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Role of Autophagy in Lipid Accumulation and Metabolic Dysfunction in Obesity

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ABSTRACT

Obesity, a global public health challenge, is closely associated with lipid accumulation and metabolic dysfunction, contributing to the development of comorbidities such as type 2 diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease (NAFLD). Autophagy, a highly conserved cellular process responsible for degrading and recycling cytoplasmic components, plays a pivotal role in maintaining cellular homeostasis. Dysregulation of autophagy has been implicated in the pathogenesis of obesity and its associated metabolic disturbances. This review explores the mechanisms by which autophagy influences lipid metabolism, lipid droplet turnover, and energy balance, focusing on its role in adipocytes, hepatocytes, and muscle cells. We discuss the interaction between autophagy and critical metabolic pathways such as lipophagy and mitophagy and their implications for lipid storage, insulin sensitivity, and mitochondrial function. Additionally, we examine the contribution of autophagy to obesity-induced inflammation and the progression of metabolic diseases. Understanding the complex relationship between autophagy and lipid metabolism may offer novel therapeutic strategies for combating obesity and its metabolic complications.

Keywords: Autophagy, Lipid metabolism, Obesity, Lipid accumulation, Metabolic dysfunction, Lipophagy, Mitophagy, Insulin resistance

INTRODUCTION

Obesity has emerged as a global epidemic, characterized by abnormal or excessive fat accumulation that leads to a range of metabolic disturbances[1–3]. These disturbances include insulin resistance, dyslipidemia (abnormal lipid levels), and chronic low-grade inflammation[4–6]. The development of obesity is primarily driven by excessive caloric intake, a sedentary lifestyle, and genetic predisposition, which together lead to energy imbalance and lipid accumulation in various tissues[3, 7, 8]. The most affected organs include adipose tissue, liver, and skeletal muscle, all of which play critical roles in maintaining energy homeostasis[9, 10]. As lipid levels increase in these tissues, metabolic dysfunction sets in, further exacerbating obesity-related complications. The pathophysiology of obesity is complex and multifactorial. Excessive fat accumulation in adipose tissue leads to its dysfunction, which results in an altered secretion of adipokines (hormones produced by fat cells) and pro-inflammatory cytokines [11]. This contributes to systemic inflammation and the onset of insulin resistance, a condition where cells no longer respond properly to insulin, impeding glucose uptake and promoting further metabolic disturbances[12]. Furthermore, lipid accumulation in non-adipose tissues like the liver (leading to non-alcoholic fatty liver disease) and skeletal muscle impairs energy homeostasis, contributing to the development of dyslipidemia and insulin resistance.

Role of Autophagy in Obesity

Autophagy is a highly conserved cellular process responsible for degrading and recycling damaged organelles, misfolded proteins, and lipids. This process is crucial for maintaining cellular homeostasis, especially in metabolically active tissues. In the context of obesity, autophagy plays a particularly important role in regulating lipid turnover through a specialized form known as lipophagy, which involves the breakdown of

lipid droplets within cells[13]. By breaking down these lipid droplets, lipophagy contributes to maintaining lipid homeostasis and preventing excessive lipid accumulation that would otherwise lead to metabolic dysfunction[14]. However, in obesity, there is often a disruption in autophagic pathways, which leads to impaired lipophagy and subsequent lipid accumulation. This impairment contributes to the pathogenesis of several obesity-related metabolic abnormalities, including insulin resistance and hepatic steatosis (fatty liver)[15]. Disrupted autophagy also affects other processes involved in energy regulation, such as mitochondrial function and the removal of reactive oxygen species (ROS), further aggravating metabolic dysfunction[16].

Mechanistic Links Between Autophagy and Lipid Metabolism

Autophagy and lipid metabolism are intricately linked, with autophagy playing a key role in lipid mobilization and degradation[17]. During states of energy deprivation, autophagy is upregulated to break down lipid stores into free fatty acids, which can be used for energy production. Conversely, under conditions of excessive nutrient availability, such as in obesity, autophagy is often downregulated, contributing to lipid accumulation in tissues like the liver and adipose tissue. Several key regulators of autophagy have been identified, including AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR), which respond to changes in nutrient levels and energy status. In obesity, nutrient excess leads to hyperactivation of mTOR, which suppresses autophagy and promotes lipid storage rather than lipid breakdown[18, 19]. This dysregulation of autophagy exacerbates the metabolic disturbances associated with obesity, including insulin resistance and chronic inflammation.

Therapeutic Potential of Targeting Autophagy in Obesity

Given the critical role of autophagy in regulating lipid metabolism, targeting autophagic pathways presents a promising therapeutic strategy for treating obesity and its associated metabolic disorders. Modulating autophagy to restore its function could help reduce lipid accumulation, improve insulin sensitivity, and mitigate inflammation[20]. Several pharmacological agents have been identified that can modulate autophagy, including **rapamycin**, which inhibits mTOR and thus promotes autophagy, and **metformin**, an antidiabetic drug that activates AMPK and enhances autophagic activity[21]. However, while preclinical studies have shown promising results in improving metabolic outcomes by modulating autophagy, more research is needed to fully understand the context-dependent effects of autophagy in different tissues and stages of obesity. Additionally, the long-term safety and efficacy of autophagy-modulating therapies remain to be established.

Autophagy Mechanism

Autophagy is a catabolic process that facilitates the degradation of intracellular components through lysosomal machinery. Three major forms of autophagy—macroautophagy, microautophagy, and chaperone-mediated autophagy—operate to maintain cellular energy levels and eliminate damaged proteins, lipids, and organelles[22, 23].

Macroautophagy involves the formation of double-membraned vesicles called autophagosomes, which sequester cytoplasmic materials and deliver them to lysosomes for degradation.

Microautophagy directly engulfs cellular components into lysosomes.

Chaperone-mediated autophagy selectively degrades proteins that are identified by chaperones and translocated into lysosomes.

Autophagy is regulated by nutrient availability and metabolic cues, primarily through the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) signaling pathways. During nutrient deprivation, autophagy is activated to mobilize stored energy from lipids and proteins, a process crucial for maintaining metabolic balance.

Autophagy and Lipid Metabolism

Lipophagy: Role in Lipid Droplet Turnover

Lipophagy is a selective form of autophagy that mediates the degradation of lipid droplets (LDs) in hepatocytes and adipocytes. It plays a significant role in regulating lipid storage and utilization[16]. LDs, which store triglycerides and cholesterol esters, are engulfed by autophagosomes and delivered to lysosomes for hydrolysis, releasing free fatty acids (FFAs) that are subsequently used for β-oxidation. In obesity, the dysregulation of lipophagy leads to excessive lipid accumulation in adipocytes and hepatocytes, contributing to steatosis, insulin resistance, and NAFLD. Defective lipophagy hampers the turnover of LDs, exacerbating lipid overload in metabolic tissues and driving obesity-related complications [15].

Mitophagy: Mitochondrial Quality Control and Lipid Oxidation

Mitophagy, the selective degradation of damaged mitochondria, is essential for maintaining mitochondrial function and energy production. Mitochondria are central to lipid metabolism, as they mediate fatty acid oxidation (FAO). In obesity, impaired mitophagy results in dysfunctional mitochondria, reduced FAO, and increased lipid storage in tissues like the liver and muscle, contributing to insulin resistance and metabolic inflexibility. Reduced mitochondrial function in obese individuals compromises lipid oxidation, leading to elevated lipid intermediates such as ceramides and diacylglycerols (DAG), which interfere with insulin signaling and exacerbate metabolic dysfunction[24, 25].

Autophagy in Key Metabolic Tissuese

Adipose Tissue

Adipose tissue expansion in obesity results in hypertrophic adipocytes, which exhibit reduced autophagic activity. Dysregulation of autophagy in adipocytes impairs lipid turnover, exacerbating lipid accumulation. Additionally, impaired autophagy in adipose tissue contributes to increased secretion of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), driving systemic inflammation and insulin resistance. Adipose tissue autophagy also plays a role in adipogenesis, as autophagy deficiency leads to defective adipocyte differentiation and altered lipid storage capacity[26].

Liver: In the liver, autophagy is crucial for maintaining lipid homeostasis, primarily through lipophagy. Hepatic autophagy deficiency leads to the accumulation of lipid droplets and the development of NAFLD. Mice with autophagy-deficient livers exhibit steatosis, hyperlipidemia, and insulin resistance, underscoring the importance of autophagy in preventing lipid overload in the liver[27].

Skeletal Muscle: Skeletal muscle is a major site for glucose and fatty acid oxidation. Deficient autophagy in muscle cells reduces mitochondrial function, impairs lipid oxidation, and promotes lipid accumulation. This leads to insulin resistance and decreased metabolic flexibility, both of which are hallmarks of obesity-related metabolic dysfunction[28].

Autophagy, Inflammation, and Metabolic Dysfunction

Chronic low-grade inflammation is a hallmark of obesity, and autophagy plays a dual role in modulating immune responses. While autophagy can suppress excessive inflammation by removing damaged organelles and preventing the release of pro-inflammatory factors, impaired autophagy promotes inflammation by allowing the accumulation of dysfunctional mitochondria and reactive oxygen species (ROS). This, in turn, activates inflammatory pathways, exacerbating metabolic dysfunction in obesity[21].

Therapeutic Potential of Targeting Autophagy in Obesity

Given the critical role of autophagy in regulating lipid metabolism, targeting autophagic pathways offers a promising therapeutic strategy for obesity and its associated metabolic diseases. Pharmacological agents that activate autophagy, such as rapamycin and AMPK activators, have shown potential in reducing lipid accumulation and improving insulin sensitivity. Moreover, lifestyle interventions like caloric restriction and exercise are known to enhance autophagy and may serve as complementary therapies for obesity management.

CONCLUSION

Autophagy plays a central role in lipid metabolism, energy homeostasis, and the prevention of metabolic dysfunction in obesity. Dysregulation of autophagy contributes to lipid accumulation, insulin resistance, and chronic inflammation, driving the progression of obesity-related metabolic diseases. Therapeutic strategies aimed at restoring autophagic function may provide novel approaches to combating obesity and its complications. Further research is needed to fully elucidate the molecular mechanisms of autophagy in lipid metabolism and to develop targeted interventions for metabolic disorders.

REFERENCES

1. Abdalla, M.M.I.: Role of visfatin in obesity-induced insulin resistance. World J Clin Cases. 10, 10840–10851 (2022). https://doi.org/10.12998/wjcc.v10.i30.10840
2. Arhire, L.I., Mihalache, L., Covasa, M.: Irisin: A Hope in Understanding and Managing Obesity and Metabolic Syndrome. Frontiers in Endocrinology. 10, (2019). https://doi.org/10.3389/fendo.2019.00524
3. Balderas-Peña, L.-M.-A., Sat-Muñoz, D., Mireles-Ramírez, M.-A., Martínez-Herrera, B.-E., Nava-Zavala, A.-H., Cervantes-González, L.-M., Muñoz-García, M.-G., Rubio-Jurado, B., Páramo, M.S., Sánchez, E.G., Nuño-Guzmán, C.-M., Balderas-Peña, L.-M.-A., Sat-Muñoz, D., Mireles-Ramírez, M.-A., Martínez-Herrera, B.-E., Nava-Zavala, A.-H., Cervantes-González, L.-M., Muñoz-García, M.-G., Rubio-Jurado, B., Páramo, M.S., Sánchez, E.G., Nuño-Guzmán, C.-M.: Influence of Chronic Low-

Grade Inflammation (Obesity) on the Systemic Inflammatory Response. In: Multisystem Inflammatory Syndrome - Natural History. IntechOpen (2023)
4. Uti, D.E., Ibiam, U.A., Omang, W.A., Udeozor, P.A., Umoru, G.U., Nwadum, S.K., Bawa, I., Alum, E.U., Mordi, J.C., Okoro, E.O., Obeten, U.N., Onwe, E.N., Zakari, S., Opotu, O.R., Aja, P.M.: Buchholzia coriacea Leaves Attenuated Dyslipidemia and Oxidative Stress in Hyperlipidemic Rats and Its Potential Targets In Silico. Pharmaceutical Fronts. 05, e141–e152 (2023). https://doi.org/10.1055/s-0043-1772607
5. Uti, D.E., Atangwho, I.J., Eyong, E.U., Umoru, G.U., Egbung, G.E., Nna, V.U., Udeozor, P.A.: African walnuts attenuate ectopic fat accumulation and associated peroxidation and oxidative stress in monosodium glutamate-obese Wistar rats. Biomedicine & Pharmacotherapy. 124, 109879 (2020). https://doi.org/10.1016/j.biopha.2020.109879
6. Uti, D.E., Atangwho, I.J., Eyong, E.U., Umoru, G.U., Egbung, G.E., Rotimi, S.O., Nna, V.U.: African Walnuts (Tetracarpidium conophorum) Modulate Hepatic Lipid Accumulation in Obesity via Reciprocal Actions on HMG-CoA Reductase and Paraoxonase. Endocrine, Metabolic & Immune Disorders - Drug Targets(Formerly Current Drug Targets - Immune, Endocrine & Metabolic Disorders). 20, 365–379 (2020). https://doi.org/10.2174/1871530319666190724114729
7. Cerdó, T., García-Santos, J., G. Bermúdez, M., Campoy, C.: The Role of Probiotics and Prebiotics in the Prevention and Treatment of Obesity. Nutrients. 11, 635 (2019). https://doi.org/10.3390/nu11030635
8. Cavaliere, G., Cimmino, F., Trinchese, G., Catapano, A., Petrella, L., D'Angelo, M., Lucchin, L., Mollica, M.P.: From Obesity-Induced Low-Grade Inflammation to Lipotoxicity and Mitochondrial Dysfunction: Altered Multi-Crosstalk between Adipose Tissue and Metabolically Active Organs. Antioxidants. 12, 1172 (2023). https://doi.org/10.3390/antiox12061172
9. Cheng, L., Wang, J., Dai, H., Duan, Y., An, Y., Shi, L., Lv, Y., Li, H., Wang, C., Ma, Q., Li, Y., Li, P., Du, H., Zhao, B.: Brown and beige adipose tissue: a novel therapeutic strategy for obesity and type 2 diabetes mellitus. Adipocyte. 10, 48–65. https://doi.org/10.1080/21623945.2020.1870060
10. Chitraju, C., Fischer, A.W., Ambaw, Y.A., Wang, K., Yuan, B., Hui, S., Walther, T.C., Farese, R.V.: Mice lacking triglyceride synthesis enzymes in adipose tissue are resistant to diet-induced obesity. eLife. 12, RP88049 (2023). https://doi.org/10.7554/eLife.88049
11. Pestel, J., Blangero, F., Watson, J., Pirola, L., Eljaafari, A.: Adipokines in obesity and metabolic-related-diseases. Biochimie. 212, 48–59 (2023). https://doi.org/10.1016/j.biochi.2023.04.008
12. Landecho, M.F., Tuero, C., Valentí, V., Bilbao, I., De La Higuera, M., Frühbeck, G.: Relevance of Leptin and Other Adipokines in Obesity-Associated Cardiovascular Risk. Nutrients. 11, 2664 (2019). https://doi.org/10.3390/nu11112664
13. Khawar, M.B., Gao, H., Li, W.: Autophagy and Lipid Metabolism. 1206, 359–374 (2019). https://doi.org/10.1007/978-981-15-0602-4_17
14. Shin, D.: Lipophagy: Molecular Mechanisms and Implications in Metabolic Disorders. Molecules and Cells. (2020)
15. Zhang, S., Peng, X., Yang, S., Li, X., Huang, M., Wei, S., Liu, J., He, G., Zheng, H., Yang, L., Li, H., Fan, Q.: The regulation, function, and role of lipophagy, a form of selective autophagy, in metabolic disorders. Cell Death Dis. 13, 132 (2022). https://doi.org/10.1038/s41419-022-04593-3
16. Singh, R., Cuervo, A.M.: Lipophagy: Connecting Autophagy and Lipid Metabolism. International Journal of Cell Biology. 2012, 1–12 (2012). https://doi.org/10.1155/2012/282041
17. Singh, R., Kaushik, S., Wang, Y., Xiang, Y., Novak, I., Komatsu, M., Tanaka, K., Cuervo, A.M., Czaja, M.J.: Autophagy regulates lipid metabolism. Nature. 458, 1131–1135 (2009). https://doi.org/10.1038/nature07976
18. Singh, R.: Autophagy and Regulation of Lipid Metabolism. 52, 35–46 (2011). https://doi.org/10.1007/978-3-642-14426-4_4
19. Christian, P., Sacco, J., Adeli, K.: Autophagy: Emerging roles in lipid homeostasis and metabolic control. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids. 1831, 819–824 (2013). https://doi.org/10.1016/j.bbalip.2012.12.009
20. Kim, J., Lim, Y.-M., Lee, M.-S.: The Role of Autophagy in Systemic Metabolism and Human-Type Diabetes. Molecules and Cells. (2018)
21. Friuli, M., Sepe, C., Panza, E., Travelli, C., Paterniti, I., Romano, A.: Autophagy and inflammation an intricate affair in the management of obesity and metabolic disorders: evidence for novel

pharmacological strategies? Front. Pharmacol. 15, 1407336 (2024). https://doi.org/10.3389/fphar.2024.1407336
22. Kuchitsu, Y., Taguchi, T.: Lysosomal microautophagy: an emerging dimension in mammalian autophagy. Trends in Cell Biology. 34, 606–616 (2024). https://doi.org/10.1016/j.tcb.2023.11.005
23. Yamamoto, H., Matsui, T.: Molecular Mechanisms of Macroautophagy, Microautophagy, and Chaperone-Mediated Autophagy. J Nippon Med Sch. 91, 2–9 (2024). https://doi.org/10.1272/jnms.JNMS.2024_91-102
24. Shao, D., Stephen C Kolwicz, J., Wang, P., Roe, N.D., Villet, O., Nishi, K., Hsu, Y.-W.A., Flint, G.V., Caudal, A., Wang, W., Regnier, M., Tian, R.: Increasing Fatty Acid Oxidation Prevents High Fat Diet Induced Cardiomyopathy through Regulating Parkin Mediated Mitophagy. Circulation. 142, 983 (2020). https://doi.org/10.1161/CIRCULATIONAHA.119.043319
25. Tong, M., Saito, T., Zhai, P., Oka, S., Mizushima, W., Nakamura, M., Ikeda, S., Shirakabe, A., Sadoshima, J.: Mitophagy Is Essential for Maintaining Cardiac Function During High Fat Diet-Induced Diabetic Cardiomyopathy. Circulation research. 124, 1360 (2019). https://doi.org/10.1161/CIRCRESAHA.118.314607
26. Romero, M., Zorzano, A.: Role of autophagy in the regulation of adipose tissue biology. Cell Cycle. 18, 1435 (2019). https://doi.org/10.1080/15384101.2019.1624110
27. An, L., Wirth, U., Koch, D., Schirren, M., Drefs, M., Koliogiannis, D., Niess, H., Andrassy, J., Guba, M., Bazhin, A.V., Werner, J., Kühn, F.: Metabolic Role of Autophagy in the Pathogenesis and Development of NAFLD. Metabolites. 13, 101 (2023). https://doi.org/10.3390/metabo13010101
28. Axelrod, C.L., Fealy, C.E., Erickson, M.L., Davuluri, G., Fujioka, H., Dantas, W.S., Huang, E., Pergola, K., Mey, J.T., King, W.T., Mulya, A., Hsia, D., Burguera, B., Tandler, B., Hoppel, C.L., Kirwan, J.P.: Lipids Activate Skeletal Muscle Mitochondrial Fission and Quality Control Networks to Induce Insulin Resistance in Humans. Metabolism: clinical and experimental. 121, 154803 (2021). https://doi.org/10.1016/j.metabol.2021.154803

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