Biochimica et Biophysica Acta 1791 (2009) 514–518

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Filling up adipocytes with lipids. Lessons from caveolin-1 deficiency

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ARTICLE INFO

Article history:
Received 29 April 2008
Received in revised form 13 October 2008
Accepted 28 October 2008
Available online 7 November 2008

Keyword:
Caveolin
Cholesterol
Fatty Acid
Lipid Droplet
Lipoatrophy

ABSTRACT

Caveolins are primarily known as the main constituents of the protein coat of caveolae invaginations at the plasma membrane. They have also been found at the surface of intracellular lipid droplets but their function in this lipid storage organelle remains poorly understood. This paper reviews recent studies in adipocytes, the specialized cell type for fatty acid storage, which suggest a role for caveolins in the formation, maintenance or mobilization of lipid droplet stores. These new functions emerged from studies of fat cells in which caveolin expression was invalidated, highlighting the metabolic phenotype of caveolin-deficient mice or human patients who develop progressive lipoatrophy.

1. Adipocyte, the specialized cell for lipid storage

Almost every cell type, from bacteria to humans, is able to save up energy, in the form of cytoplasmic glycogen deposits or organized lipid droplet organelles when placed under conditions of nutritional plethora [1]. Intracellular energy stores need to be limited in size, otherwise cell function would be impaired, which means that cellular demands can only be met for limited periods of time. In mammals and birds, integrated management of energy stores at the whole body level has emerged as a specialized function, with the appearance of adipose organs dedicated to the storage of lipids. In this regard, adipose cells present a unique morphology, having a prominent lipid droplet organelle that occupies almost the entire cell volume, therefore pushing other intracellular compartments to the cell periphery. Contrary to adipose cells which can cope and function in a highly enriched lipid environment, ectopic lipid storage in other cell types can be deleterious to a wide range of cellular functions and is referred to as lipotoxicity [2]. This indicates that adipocytes have developed unique lipid handling processes that minimize lipotoxic cell injury. Therefore, detailed studies on the mechanisms of lipid trafficking in or out of adipocyte lipid droplets are of particular interest in the context of metabolic diseases caused by nutrient excess and lipotoxicity, such as in obesity, diabetes and atherosclerosis. A prevalent idea in the research field suggests that as long as nutrient excess can be efficiently sequestered into the adipocyte lipid droplet, hence preventing "lipid overspill" and lipotoxic damages to other tissues, the onset of severe metabolic complications is delayed [2]. To date, little is known on the specificity of lipid trafficking in and out of the adipocyte lipid droplet. In this respect, the present paper will review some interesting new features about specific lipid associated proteins, called caveolins, that might be of potential significance for future research.

2. The conventional view of adipocyte lipid storage

Free fatty acids, either generated by intravascular hydrolysis of triglyceride-rich lipoproteins or synthesized *de novo* from glucose through the lipogenic pathway are the building blocks for triglyceride storage in adipocyte lipid droplets. According to a biochemical pathway primarily elucidated in the liver, fatty acid esterification along sequential reactions requires the activity of acyl transferases located in the endoplasmic reticulum [3]. Thus, in line with this subcellular localization, it is predicted that free fatty acids are first taken up by cytosolic fatty acid binding proteins, activated to acyl-coA derivatives and transported to the endoplasmic reticulum for processing into triglycerides. This "classical" view does not differentiate adipocyte lipid storage from that of liver, except for remarkably high expression of particular enzyme isoforms or adipose-specific proteins involved in the transport/esterification pathway. Several unrelated experimental observations, however, question this paradigm by pointing out original structures or metabolic features related to caveolae abundance that distinguish lipid storage in the adipocyte (Fig. 1).

3. The caveolin connection to lipid droplets

Caveolins define an evolutionary conserved family of small molecular weight proteins that form the protein coat of caveolae invaginations at the plasma membrane [4]. They consist of three

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doi:10.1016/j.bbalip.2008.10.008

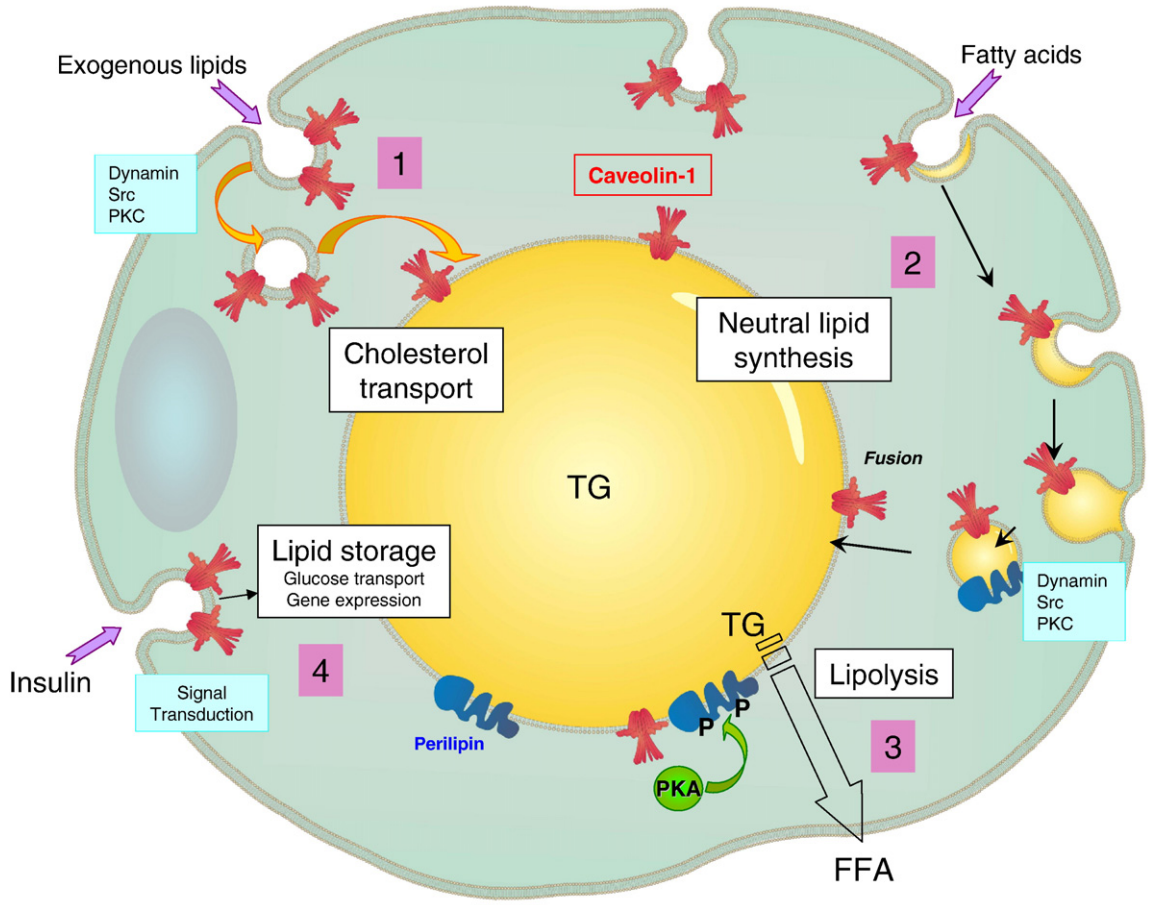

Fig. 1. Schematic representation of the potential roles for caveolin-1 in adipocyte lipid storage. 1: Caveolin-1 (in red) redistributes from plasma membrane caveolae to lipid droplets in a dymanin-, src- and PKC-dependent manner in the presence of exogenous lipids such as cholesterol. This pathway might be involved in the transport of free cholesterol to the lipid droplet surface. 2: The study of human adipocytes has also revealed a subclass of caveolae involved in neutral lipid synthesis, which might contribute to the storage of exogenous fatty acids after fusion of new caveolae-derived lipid droplets with the main lipid storage organelle. 3: Caveolin-1 can also positively regulate fatty acid mobilization from lipid droplets by facilitating cAMP-dependent protein kinase (PKA) phosphorylation of perilipin (in blue), a crucial step in adipocyte lipolysis. 4: Finally, because signalling from the insulin receptor occurs in caveolae, plasma membrane caveolin behaves as a positive regulator of insulin signal transduction in fat cells.

distinct members in mammals (caveolin-1, -2 and -3), which are synthesized from distinct genes that mostly differ in their tissue distribution. As a common feature, they insert in lipid bilayers through a hydrophobic central lipid binding domain and adopt a hairpin conformation with their C- and N-terminal ends facing the cytoplasm. Caveolins preferentially associate with plasma membrane microdomains of specific composition i.e. cholesterol and sphingolipids enriched lipid rafts, a feature they share with Flotillins/Reggie proteins [5].

Besides the vascular endothelium, in which caveolin expression is quantitatively and functionally important [6], adipose tissue is rapidly recognized as the single most abundant source of caveolin [7]. It has been estimated that a third of the adipocyte plasma membrane is covered with caveolae membrane [8]. Caveolin gene expression is also strongly induced during differentiation of 3T3-L1 fibroblasts to adipocytes [7,9] and caveolin protein was shown to be tyrosine phosphorylated in response to insulin [10], a major regulatory hormone controlling the storage of lipids in adipocytes. These pioneering observations suggested a specific role for these proteins in adipose cell function. However, 15 years later, their function still remains poorly understood.

3.1. Regulated caveolin trafficking to lipid droplets in adipocytes

The observation by three different groups that caveolins can be recovered on cytoplasmic lipid droplets was the first link to a potential role of caveolins in the storage of neutral lipids [11,12,13]. The conditions of caveolin association to lipid droplets, first described to occur in cultured cell lines under special circumstances (caveolin overexpression and exogenous fatty acid supply), was rapidly recognized to take place "physiologically" with endogenous caveolins in primary cells (hepatocytes and adipocytes) [14,15] where neutral lipid metabolism is a central function. Moreover, caveolin association to lipid droplets was reported to occur *in vivo*, during liver regeneration following partial hepatectomy [16].

Conditions to the association of caveolins to lipid droplets have been well documented. It was first demonstrated that exogenous lipids (fatty acids or cholesterol) were triggering factors for caveolin association [15,14]. However, because most cell types do not contain visible lipid droplets in the absence of an exogenous lipid supply, it was not clear whether the presence of caveolin was linked to the initial formation of lipid bodies from the endoplasmic reticulum or whether caveolins associated with already formed mature lipid droplets. The study of adipocytes, which contain large persistent lipid droplets, has established that exogenous cholesterol or oleate could acutely stimulate (within minutes) caveolin association to lipid droplets, suggesting the existence of a regulated trafficking pathway to this organelle [15] (Fig. 1). Further studies elucidated the cholesterol-induced trafficking of caveolins to lipid droplets as dynamin- and protein kinase C (PKC)-dependent processes that are modulated by Src tyrosine kinase activation. This indicated that caveolin association to adipocyte lipid droplets shared many common features with the caveolar endocytic pathway [15]. In agreement with

this, it was shown that cholesterol addition was able to stimulate caveolae budding from the adipocyte cell surface [15]. However, the nature of the cargo transported by this novel caveolar endocytic pathway from the cell surface to the lipid droplet is not completely elucidated. Given that caveolins are *bona fide* cholesterol binding proteins [17] and that adipocyte lipid droplets contain significant amounts of free cholesterol, that can be stained by filipin, a cholesterol binding drug [18], it is possible that caveolin trafficking between the cell surface caveolae and the adipocyte lipid droplet might serve as cholesterol transport. Consistent with this, we observed that lipid droplets isolated from adipocytes of mice that do not express caveolins have a drastically reduced free cholesterol content compared to lipid droplets from fat cells of control mice [15]. The reason why free cholesterol accumulates in a caveolin-dependent manner at the lipid droplet surface is still not well understood. Interestingly, once transported to this site, cholesterol trafficking out of the lipid droplet appears to be independent of that of fatty acids, as no change in cholesterol efflux can be seen during lipolytic mobilization of fatty acids in the adipocyte [19]. Whether solely intracellular distribution of cholesterol is altered by caveolin association to lipid droplets or by a larger panel of lipid species remains to be investigated. In addition, how cholesterol intracellular balance and neutral lipid storage are intertwined is still unclear.

4. Adipocyte caveolae as a potential site for neutral lipid synthesis

Several studies pointed out a link between fatty acid uptake and caveolae. Firstly, caveolar membrane consists of detergent resistant domains with the membrane solubilizing properties of free fatty acids. Secondly, in addition to caveolins, there are numerous other fatty acid binding proteins located in caveolae, such as FAT/CD36 also called fatty acid translocase [20,21] as well as several members of the fatty acid transport protein (FATP) family [22]. Thirdly, free fatty acid uptake is decreased in mouse fibroblasts from caveolin-1 null mice, in line with the decreased presence of CD36 at the cell surface [23].

Recently, the possibility that adipocyte cell surface caveolae might not only be portals for fatty acid entry but also sites for triglyceride synthesis, was proposed by Stralfors et al. [24]. They observed a *de novo* triglyceride synthesis in purified caveolae-enriched membrane fractions of human adipocytes and suggested that a subclass of caveolae might contain the required enzymes for the conversion of fatty acids to neutral lipids [25] (Fig. 1). Such propositions for neutral lipid synthesis at the plasma membrane differ strikingly from the classical view of fatty acid esterification in the endoplasmic reticulum and are reminiscent of neutral lipid formation in bacteria, in which no intracellular compartment exists [26]. In the context of adipocytes, one has to keep in mind the extreme proximity of the plasma membrane with cytoplasmic organelles, as a result of the central position of the prominent lipid droplet. No information is yet available on the relative contributions of the caveolae-associated and the classical endoplasmic reticulum pathways in total lipid synthesis. Although adipocytes from rodents used in most studies, may not be the best models to use since they synthesize neutral lipids using fatty acids from *de novo* lipogenesis generated in the cytoplasm. Instead, human fat cells that preferentially use exogenous fatty acids may be more appropriate. Based on this species-specific difference, it is possible that two distinct pathways for triglyceride synthesis exist in fat cells, one for exogenous fatty acids converted at the plasma membrane, the other taking place in the endoplasmic reticulum for esterification of endogenous fatty acids produced in the cytoplasm from *de novo* lipogenesis or from lipolysis of stored triglycerides.

The existence of a potential additional caveolar-associated site for neutral lipid synthesis, besides the classical endoplasmic reticulum localization sheds a new light on the previously discussed association of caveolins to lipid droplets. Indeed, if neutral lipids can be synthesized within cell surface caveolae, then those lipid-rich caveolae could easily generate new lipid droplets upon budding from the plasma membrane. In this scheme, regulated endocytosis of caveolin to lipid droplets would in fact result from the pinching off of nascent lipid droplets directly from triglyceride-rich caveolae. Some support for this model arose from the finding that a small proportion of perilipin, the adipocyte-specific protein covering lipid droplets, could be detected in the detergent insoluble fractions of adipocyte lysates, suggesting an association of perilipin with caveolae at the plasma membrane [27]. By applying the high resolution technique of freeze-fracture electron microscopy combined with immunogold labeling, it was demonstrated that lipid droplets were closely apposed to the plasma membrane, and that lipid droplets might gain perilipin by interaction with specialized plasma membrane domains [28]. Obviously, more investigation is needed to document this caveolar-based model for lipid droplet formation in adipocytes. In particular lipidomic analysis of primary adipocyte lipid droplets could be of invaluable asset in this respect. Indeed such a model could predict that the phospholipid monolayer covering such caveolae-derived lipid droplets would be enriched in the sphingolipid species found in caveolae, whereas that of the endoplasmic reticulum origin would be enriched with glycerophospholipids.

5. The lipoatrophic phenotype of caveolin-1 null mice

Caveolin-1, caveolin-2 and caveolin-3 null mice strains have been generated and have revealed interesting phenotypes (reviewed in [29]) related to the tissue-specific expression of each caveolin isoform. For example, caveolin-3 null mice suffer from muscle degeneration resembling Limb-Girgle muscular dystrophy type 1C caused by mutations in the human caveolin-3 gene, whereas caveolin-2 null mice display severe pulmonary dysfunction with alveolar septal thickening and endothelial hyperproliferation. These mice strains constitute interesting models for human diseases, but the pathogenic role of the lack of caveolin is still unresolved at the molecular level. In agreement with the broad expression of caveolin-1 in many cell types, a variety of defects ranging from vascular dysfunctions to cardiac hypertrophy and disorders of lipid metabolism have been reported in caveolin-1 null mice [29]. It has been recently established that re-expression of caveolin-1 specifically in endothelial cells was able to rescue the vascular contractile tone and cardiac phenotypes, underlining major functions for caveolin-1 in the physiology of endothelial cells [30].

A specific metabolic profile has been described in caveolin-1 null mice, likely the result of the normally high expression of caveolins in adipocytes. It consists mainly of a lipoatrophic phenotype accompanied by hyperlipidemia, with mice resisting development of obesity when fed a high fat diet [31]. It is noteworthy that a recent report of a patient with Berardinelli Seip Congenital Lipodistrophy bearing a homozygous nonsense mutation in the caveolin-1 gene [32], followed by a paper describing heterozygous frameshift mutations in patients with partial lipodystrophy [33], indicates that caveolin-1 is a new locus for human lipodystrophy, and are in favour of a major role of caveolin-1 in the adipose tissue lipid storage in humans as well as in mice.

The reason why caveolin-1 null mice develop progressive lipoatrophy and do not expand their adipose tissue when challenged by a high fat diet is still not completely understood. Caveolin-1 is not required for the formation of new adipocytes and mouse embryonic fibroblasts from caveolin-1 null mice can differentiate into adipocytes in culture [15,34], although with slightly lower lipid deposition. No major abnormalities in energy balance that could explain the lean phenotype of these mice were reported. Caveolin-1 null mice do not eat less than their wild type counterparts and they can absorb nutrients normally [31]. Energy expenditure assessed in metabolic chambers did not revealed significant changes and brown adipose tissue, a major component for energy dissipation as heat, was even less active in mutant mice [35]. Thus, the reduction of adipose tissue in the caveolin-1 null mice must result from altered lipid deposition and improper storage of lipids outside of the adipose tissue. In line with

this, increased lipid levels were found in the serum of caveolin-1 null mice, with massive elevation of free fatty acid and hypertriglyceride [31]. Thus it appears that the lean phenotype of caveolin-1 null mice is primarily related to the inability of the adipose tissue to store lipids, which consequently remain in the circulation.

6. Caveolins and lipolysis

Lipoatrophy and defective lipid accretion in adipose tissue of caveolin-1 null mice might result from exacerbation of lipolysis, a possibility reinforced by the demonstration of the presence of caveolin at the site of lipolysis, i.e. the lipid droplet surface. However, the study of the lipolytic response of isolated adipocytes to beta-3 adrenergic agonists has revealed blunted rather than exacerbated lipolysis in caveolin-1 null mice [34], indicating that lipoatrophy and age-related loss of adipose tissue in caveolin-1 null mice cannot be accounted for by exaggerated breakdown of adipose tissue stored lipids. Even if hyperactive lipolysis can be ruled out as a causative defect of caveolin-1 induced lipoatrophy, the latter study pointed out previously unrecognized links between caveolin-1 and the lipolytic machinery on the lipid droplet surface. It was observed that caveolin-1 may facilitate the protein kinase A (PKA)-mediated phosphorylation of perilipin, a key step in the lipolytic cascade (Fig. 1). Indeed changes in the conformation of the lipid droplet-coating the protein perilipin, through phosphorylation are necessary to permit access of lipases to their triacylglycerol substrates [36]. Caveolin-1, by directly interacting with the catalytic subunit of PKA and perilipin, was shown to favour perilipin phosphorylation. This is the first description of a role for caveolin at the lipid droplet surface that can potentially explain why stimulated lipolysis is blunted in caveolin-1 null mice.

7. Concluding remarks

The study of adipocytes might include an additional scheme to the picture of multiple functions of caveolins by highlighting a new role for lipid droplet biology and neutral lipid storage. It has to be kept in mind, however, that multiple facets of caveolins might be driven by their molecular scaffolding properties and their abilities to promote physical interactions with a large variety of signalling protein partners (review in [37]). Regarding adipose tissue, caveolins operate as positive regulators of insulin signal transduction [38], a key event for orchestration of fat storage (Fig. 1). However, the metabolic phenotype of caveolin-1 null mice is not equivalent to that of the FIRKO mice with *f*at-specific *i*nsulin *r*eceptor *k*nock-*o*ut [39]. These mice exhibit a polarization of white adipose tissue into two populations of small or large size cells which differs from progressive lipoatrophy observed in the absence of caveolin. Although probable differences in the genetic background might obviously confound comparison of phenotypes of caveolin-1 null and FIRKO mice strains, this is in still agreement with the view that caveolin-1 function in the adipocyte might extend beyond the insulin signalling pathway.

Acknowledgements

We would like to thank F. Darakhshan for critical reading. CMB is supported by the French ministry for research. Work in our laboratory is supported by INSERM and from the European Community's Seventh Framework Programme FP7/2007–2013 under Grant Agreement No. 202272.

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