Biochimie 96 (2014) 102–105

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Mini-review

Lysosome/lipid droplet interplay in metabolic diseases

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ARTICLE INFO

Article history:
Received 19 March 2013
Accepted 8 July 2013
Available online 20 July 2013

Keywords:
Lipid storage
Autophagy
Degradation
Inflammation
Adipocyte

ABSTRACT

Lysosomes and lipid droplets are generally considered as intracellular compartments with divergent roles in cell metabolism, lipid droplets serving as lipid reservoirs in anabolic pathways, whereas lysosomes are specialized in the catabolism of intracellular components. During the last few years, new insights in the biology of lysosomes has challenged this view by providing evidence for the importance of lysosome recycling as a sparing mechanism to maintain cellular fitness. On the other hand the understanding of lipid droplets has evolved from an inert intracellular deposit toward the status of an intracellular organelle with dynamic roles in cellular homeostasis beyond storage. These unrelated aspects have also recently converged in the finding of unexpected lipid droplet/lysosome communication through autophagy, and the discovery of lysosome-mediated lipid droplet degradation called lipopagy.

Furthermore, adipocytes which are professional cells for lipid droplet formation were also shown to be active in peptide antigen presentation a pathway requiring lysosomal activity. The potential importance of lipid droplet/lysosome interplay is discussed in the context of metabolic diseases and the setting of chronic inflammation.

1. Lysosomes and lipid droplets: two organelles with divergent functions

1.1. Lysosomes more than wastebaskets

Lysosomes are digestive organelles with acidic intralumenal pH which contain at least 50 soluble hydrolases [1], with hydrolytic activities as proteases, glycosidases, lipases, nucleases, phosphatases or sulfatases. Integral membrane proteins, specific to lysosomes, like Vacuolar ATPase crucially maintains intravesical pH in the favorable acid range for the activity of hydrolases. Other proteins in its limiting membrane, such as the highly glycosylated proteins LAMPs (lysosome-associated membrane proteins) as well as LIMP (lysosomal integral membrane protein) also play major roles by contributing to the targeting of substrates [2]. Other key lysosomal components are membrane associated transporters involved in the exit of degradation products to the cell cytoplasm [3]. Lysosomal hydrolases are targeted to the organelle by the mannose 6-phosphate receptor shuttle from the Golgi, whereas lysosomal membrane components are sorted depending on short sequence motifs within their cytoplasmic tails. Disruption of lysosomal function due to deficiency of a particular hydrolase, cofactor or transporter leads to the heterogeneous group of lysosomal storage diseases [4]. Related to their degradative roles, lysosomes are required for intracellular remodeling of cell components and organelles, especially through the autophagy pathway, and therefore crucially help to maintain homeostasis in long-lived cell types. As the dead-end of most cell entry pathways by endocytosis, phagocytosis or pinocytosis, they are key effectors in the elimination of pathogens that might have enter cells. Lysosomes also participate in immune responses in the process of antigen presentation through MHC class II. Whereas MHC class I molecules primarily present peptides produced by proteasomal proteolysis, MHC class II mainly display degradation products from lysosomes, which can be both self- and pathogen-derived molecules delivered to lysosomes by macroautophagy [5]. Most likely, antigen fragments and self peptides are loaded onto MHC class II in specific late endosomal/lysosomal compartments called MIICs (MHC class II containing compartments), stabilized and further transported to the cell surface for T cell recognition.

Although long considered as an organelle dedicated to the degradation of products coming from inside or outside cells, the view on lysosome is now evolving toward recycling and reuse of intracellular components, which can be considered as an energy sparing and cellular health maintaining process. This is linked to the ability of lysosomal hydrolytic activities to generate building-block metabolites which can be transported out of lysosomes to the cytosol, and re-used in anabolic pathways [3]. Therefore,

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http://dx.doi.org/10.1016/j.biochi.2013.07.008

lysosomes fuel intracellular recycling by providing amino acids, simple sugars, or fatty acids, and can be viewed as energy sparing organelles. Noteworthy, cholesterol whose multi-step synthetic pathway has high energetic costs is not degraded but exported out of lysosomes by Niemann Pick proteins, which also illustrates contribution to cellular energy preservation. The energy-sparing function of lysosome recycling is also strengthened by the lean phenotypes of mice with lysosome dysfunction. Indeed, negative whole body energy balance producing extreme leaness, low leptin levels and modest adipose storage was reported in five different mice models of lysosomal storage diseases with distinct molecular etiologies [6]. Of note, one of these mice models with spontaneous gene mutation causing mucopolysaccharidosis type VII (MPSVII) in which partially degraded glycosaminoglycans accumulate due to β-glucuronidase deficiency was described originally as the Adipose Storage Deficiency (ASD) mouse.

Beyond degradative and energy recycling, lysosomes have been shown more recently to participate in non-degradative homeostatic processes such as plasma membrane repair or exosome secretion [7]. This was revealed by studies on cellular response to plasma membrane injury and subsequent recovery for membrane resealing. The rapid (10–30 s) delivery of intracellular membrane to wound sites, resembling Ca^{2+}-regulated exocytosis was shown to be crucial in this process, and lysosomal protein markers could be identified in membrane patches formed in response to acute membrane injury, indicating active lysosomes contribution in this process [7]. Furthermore, membrane resealing can be inhibited by antibodies against the cytosolic domain of Lamp1, which specifically aggregates lysosomes [7]. Linked to their function in membrane repair, lysosome fusion to the cell membrane can lead to delivery of their hydrolase content within the extracellular space, likely contributing to extracellular matrix remodeling. These unexpected findings led to the emergence of new roles and concepts on lysosomes, making the view on this organelle much more complex than a simple wastebasket.

1.2. Lipid droplets as reservoirs

The management of cell energy is a crucial issue, and intermittent storage represents a fruitful strategy to survive periods of scarcity. In this regard, all eukaryotic cells from yeasts to mammalians can accumulate fat and built up lipid droplets. Those lipid droplets are well organized intracellular organelles filled with neutral lipids, which are the best fitted molecules for energy storage, as totally hydrophobic with high number of carbons to be oxidized for ATP production. The lipid droplet–cytoplasm interface is formed of phospholipids, organized as a phosphatidylcholine-enriched monolayer, acting as a surfactant to prevent spontaneous coalescence. With developing technology for proteome analysis, it is now well established that a large diversity of proteins reside at the lipid droplet surface, either transiently or permanently. Most abundant lipid droplet-associated proteins are the perilipins, sharing a common PAT (Perilipin-ADRP-TIP47) domain [8]. Interestingly, the conserved PAT domain is not required for lipid droplet targeting, but all Perilipin proteins identified so far by sequence homology have been shown to interact with lipid droplets by living cell imaging. Perilipin proteins are generally believed to operate as conditional shells on lipid droplets, with packaging properties that critically regulate neutral lipids hydrolysis by cytoplasmic lipases. In the last years, knowledge on lipid droplets improved dramatically, evolving from a picture of inert lipid tank to dynamic intracellular organelle. Several recent reviews provide extensive updated information on this subject [9–12].

During evolution, the widespread ability to form lipid droplets evolved toward the emergence of a specialized cell type, the adipocyte, whose function is entirely devoted to the management and packaging of lipid stores. A striking feature is the overt development of the adipocyte lipid droplet which becomes the most prominent intracellular organelle, occupying a central position and filling almost the whole cytoplasmic space. Mitochondria are often closely apposed to lipid droplets in fat cells, but no protein complex indicative of specific contact points like those linking ER to mitochondria referred as MAM (*m*itochondria *a*ssociated *m*embrane) has been described so far. Similarly, relationships between lipid droplets and the Endoplasmic Reticulum (ER), from which lipid droplets are thought to emerge (although no direct observation of a nascent lipid droplet has ever been made) still need to be clarified.

The adipocyte lipid droplet is a prototype for the study of lipid storage organelles, now at the center of the stage with the burst of epidemic obesity and related metabolic diseases. Adipocyte lipid droplets are clearly impacted in obesity as their size is dramatically increased, but little is known on how lipid droplet surface proteins adapt as lipid stores enlarge. Enrichment with caveolin-1 onto lipid droplet surface of obese Zucker rat adipocytes was reported [13], together with regulated association of caveolin-1 to lipid droplets during adipocyte differentiation [14]. Conversely, lack of adipocyte caveolin expression induces lipoatrophic growth of adipose tissue in mice models [15], and it has been suggested that caveolin association to lipid droplets might participate in the organization of lipid droplet interface with cytoplasm [16]. How this connects with the filling of the organelle with neutral lipids still remains incompletely understood. Beyond their function in cellular energy homeostasis, lipid droplets are believed to protect against lipotoxicity by recycling and storing excess fatty acids [17]. A recent study also suggested a modulatory role in stress response, by identifying connections between lipid droplet-associated Fsp27/CIDEC protein and adipocyte transcriptional regulation [18].

2. Lipophagy: lipid droplets meet lysosomes

Although direct interaction between lipid droplets and lysosomes has never been reported, recent experiments revealed an unexpected link between these two intracellular organelles related to the mobilization of intracellular lipid stores. Established for long was the key role of cytoplasmic lipases, activated under fasting conditions in the process of lipid droplet fat mobilization, also called lipolysis. Quite extensive knowledge on fat mobilization also highlights the importance of perilipins and that of newly characterized lipases such as the adipose triglyceride lipase (ATGL) and its co-lipase activator CGI-58 [19]. Although the importance of cytoplasmic lipases for lipid droplet degradation is not questionable in some cell types such as adipocytes, in which HSL and ATGL double knock-down abolish more than 90% of lipolytic activity [20], another lipid droplet degradation process has recently been described and referred to as lipophagy [21]. In this process, the autophagic machinery normally used for sequestration within autophagosomes and delivery to lysosomes for catabolism, serves to target lipid droplet organelles, allowing degradation of hydrophobic core by lysosomal lipases. Lipophagy was first discovered in studies investigating the causes of lipid accumulation in mice with liver-specific invalidation of autophagic genes (Atg5, Atg7). It was established as a key regulatory event for lipid metabolism in fasting hepatocytes, which comprise abundant lipid droplets and have low cytoplasmic lipase activities. In a similar approach, adipose-specific invalidation of atg7 gene was shown to compromise white adipocyte differentiation and lead to brown-like fat cells [22–24], suggesting connections between autophagy and adipocyte differentiation rather than lipid mobilization. However, it cannot be excluded that lipophagy might substitute to impaired fat cell lipolysis in unusual adipocyte settings such as caveolin