more effectively. Inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) have already revolutionized cholesterol management (Grewal and Buechler, 2022), while other promising targets, such as peroxisome proliferator-activated receptors (PPARs), sterol regulatory element-binding proteins (SREBPs) (Su and Koeberle, 2024), and fibroblast growth factor 21 (FGF21), are being investigated for their roles in lipid regulation (Velingkar *et al.,* 2023). Additionally, gene-editing technologies like CRISPR offer exciting possibilities for correcting genetic defects linked to lipid disorders (Stankov and Cuchel, 2023; Torella *et al.,* 2024).

Precision medicine is another transformative approach in lipid metabolism research (Singh *et al.,* 2023). By integrating multi-omics data—including lipidomics, scientists can develop highly personalized interventions. This tailored approach enhances disease prevention and management by considering an individual's unique metabolic profile, ultimately improving treatment outcomes for lipid-related disorders (Singh *et al.,* 2023).

Therapeutic Targeting Strategies of Cholesterol Mediated Maladies

Recent studies have implicated cholesterol metabolism in a variety of other diseases. In cancer, tumor cells often exhibit altered cholesterol metabolism to support rapid growth and proliferation (Jiang *et al.,* 2024). Some cancers overexpress enzymes in the cholesterol biosynthesis pathway, providing them with the necessary building blocks for cell membranes and signaling molecules (Wu *et al.,* 2024). Conversely, in some neurodegenerative diseases, such as Alzheimer's, disruptions in cholesterol metabolism in the brain contribute to the formation of amyloid plaques and neuronal dysfunction (Shin *et al.,* 2024). Understanding the specific roles of cholesterol in these diverse contexts is an active area of research. Several innovative therapeutic strategies are being explored to target cholesterol metabolism:

CRISPR-Cas9 technology offers the potential for precise gene editing. It has been applied to target genes involved in cholesterol metabolism, such as *PCSK9* and *ANGPTL3* (encoding angiopoietin-like 3, a regulator of lipoprotein lipase) (Wu *et al.,* 2024; Zadeh and Shapiro, 2024). CRISPR-based therapies aim to permanently correct genetic defects that lead to hypercholesterolemia, offering a long-term solution. Clinical trials are underway to assess the safety and efficacy of these approaches (Zadeh and Shapiro, 2024).

RNA-based therapeutics, including small interfering RNA (siRNA) and antisense oligonucleotides (ASOs), provide another avenue for targeting specific genes (Tani, 2024). Inclisiran, an siRNA that inhibits PCSK9 expression, has been approved for clinical use (Mansoor *et al.,* 2024). It offers sustained LDL cholesterol lowering with infrequent dosing. ASOs can target other genes involved in cholesterol metabolism, providing a versatile platform for therapeutic development.

The gut microbiota plays a surprisingly significant role in modulating cholesterol metabolism. Gut microbes can influence bile acid metabolism, produce short-chain fatty acids that affect lipid metabolism, and directly impact cholesterol absorption (Stankov and Cuchel, 2023; Torella *et al.,* 2024). Dysbiosis, an imbalance in the gut microbiota, has been linked to dyslipidemia and increased CVD risk. Probiotics and microbiome-targeted therapies are being investigated as potential strategies to improve cholesterol homeostasis and overall metabolic health. For example, some bacterial species can convert cholesterol into coprostanol, which is poorly absorbed, effectively reducing cholesterol levels (Stankov and Cuchel, 2023; Torella *et al.,* 2024).

Beyond HMG-CoA reductase, other enzymes in the cholesterol biosynthesis pathway are being investigated as potential drug targets. Inhibiting specific enzymes could potentially offer more tailored approaches to managing cholesterol levels, particularly in combination with existing therapies (Verma *et al.,* 2024).

Given the regulatory role of miRNAs in cholesterol metabolism, miRNA-based therapies are also being explored. miRNA mimics (to increase the levels of specific miRNAs) or antimiRs (to inhibit miRNA activity) could be used to modulate cholesterol homeostasis (La Sala *et al.,* 2024).

Conclusion

Lipid metabolism is a complex and essential process with profound implications for health and disease. Understanding its intricate pathways and regulatory mechanisms is crucial for developing effective strategies to prevent and treat metabolic disorders. Advances in lipidomics, microbiome research, drug development, and precision medicine are shaping the future of this field, offering new opportunities for improved diagnostics and therapies.

One significant breakthrough in lipid metabolism research is the growing understanding of cholesterol homeostasis. The discovery of PCSK9 and the development of PCSK9 inhibitors have revolutionized the management of hypercholesterolemia, significantly reducing cardiovascular disease risk. Furthermore, emerging therapeutic strategies targeting cholesterol synthesis, uptake, and reverse transport continue to enhance treatment options. The gut microbiota's influence on lipid metabolism, along with the potential of CRISPR-Cas9 and RNA-based therapies, holds great promise for personalized medicine approaches to cholesterol-related disorders.

Continued research into the intricate regulatory networks governing lipid and cholesterol metabolism, including the roles of microRNAs and other non-coding RNAs, will pave the way for innovative treatments. By unraveling these complexities, scientists can develop more effective interventions, ultimately leading to better health outcomes.

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