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A new look at adipocyte lipid droplets: towards a role in the sensing of triacylglycerol stores?

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Abstract. Lipid droplets have been considered for a long time as inert intracytoplasmic deposits formed within cells under various conditions. Recently, new tools and new approaches have been used to visualize and study these intracellular structures. This revealed new aspects of lipid droplets biology and pointed out their organized structure and dynamic composition. In adipocytes, the specialized cell type for the storage of energy as fat, lipid droplets are particularly well-developed organelles and exhibit unique properties. Also discussed in this paper is the view that lipid droplets, through specific candidate constituents, can play a role in sensing the level of their lipid stores by adipocytes.

Keywords. Adipocyte, fatty acid storage, cholesterol, perilipin, caveolin.

Introduction

Intracellular lipid droplets can be formed in virtually any cell from bacteria to mammals, and constitute an intracellular reservoir of lipids. They can accumulate many different lipid species in relation to the various cell functions that might require temporary storage of lipids. For example, the storage of esterified cholesterol plays an important role in steroidogenesis by providing cholesterol precursors for steroid hormone synthesis [1]. Retinol esters can also be stored as a source of pigment for retinal cells [2]. Besides specialized roles for specific lipid molecules, a wide spread function for lipid bodies concerns the storage of energy. Because fatty acids, provide a large amount of energy when oxidized compared to glucose, and because their storage does not require associated water molecules, triacylglycerols can be used for the intracellular storage of large amounts of energy. In this paper, we will concentrate on triacyglycerol-rich lipid droplets and their role in energy homeostasis. In this regard, particular attention will be given to adipose cells that contain well-developed lipid droplets and represent the specialized tissue devoted to the storage energy at the whole-body level. We will examine recent developments in the literature that suggest that in addition to their role in the storage of fat, these structures might play an active role in sensing whole-body lipid stores in fat cells. This new emerging function might be particularly important in the context of obesity, an epidemic that has developed from the changing of nutritional habits in industrialized countries.

From inert intracellular lipid loads to structured organelles

The vision of lipid droplets has evolved considerably during the last few years because newly available tools have been applied for their analysis or visualization.

The perilipin coat of lipid droplets

In the early 1990 s, the first protein specifically associated with the fat cake in rodent adipocyte lysates was discovered by Londos and colleagues [3], and called perilipin. Perilipin is an abundant protein found mainly in adipocytes and to a lesser extent in steroidogenic tissues. Upon cloning of its complemen-

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tary DNA (cDNA), it became evident that closely related sequences sharing significant homology were present in databases, defining a new protein family called PAT (Perilipin, ADRP, TIP47) [4], in which is found the ubiquitously expressed ADRP (Adipose Differentiation Related Protein) and TIP47 (Tail Interacting Protein 47). All these proteins were subsequently shown to interact with the lipid droplet surface by immunofluorescence. However, the conserved PAT domain is not sufficient for addressing proteins to lipid droplets, and its function still remains unclear. In adipocytes, perilipin plays a key functional role by protecting the lipid droplet from degradation by intracytoplasmic lipases [5]. Such a protective role is emphasized by the phenotype of perilipin null mice, which are lean and have reduced fat stores due to exaggerated basal lipolysis [6]. Perilipin also plays a role in the activation of lipolysis that characterizes the fasting state. In this physiological situation, adipose tissue lipolysis can provide fatty acids to serve as an energy source for other tissues. The protective role of perilipin is then abolished through phosphorylation, leading to conformational change [5]. Indeed, perilipin is a major substrate for Protein Kinase A, which is activated by rising cAMP upon fasting. Interestingly, the phosphorylation of perilipin appears to act as a switch for the conversion of perilipin from a protective antilipolytic shield to a lipase anchoring factor.

The lipid droplet surface is covered with a phospholipid monolayer

In 2002, the use of cryoelectromicroscopy revealed the structural organisation of the lipid droplet surface, which could not be approached by conventional electron microscopy of resin-embedded sections. Using hepG2 cells, it was shown for the first time that a single electron dense line of about 2.5 nm in width, likely a phospholipid monolayer, was present at the rim of lipid droplets [7]. Subsequent lipid fractionation and analyses indicated that lipid droplets contained significant amounts of phosphatidylcholine, in addition to abundant neutral lipids. Fatty acid composition of lipid droplet phospholipids indicated an original composition, distinct from that of endoplasmic reticulum and plasma membranes [7].

The lipid droplet surface is a hemi-membrane containing free cholesterol

Among phospholipids associated with the lipid droplet surface in HepG2 cells, free cholesterol is also present [7], at a lower molar ratio than that found in the plasma membrane. In adipocytes, however, high levels of free cholesterol are found (approximately at a ratio of 1/1000 in weight relative to triacylglycerols). Such abundance can explain why filipin, a free cholesterol binding fluorescent drug, can label the lipid droplet surface of adipocytes [8] but not other cell types.

Association with a large variety of proteins revealed by proteomics of lipid droplets

The recent progress in proteomics applied to purified lipid droplets has led to several reports on the protein composition of lipid bodies [9–12], one of them conducted in 3T3-L1 adipocytes. These studies identified a large variety of lipid droplet-associated proteins ranging from proteins with unknown functions to enzymes involved in lipid synthesis. Surprisingly, some proteins that function in vesicular traffic, such as several Rab GTPases, were also identified, suggesting that lipid droplets might actively communicate with other intracellular compartments [13]. The protein diversity at the lipid droplet surface was also illustrated by reports from different groups around the world that identified caveolins, the protein structural components of caveolae on lipid bodies [14–16]. Caveolae are small flask-shaped invaginations of the plasma membrane, coated with caveolin oligomers that are abundantly found in endothelial cells, pneumocytes and adipocytes. They appear to play a role in multiple cell functions, from endocytosis of exogenous molecules to lipid traffic and signalling by hormonal signals [17].

The sensing of lipid stores by adipocytes

The pivotal role of adipose tissue in the storage of energy had been recognized for a long time, but a new role for this tissue has emerged since the discovery of leptin, which pointed out its ability to secrete hormonal factors and to communicate with other tissues. Remarkably, the main function of leptin is to provide information regarding the levels of fat stores, so that leptin production by adipocytes is linearly correlated to fat cell size and lipid loads [18]. The tight control on leptin secretion by fat cells indicates that some mechanisms might exist by which adipocytes can be informed of their intracellular lipid contents. In addition to leptin, fat cells can produce a large variety of secretory products, such as cytokines [19], adiponectin [20], and resistin [21]. Disregulated production of all these factors is a constant feature of excessive lipid accumulation and obesity, suggesting that the process of fat store sensing is a key event in the control of adipocyte-derived secretion. The molecular mechanisms involved in this process still remain unknown. Some recent data from the literature indicate that lipid droplets, the specialized organelles for fat storage, might play a role in this process (Fig. 1).

Table 1. Compilation of published studies using proteomic analysis of lipid droplets in mammalian cells. Four independent publications reported on the analysis of lipid droplets by proteomics [9–12]. The proteins identified are indicated by their accession number in the column corresponding to the study. Note that nearly 100 proteins were identified in addition to classical proteins of the PAT family, some of them being found in three out of four independent studies.

Group	Name	Human hepatocyte cell line HuH7	CHO K2	Human A431 carcinoma	Murine 3T3-L1
PAT family					
	Perilipin				28316726
	ADRP	Q99541	26347669	Q99541	1168362
	TIP47	O60664		O60664	12849312
	S2–12		10181204		10181204
Lipid metabolism					
	Acetyl-coenzyme A carboxylase alpha		28510783	NP_000655	
	CGI-58 protein			NP_057090	13385690
	Lanosterol synthase	P48449	26346907	P48449	22122469
	Long-chain acyl-CoA synthetase 3	O95573	28479913	O95573	20455039
	Acyl-CoA synthetase long-chain family member 1				31560705
	Acyl-CoA synthetase long-chain family member 4	O60488	617241		617241
	Squalene epoxidase		6678127	AAD10823	
	Sterol-4-alpha-carboxylate 3-dehydrogenase, decarboxylating	Q15738		Q15738	
	NADH-cytochrome b5 reductase	P00387	19745150	P00387	19745150
	(17-beta-HSD 7)		20385196	P56937	20385196
	Dehydrogenase/reductase (SDR family) member 8		16716597	NP_057329	18043266
	Dehydrogenase/reductase (SDR family) member 1		31980844		
	Homo sapiens retinal short-chain dehydrogenase/reductase retSDR2	AF126780			
	Lipoprotein lipase				367406
	Palmitoyl-protein thioesterase 1		6679451		
	Hormone-sensitive lipase				1706847
	Transport-secretion protein 2.1 (TTS-2.1)			CAC01131	
Chaperones					
	GRP94			P14625	
	Heat shock 70 kDa protein 8 isoform 1			NP_006588	31981690
	Heat shock protein HSP 90-alpha			P07900	
	Heat shock protein HSP 90-beta			P08238	
	78 kDa glucose-regulated protein precursor (GRP 78) BiP		2506545	P11021	121570
	60-kDa heat shock protein,			P10809	
	prolyl 4-hydroxylase, beta subunit		12838858	NP_000909	
	Calnexin				3123183
	dnaK-type molecular chaperone hsc73				2119718
Traffic					
	Ras-related protein Rab-7		6679599	P51149	6679599
	Ras-related protein Rab-10		7710086	O88386	
	RAB18, member RAS oncogene family	6755258		NP_067075	6755258
	RAB14, member RAS oncogene family		18390323		18390323
	Rab5c protein	P51148	18606182		20072723
	Rab2		10946940		
	Rab 11a		8394127		
	Rab 11b		6679583		

Table 1 *(Continued)*

Group	Name	Human hepatocyte cell line HuH7	CHO K2	Human A431 carcinoma	Murine 3T3-L1
	Ras-related protein Rab-6A (Rab-6)			P20340	
	Ras-related protein Rap-1b	P09526	27692431		
	SEC22 vesicle trafficking protein-like 1		6755448		
	N-Ethylmaleimide-sensitive fusion protein attachment protein alpha		13385392		
	Ral-A protein; RAS-like, family 1		9507025		
	Rho GTPase activating protein 1		22122649		
	Vesicle amine transport protein 1 homolog		23623337		
Structure					
	(Cytokeratin 8)			P05787	
	(Cytokeratin 18)			P05783	
	Actin, beta			AAH08633	
	Collagen, TypeIV, alpha3				4104232
	Collagen, TypeVI, alpha2				420193
	Collagen, TypeVI, alpha3				31791061
	Tubulin, beta 5				7106439
	Villin 2			AAH13903	
	Stomatin			P27105	
	Vimentin				31982755
	Prohibitin				6679299
Signalling					
	EH-domain containing 2				23346469
	B-cell receptor-associated protein 37		6671622		28526501
	B-cell receptor-associated protein 31	P51572			
	Caveolin 1				6705981
	Voltage-dependent anion-selective channel protein 1		10720404		
	Protein kinase D2			NP_057541	
	Calcium-binding protein p22			Q99653	
Miscellaneous					
	Ancient ubiquitous protein isoform a				6671604
	Cell death-inducing DFFA-like effector c				30410022
	Apoptosis-inducing factor (AIF)-like mitochondrion-associated inducer of death			NP_116186	
	Ribophorin I				31543605
	ATP synthase beta-subunit				2623222
	Polymerase I and transcript release factor				6679567
	Pyruvate carboxylase				6679237
	Expressed sequence AI462440				23600211
	P63	S33377			
	Homo sapiens expressed in T-cells and eosinophils in atopic dermatitis	BC006145			
	GAPDH	P04406			
	Annexin II	P07355			
	Unknown protein		28436938		
	Unknown protein		282204956		
	Unnamed protein product		26325938		
	Unnamed protein product		26351449		

Table 1 *(Continued)*

Group	Name	Human hepatocyte cell line HuH7	CHO K2	Human A431 carcinoma	Murine 3T3-L1
	Unnamed protein product		26344914		12850393

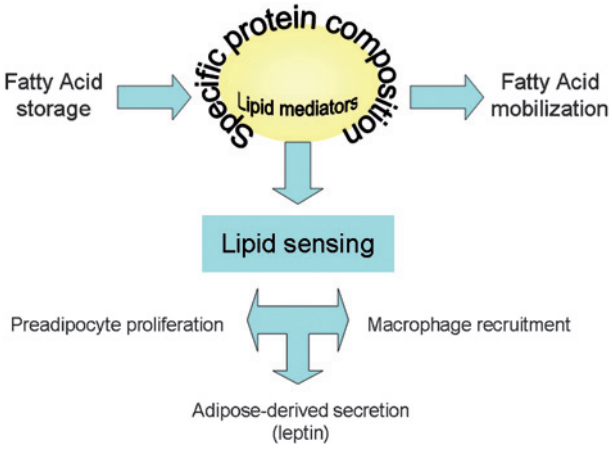

Figure 1. Schematic representation of the role of lipid droplets in the sensing of their triglyceride stores by adipocytes. The triglyceride content of the adipocyte lipid droplet is regulated by the balance between fatty acid storage and mobilization. Changes in fat storage might be sensed through specific changes in the protein composition of lipid droplets or through the production of lipid mediators. In turn, these modifications could regulate the production of adipocyte-derived secreted products such as leptin, together with the recruitment of macrophage or new preadipocytes in adipose tissue.

Lipid droplet constituents as candidates for a role in lipid sensing

Perilipin is required for accurate lipid sensing in adipocytes

The invalidation of the perilipin gene in mice [6] has produced lean animals with exacerbated basal lipolysis. However, an unexpected phenotypic trait in these mice was their abnormal leptin production. Indeed, leptin levels in perilipin null mice are much higher than expected given their low adiposity [6]. This was the first experimental indication that changes in lipid droplet composition compromised the sensing of their lipid stores by adipocytes and induce inadequate leptin production by fat cells. In line with this observation, a relative deficit in perilipin was reported in adipocytes from obese rodents or humans [22], a situation in which the production of adipose-derived factors is severely impaired. These observations suggest that a link between perilipin concentration on the lipid droplet surface and regulation of the production of adipose-derived hormones by fat cells.

The potential role of lipid droplet caveolin

Another lipid droplet protein component that might play a role in the sensing of their lipid stores by adipocytes is caveolin. Although the function of caveolin is mainly related to the plasma membrane through its role on caveolae formation, the finding that caveolin can localize on lipid droplets under some circumstances [14–16] has raised the question of the consequences, if any, of its presence on lipid droplets. The unexpected localization of caveolin on lipid droplets was first interpreted as a mistargeting event of the protein en route to the plasma membrane, due to overexpression [23]. However, it has subsequently been demonstrated that endogenous caveolin could be targeted to the lipid droplet in the presence of exogenous fatty acids [24], thus linking caveolin association to lipid droplets and the storage of lipids. Accordingly, caveolin-1 null mice, when exposed to high fat diets, are unable to cope with lipid overload by increasing their adipose stores, remain lean, and resist obesity [25]. The functional consequences of the presence of caveolin on lipid droplets remain elusive. Some data indicate a facilitating role in lipolysis [26] or in lipid droplet mobility [24], but the reason caveolin null mice exhibit defective fatty acid storage is still unclear. By analogy with its role at the level of the plasma membrane, and given its well-known properties as a scaffold for protein-protein interactions [27], it can be postulated that lipid droplet caveolin might participate in sensing of lipid stores by initiating a signalling network. Noteworthy is the observation by [26] that the architecture of the lipid droplet cortex of adipocytes from caveolin 1 null mice lacks the electron-dense surrounding material that is present in wild-type controls. In this regard, it will be important to identify protein partners for caveolin at the surface of lipid droplets, and to examine whether caveolin concentration is regulated in physiological situations where lipid storage varies.

Lipid mediators linked to fatty acid storage

A simple mechanism for lipid droplets to signal the levels of their stores would be to produce lipid mediators. Accordingly, the presence of several enzymes involved in lipid synthesis in purified lipid droplets fractions was recently reported [11]. How-

ever, the literature provides no evidence of any regulation of these enzymes that would suggest controlled production of these mediators.

Some experimental evidence exists for other mechanisms involving lipid mediators. In this regard, cholesterol might be a potential candidate, since a close link exists between the storage of triaclyglycerols and the intracellular distribution of cholesterol. Indeed, in fat cells [28] a new steady state in intracellular cholesterol distribution is reached during the process of lipid loading, cholesterol being redistributed at the lipid droplet surface at the expense of plasma membranes [8, 29]. The route followed by cholesterol during this process is not known, but it is possible that the lipid droplet surface might act as a sink for free cholesterol. Such a trapping role for free cholesterol might be linked to the presence of caveolin, a cholesterol binding protein [30] on the surface of adipocyte lipid droplets. Whatever the mechanism involved, it has been observed that cholesterol redistribution in lipid-loaded cells could be sensed by cholesterol sensors in the ER, leading to the activation of the SREBP (Sterol-Responsive Element Binding Protein) system [31]. Thus it appears from these data that the packaging of fatty acids into lipid droplets can profoundly alter the trafficking and distribution of other lipid species, for example cholesterol, that behave thereafter as second messengers for intracellular regulation of cell metabolism.

Concluding remarks

The structural complexity that has been revealed by recent studies of lipid droplets is no longer compatible with the view of inert intracellular deposits. Rather, it suggests dynamic structures that possibly are able to communicate with many other intracellular compartments. The physiological relevance of this complex organisation is far from being understood, especially in tissues that have developed particular abilities for lipid storage, such as adipose tissue. Such a complex organisation can appear surprising with regard to lipid droplets as simple reservoirs for fat, but not considering that lipid droplets might participate in the sensing of the intracellular energy stores by cells. This possibility raises new, interesting perspectives for the future management of exaggerated lipid storage, a common trait in our societies of abundant food supply and nutritional imbalance.

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