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Lipid Droplet Biology in Obesity: Mechanisms of Lipid Storage and Mobilization in Metabolic Disease

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ABSTRACT

Lipid droplets (LDs) are dynamic organelles that play a central role in lipid storage and mobilization, particularly in the context of metabolic diseases like obesity. Obesity is characterized by excessive accumulation of triglycerides within adipocytes, leading to metabolic dysregulation and associated comorbidities such as insulin resistance, type 2 diabetes, and cardiovascular disease. This review explores the biology of lipid droplets in the setting of obesity, focusing on the mechanisms of lipid storage and mobilization. We discuss the key regulatory proteins involved in LD formation and degradation, including perilipins, adipose triglyceride lipase (ATGL), and hormone-sensitive lipase (HSL). Additionally, the roles of lipophagy, autophagy, and lipolysis in lipid mobilization are explored. We also highlight how dysregulation of lipid droplet biology contributes to obesity-related metabolic disorders, with emphasis on the impact of lipid droplet dysfunction on cellular signaling, lipid metabolism, and inflammation. Finally, we discuss the potential of targeting LDs as a therapeutic strategy for treating obesity and its metabolic complications.

Keywords: Lipid droplets, Obesity, Lipid storage, Lipid mobilization, Metabolic disease, Lipolysis, Lipophagy, Triglycerides

INTRODUCTION

Lipid droplets (LDs) are unique intracellular organelles central to lipid storage and homeostasis, composed of a core of neutral lipids such as triglycerides (TAG) and cholesterol esters, surrounded by a phospholipid monolayer embedded with specific proteins[1, 2]. Initially thought to be passive fat stores, LDs have emerged as highly dynamic structures that play key roles in various cellular processes. These include not only lipid metabolism but also energy regulation, membrane trafficking, protein degradation, and cellular signaling. LDs contribute to balancing energy supply and demand, especially during states of caloric excess or deficit, by dynamically storing and mobilizing lipids in response to physiological cues[3, 4]. In the context of obesity, the dysregulation of lipid metabolism leads to an increase in both the size and number of LDs in adipocytes (fat cells). This process, known as hypertrophy (increase in cell size) and hyperplasia (increase in cell number), is driven by chronic caloric surplus, leading to excessive lipid storage. As LDs expand, they accommodate more neutral lipids, particularly TAG, exacerbating lipid accumulation. This excessive lipid deposition not only alters adipocyte function but also contributes to a cascade of metabolic disturbances, including insulin resistance, chronic inflammation, and ectopic lipid deposition in organs such as the liver and muscle[5, 6].

Obesity is now considered a global health crisis, with over 650 million adults classified as obese according to the World Health Organization (WHO) in 2023. It is closely linked with an increased prevalence of metabolic diseases, including type 2 diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease (NAFLD)[7–10]. These disorders arise in part due to the inability of adipocytes to efficiently manage lipid storage, leading to lipid spillover and accumulation in tissues that are not designed to store fat[10, 11]. Understanding the regulatory mechanisms that control LD formation, expansion, and breakdown is essential for developing therapeutic strategies targeting obesity and related metabolic disorders. LD biogenesis is regulated by various proteins, including perilipins, which coat the surface of LDs and protect them from premature lipolysis (breakdown of lipids).

Key enzymes like adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) are responsible for the mobilization of stored lipids during energy demand, a process regulated by hormones such as insulin and catecholamines[12, 13].

However, in obesity, the normal regulation of lipid metabolism is disrupted, leading to impaired lipolysis and excessive lipid storage. This dysfunction in lipid mobilization is a major contributor to metabolic diseases. For example, in insulin resistance, adipocytes fail to respond appropriately to insulin, leading to unchecked lipolysis and elevated circulating free fatty acids, which exacerbate metabolic dysregulation in other tissues. Targeting the proteins and pathways involved in LD dynamics could offer new therapeutic avenues for treating obesity and its associated complications. Potential strategies include modulating LD-associated proteins like perilipins, enhancing lipolysis through pharmacological activation of ATGL or HSL, or regulating lipid droplet expansion through inhibitors of enzymes involved in TAG synthesis[14]. Moreover, understanding how LDs interact with other organelles, such as mitochondria and the endoplasmic reticulum, may provide insights into how lipid homeostasis is coordinated at the cellular level, revealing additional therapeutic targets.

Lipid Droplet Formation and Structure

LDs originate from the endoplasmic reticulum (ER) membrane, where neutral lipids accumulate between the bilayer, forming a lens-shaped structure. As the core of the LD grows, it buds off into the cytosol, forming a monolayer phospholipid membrane surrounding a hydrophobic core of triglycerides and cholesterol esters[15, 16]. The phospholipid monolayer is embedded with various proteins that regulate LD function, including perilipins (PLINs), enzymes involved in lipolysis, and proteins governing lipid trafficking.

Perilipins and LD Stability

Perilipins are a family of LD-coating proteins essential for regulating lipid storage and mobilization. Of these, perilipin-1 (PLIN1) is the most studied and is predominantly expressed in adipocytes. PLIN1 plays a protective role by inhibiting the access of lipases to the triglyceride core, thereby preventing uncontrolled lipolysis . Under lipolytic stimuli, PLIN1 is phosphorylated, facilitating the recruitment of lipases to the LD surface and promoting lipid breakdown[17, 18] .

Lipid Droplet Expansion

In obesity, lipid droplets (LDs), the main intracellular storage sites for neutral lipids, undergo substantial expansion due to enhanced triglyceride (TG) synthesis and accumulation. This expansion is a direct consequence of the body's attempt to store excess energy, primarily in the form of triglycerides. The process is heavily influenced by the upregulation of lipogenic pathways, where enzymes like diacylglycerol acyltransferase (DGAT) play a central role. DGAT catalyzes the final step in triglyceride synthesis, which involves the conversion of diacylglycerol (DAG) and acyl-CoA into triglycerides[19]. This enzyme's activity is pivotal for the storage of energy within lipid droplets in adipocytes (fat cells). In the context of obesity, excess caloric intake, especially from fats and carbohydrates, stimulates several metabolic and hormonal pathways that enhance the expression and activity of DGAT and other lipogenic enzymes, such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). These enzymes collectively drive the production of fatty acids and their incorporation into triglycerides. ACC is responsible for the conversion of acetyl-CoA to malonyl-CoA, the first committed step in fatty acid synthesis, while FAS catalyzes the production of long-chain fatty acids. Once fatty acids are synthesized, DGAT completes their esterification into triglycerides, which are then stored in lipid droplets.[20]

In obesity, this process is exaggerated due to the body's overnutrition, leading to an increased flux of fatty acids and glycerol into adipocytes[21]. The excess nutrients stimulate the upregulation of transcription factors, such as sterol regulatory element-binding proteins (SREBPs) and peroxisome proliferator-activated receptors (PPARs), which enhance the expression of lipogenic genes, including DGAT. As a result, adipocytes accumulate larger lipid droplets to store the surplus triglycerides. This not only increases the size of individual lipid droplets but also leads to adipocyte hypertrophy (enlargement of fat cells)[21]. The expansion of lipid droplets is associated with metabolic stress, as it disrupts normal adipocyte function, leading to lipotoxicity (the toxic effects of lipid accumulation on non-adipose tissues) and promoting inflammation within adipose tissue. Over time, this contributes to insulin resistance, a hallmark of obesity-associated metabolic disorders such as type 2 diabetes and cardiovascular disease. Additionally, the inability of adipocytes to store excess lipids effectively may result in ectopic fat deposition in tissues like the liver and muscle, further exacerbating metabolic dysfunction.[22].

Mechanisms of Lipid Mobilization

Lipid mobilization from LDs is primarily mediated by lipolysis and lipophagy, two distinct but interconnected pathways that regulate the release

of stored fatty acids for energy production or other cellular processes.[23, 24]

Lipolysis

Lipolysis is the enzymatic breakdown of triglycerides into free fatty acids (FFAs) and glycerol, a process regulated by key enzymes including adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoglyceride lipase (MGL). ATGL initiates the first step by hydrolyzing triglycerides into diacylglycerol, while HSL converts diacylglycerol into monoacylglycerol, which is then further hydrolyzed by MGL into FFAs and glycerol. The activation of lipolysis is tightly regulated by hormonal signals such as catecholamines, which activate protein kinase A (PKA) signaling. PKA phosphorylates PLIN1 and HSL, facilitating the translocation of HSL to the LD surface and promoting lipolysis.

Lipophagy

Lipophagy is a specialized form of autophagy that involves the degradation of LDs via lysosomal pathways. In this process, LDs are engulfed by autophagosomes, which fuse with lysosomes, leading to the breakdown of LDs and release of free fatty acids. Lipophagy plays a complementary role to lipolysis, particularly in conditions of prolonged fasting or energy deprivation, when cells need to mobilize stored lipids to meet energy demands.

Insulin Resistance and Lipid Droplets

Insulin resistance is a hallmark of obesity and is closely linked to aberrant lipid droplet biology. Normally, insulin inhibits lipolysis by suppressing the activity of ATGL and HSL, thus promoting lipid storage. However, in insulin-resistant states, this suppression is impaired, resulting in excessive lipolysis and elevated circulating free fatty acids, which contribute to ectopic fat deposition and lipotoxicity in non-adipose tissues such as the liver and skeletal muscle [25, 26] .

Inflammation and Adipose Tissue Dysfunction

The excessive lipid accumulation in obesity leads to adipose tissue inflammation, characterized by the infiltration of immune cells, particularly macrophages, into adipose tissue. These immune cells release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which further exacerbate insulin resistance and impair lipid droplet function [27].

Therapeutic Targeting of Lipid Droplets in Obesity

Given the central role of lipid droplets in obesity and metabolic diseases, they represent a promising target for therapeutic intervention. Several strategies have been proposed to modulate lipid droplet biology. One approach is the inhibition of lipid droplet formation, which involves targeting key enzymes like diacylglycerol acyltransferase (DGAT), crucial for triglyceride synthesis. By inhibiting these enzymes, it may be possible to prevent excessive lipid storage, a major factor in obesity. Another strategy focuses on enhancing lipid mobilization by activating pathways such as lipolysis or lipophagy. This activation promotes the breakdown of excess lipids, reducing adipose tissue expansion. Lastly, **anti-inflammatory approaches aim to reduce inflammation in adipose tissue, a contributor to insulin resistance. By mitigating this inflammation, it could be possible to restore normal lipid droplet function and improve metabolic health.

CONCLUSION

Lipid droplets are key organelles in the regulation of lipid storage and mobilization, playing a crucial role in the development of obesity and related metabolic diseases. The dysregulation of LD biology in obesity contributes to insulin resistance, inflammation, and ectopic fat deposition, underscoring the importance of targeting LDs in therapeutic strategies. Future research should focus on further elucidating the molecular mechanisms governing lipid droplet dynamics and exploring novel therapeutic approaches for modulating LD function in obesity.

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