Lipid droplet biology: Emerging regulators in cellular metabolism and disease.

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Introduction

Lipid droplets (LDs) are dynamic intracellular organelles traditionally viewed as passive fat storage sites, but recent discoveries have redefined them as active regulators of cellular metabolism, signaling, and homeostasis. Composed of a core of neutral lipids, primarily triglycerides and cholesterol esters, surrounded by a phospholipid monolayer embedded with specific proteins, lipid droplets play critical roles in energy storage, lipid trafficking, and protection against lipotoxicity. Their functions are tightly regulated and context-dependent, varying across cell types and physiological conditions [1, 2].

Lipid droplet formation begins at the endoplasmic reticulum (ER), where neutral lipids accumulate between the two leaflets of the ER membrane and bud off to form distinct organelles. Proteins such as perilipins, adipose triglyceride lipase (ATGL), and hormone-sensitive lipase (HSL) regulate the balance between lipid storage and mobilization. This balance is essential for maintaining energy homeostasis, especially in cells with high metabolic demands such as hepatocytes, adipocytes, and myocytes [3, 4].

Under nutrient-rich conditions, cells synthesize and store excess fatty acids in lipid droplets to prevent the accumulation of free fatty acids, which can disrupt membrane integrity and cause oxidative stress. During fasting or increased energy demand, stored lipids are hydrolyzed to release fatty acids for β-oxidation, a process crucial for ATP production. The regulation of lipid droplet turnover is therefore fundamental to adapting to metabolic changes [5, 6].

Beyond energy metabolism, lipid droplets have emerged as important players in cellular signaling and stress responses. They interact with other organelles like mitochondria, lysosomes, and peroxisomes, facilitating lipid exchange and contributing to organelle crosstalk. In addition, LDs can sequester toxic lipids and proteins, acting as buffers against cellular damage under stress conditions such as hypoxia, ER stress, and infection [6].

Lipid droplet biology is also increasingly implicated in the pathogenesis of metabolic diseases. In non-alcoholic fatty liver disease (NAFLD), the excessive accumulation of LDs in hepatocytes reflects impaired lipid metabolism and insulin signaling. Similarly, in obesity and type 2 diabetes, dysregulated lipolysis and altered LD dynamics contribute to ectopic fat deposition and systemic insulin resistance. Moreover, LDs in macrophages—known as foam cells—are hallmarks of atherosclerosis, playing a role in inflammation and plaque formation [7].

In cancer, lipid droplets support tumor progression by providing metabolic flexibility and protection against oxidative stress. Certain cancers exhibit increased LD biogenesis, allowing tumor cells to store lipids for membrane synthesis, energy production, and signaling molecule generation. These adaptations enhance survival under nutrient-limited or hypoxic conditions, common within the tumor microenvironment [8].

Viral infections also manipulate lipid droplet pathways to facilitate replication. Viruses such as hepatitis C and dengue virus hijack LDs for assembly and maturation, highlighting their role in host-pathogen interactions. Understanding these mechanisms offers potential targets for antiviral therapies [9].

Therapeutic strategies aimed at modulating lipid droplet dynamics are gaining attention. Pharmacological agents that regulate lipid storage, lipolysis, or LD-associated protein expression may offer novel treatments for metabolic and inflammatory diseases. Lifestyle interventions like exercise and dietary modifications also influence lipid droplet behavior, further underlining their responsiveness to metabolic cues [10].

Conclusion

In conclusion, lipid droplets have emerged as multifaceted organelles central to cellular metabolism and stress adaptation. Their roles extend beyond simple lipid storage to include active participation in signaling, organelle interaction, and disease modulation. As our understanding of lipid droplet biology deepens, it opens new avenues for targeting metabolic dysfunction and developing treatments for a wide range of chronic diseases.

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