Adipogenesis at a glance

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Journal of Cell Science 124, 2681-2686
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doi:10.1242/jcs.079699

The formation of adipocytes from precursor stem cells involves a complex and highly orchestrated programme of gene expression. Our understanding of the basic network of transcription factors that regulates adipogenesis has remained remarkably unchanged in recent years. However, this continues to be refined with new factors and cofactors becoming superimposed onto the network (White and Stephens, 2010). At the same time attention has also shifted to many other aspects of adipocyte development, including efforts to identify, isolate and manipulate relevant precursor stem cells. Recent studies have revealed new intracellular pathways, processes and secreted factors that can influence the decision of these cells to become adipocytes.

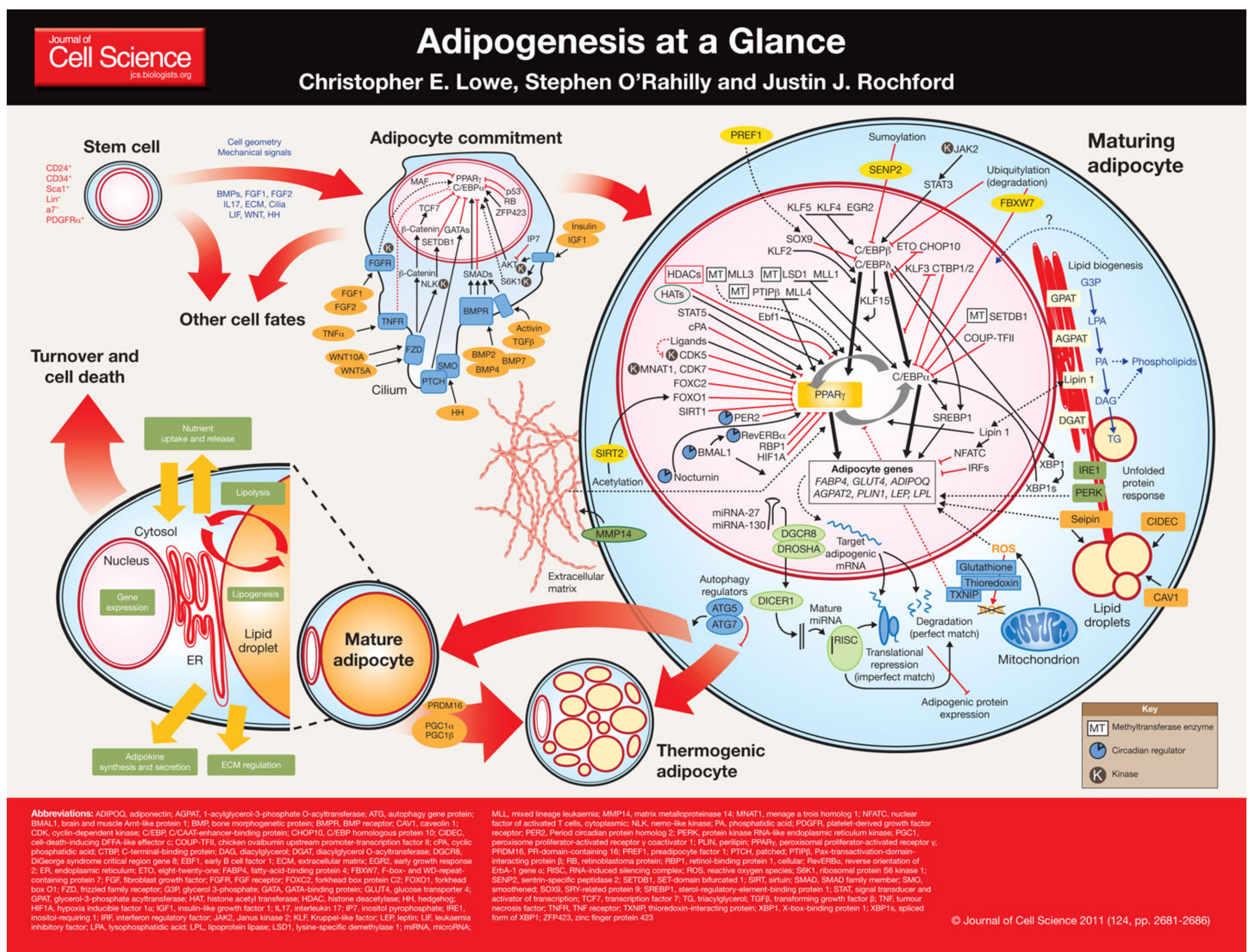
Understanding the intricacies of adipogenesis is of major relevance to human disease, as adipocyte dysfunction makes an important contribution to metabolic disease in obesity (Unger et al., 2010). Thus, improving adipocyte function and the complementation or replacement of poorly functioning adipocytes could be beneficial in common metabolic disease. Approximately 10% of adipocytes turn over in human adipose tissue each year, which indicates that ensuring the newly forming adipocytes are appropriately metabolically flexible could substantially improve metabolic diseases (Spalding et al., 2008).

This Cell Science at a Glance article reviews the transition of precursor stem cells into mature lipid-laden adipocytes, and the numerous molecules, pathways and signals required to accomplish this.

Adipocyte stem cells

Pluripotent mesenchymal stem cells (MSCs) can be isolated from several tissues, including adipose tissue. Adipose-derived MSCs have the capacity to differentiate into a variety of cell types, including adipocytes, osteoblasts, chondrocytes and myocytes. Until recently, stem cells in the adipose tissue stromal vascular fraction (SVF) have been typically isolated in pools that contain a mixture of cell types, and the ability of these SVF pools to develop into mature adipose depots in vitro or in vivo has been variable (Rodeheffer et al., 2008).

More recently, cell surface markers have been identified that define a subpopulation of stromal cells that differentiates into adipocytes and



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Journal of Cell Science

forms functional adipose depots in vivo much more efficiently (Lin$^-$, Sca1$^+$, CD34$^+$, CD24$^+$, a7$^-$, PDGFRα$^+$) (Joe et al., 2010; Rodeheffer et al., 2008; Tang et al., 2008). However, these cells show limited adipogenic capacity in vivo unless host animals are in states conducive to adipose tissue expansion, as occurs during high-fat feeding or in lipodystrophy, which demonstrates the importance of the cellular microenvironment. In addition, differences exist between adipocyte precursors from different fat depots, and this might underlie some of the differences in the expansion of these depots in response to nutrient excess (Joe et al., 2009).

Another key advance in this area has been the demonstration that brown and white adipocytes do not develop from common precursors, as previously thought. Rather, the development of thermogenic brown adipocytes is driven by the transcription factor PR-domain-containing 16 (PRDM16) from precursors that can also form myocytes (Kajimura et al., 2009; Seale et al., 2008).

Signals to differentiate

Multiple signals can influence whether stem cells form adipocytes, including extracellular factors such as the bone morphogenetic proteins (BMPs) (Huang et al., 2009), transforming growth factor β (TGFβ) (Zamani and Brown, 2010), insulin-like growth factor 1 (IGF1) (Kawai and Rosen, 2010a), interleukin 17 (IL17) (Zúñiga et al., 2010), fibroblast growth factor 1 (FGF1) (Widberg et al., 2009), FGF2 (Xiao et al., 2010) and activin (Zaragosi et al., 2010).

Extensive literature demonstrates the importance of WNT signalling in adipocyte development, both in vitro and in vivo, and that suppression of this pathway is essential for adipogenesis to proceed (Christodoulides et al., 2009; Prestwich and MacDougald, 2007). Similarly, the hedgehog (HH) signalling pathway inhibits adipogenesis, although the mechanisms involved are less clear (Cousin et al., 2007; Pospisilik et al., 2010). One study suggests that the receptors that initiate the WNT and HH signalling cascades reside on primary cilia transiently present on differentiating adipocytes (Marion et al., 2009). Impaired cilia formation during adipogenesis results in increased expression of the transcription factor peroxisomal proliferator-activated receptor γ (PPARγ), which suggests that increased adipogenesis might contribute to the obese phenotype of individuals with the inherited ciliopathy Bardet–Biedl syndrome (Marion et al., 2009).

Additional intracellular signalling pathways continue to be implicated in adipogenesis and the involvement of known regulators is constantly refined. These pathways and regulators include glutathione (Vigilanza et al., 2010), the Janus kinase-signal transducer and activator of transcription 3 (JAK-STAT3) pathway (Zhang et al., 2011), SMAD signalling (Marchildon et al., 2010; Tan et al., 2011), ribosomal protein S6 kinase 1 (S6K1) (Carnevalli et al., 2010) and components of the insulin signalling cascade, such as AKT (Zhang, H. H. et al., 2009) and a newly discovered regulator of this pathway, inositol pyrophosphate (Chakraborty et al., 2010). New transcriptional regulators of stem cell fate that are controlled by these pathways also continue to be identified. These include retinoblastoma protein (RB) (Calo et al., 2010), p53 (Molchadsky et al., 2008), the proto-oncoprotein MAF (Nishikawa et al., 2010), zinc-finger protein 423 (ZFP423) (Gupta et al., 2010) and SOX9 [for SRY (sex-determining region Y)-box 9] (Wang and Sul, 2009).

In addition to external signals, cell shape also influences the process of adipogenesis. Whereas rounded MSCs are more likely to become adipocytes, widely spread cells favour osteogenesis (Feng et al., 2010; Kilian et al., 2010). Related to this, extracellular remodelling has been shown to have important roles in adipocyte and adipose tissue development (Divoux and Clement, 2011; Mariman and Wang, 2010). For example, loss of the membrane-bound matrix metalloproteinase MMP14 impairs adipogenesis in vivo (Chun et al., 2006). Importantly, this defect was only apparent in a three-dimensional, but not a two-dimensional, cell culture system. This highlights the limitations of the two-dimensional cell culture models of adipogenesis, which recapitulate many intracellular signals and transcriptional regulators of adipogenesis but not other aspects of adipocyte development that are important in vivo. Similarly angiogenesis influences adipogenesis and adiposity, but these effects can only be fully appreciated from in vivo studies (Christiaens and Lijnen, 2010).

Regulating gene expression during adipogenesis

The transcriptional cascade regulating the terminal differentiation of adipocytes has been reviewed in detail elsewhere (Farmer, 2006; Rosen and MacDougald, 2006; Tontonoz and Spiegelman, 2008). The following sections will place newly discovered regulators in the context of this established transcriptional cascade and summarize current understanding of the mechanisms through which they are controlled.

Transcription factors that control adipogenesis

Adipogenic induction rapidly induces expression of the CAAT/enhancer-binding proteins (C/EBPs) C/EBPβ and C/EBPδ. These are key early regulators of adipogenesis, and the anti-adipogenic preadipocyte factor 1 (PREF1) has recently been shown to act through SOX9 in the direct regulation of the promoters for the genes encoding C/EBPβ and C/EBPδ (Wang and Sul, 2009). In addition, C/EBPβ appears to be the target of the proadipogenic desumoylating enzyme sentrin-specific peptidase 2 (SENP2) (Chung et al., 2010). SENP2 is required to reduce the levels of C/EBPβ sumoylation, which would otherwise lead to its increased ubiquitylation and degradation of the protein.

Among the targets of C/EBPβ and C/EBPδ are the promoters of the genes encoding the key adipogenic transcription factors C/EBPα and PPARγ and the regulator of lipogenic genes SREBP1 (for sterol-regulatory-element-binding protein 1) (Payne et al., 2010; Rosen and MacDougald, 2006; White and Stephens, 2010). PPARγ activates the promoter of the gene encoding C/EBPα and vice versa, creating a positive-feedback loop. In addition, PPARγ and C/EBPα induce the expression of genes that are involved in insulin sensitivity, lipogenesis and lipolysis, including those encoding glucose transporter GLUT4 (also known as SLC2A4), fatty-acid-binding protein (FABP4, also known as adipocyte protein 2, aP2), lipoprotein lipase (LPL), *sn*-1-acylglycerol-3-phosphate acyl-transferase 2 (AGPAT2), perilipin and the secreted factors adiponectin and leptin. Recent genome-wide binding analyses have revealed that PPARγ and C/EBPα cooperate on multiple binding sites in promoter regions, together regulating a wide range of genes expressed in developing and mature adipocytes (Lefterova et al., 2008; Nielsen et al., 2008). An array of factors regulates this central transcriptional network, such as STAT5, C/EBP homologous protein 10 (CHOP10, also known as DNA-damage-inducible transcript 3, DDIT3) and members of the Krüppel-like factor (KLF) family (Rosen and MacDougald, 2006; White and Stephens, 2010). Positive regulators include early growth response-2 (EGR2, also known as KROX20) (Chen et al., 2005), early B cell factor-1 (EBF1, also known as COE1) (Jimenez et al., 2007), KLF4 (Birsoy et al., 2008) and brain and muscle Arnt-like protein 1 (BMAL1, also known as ARNTL1) (Shimba et al., 2005), whereas inhibitory effects have been described for forkhead box protein C2 (FOXC2) (Davis et al., 2004), eight-twenty-one (ETO, also known as CBFA2T1, MTG8 and ZMYND2) (Rochford et al., 2004), globin transcription factors 2 and 3 (GATA2 and GATA3) (Tong et al., 2005), KLF3 (Sue et al., 2008), C-terminal-binding proteins 1 and 2 (CTBP1 and CTBP2) (Jack and Crossley, 2010; Sue et al., 2008) and the interferon

regulatory factors, IRF3 and IRF4 (Eguchi et al., 2008).

Some factors appear capable of both pro- and anti-adipogenic actions. For example, the orphan nuclear receptor chicken ovalbumin upstream promoter-transcription factor II (COUP-TFII, also known as NR2F2) has been reported to promote preadipocyte lineage commitment by inhibiting Wnt signalling (Li et al., 2009). However, other studies have reported that it can act as an inhibitor of adipogenesis by repressing the expression of C/EBPα and PPARγ (Okamura et al., 2009; Xu et al., 2008). Similarly, the nuclear receptor RevERBα (also known as NR1D1) promotes the early mitotic expansion phase in adipogenesis, but must be degraded by the 26S proteasome to prevent repression of PPARγ expression later in the adipogenic programme (Wang and Lazar, 2008).

PPARγ remains centre stage

Given the key role of PPARγ in adipocyte differentiation, it continues to be widely studied. Many factors influencing adipogenesis ultimately affect the activity of this crucial regulator of adipogenesis. For example, the sirtuin (Sirt) SIRT2, inhibits PPARγ indirectly by reducing the amount of forkhead box O1 (FOXO1) acetylation and phosphorylation. This leads to an increase in the nuclear localization of FOXO1, where it represses the transcription of the gene encoding PPARγ (Jing et al., 2007). Another Sirt, SIRT1 impairs adipogenesis by directly acting as a PPARγ co-repressor (Picard et al., 2004). Other newly discovered inhibitors of PPARγ include the cellular retinol-binding protein RBP1 (Zizola et al., 2010).

Multiple lipid species have been proposed to activate PPARγ by acting as endogenous ligands (Itoh et al., 2008; Tontonoz and Spiegelman, 2008); however, cyclic phosphatidic acid (cPA) has recently emerged as an inhibitory lipid that binds to PPARγ and stabilizes its association with the co-repressor nuclear receptor co-repressor 2 (NCOR2, also known as SMRT) (Tsukahara et al., 2010).

Phosphorylation of PPARγ provides another means of regulation. The kinase submodule of general transcription factor IIH (GTFIIH, also known as TFIIH), which contains both the RING finger protein menage a trois homolog 1 (MNAT1) and cyclin-dependent kinase (CDK) 7, phosphorylates PPARγ at Ser112 (Helenius et al., 2009). This phosphorylation inhibits PPARγ by several mechanisms. These include impaired recruitment of transcriptional coactivators and increased binding to the circadian regulator period homolog 2 (PER2), which inhibits binding of PPARγ to target gene promoters (Grimaldi et al., 2010). Choi et al. recently reported that phosphorylation on Ser273 by CDK5 selectively decreases expression of a subset of PPARγ target genes in adipocytes. Pharmacologically, Ser273 phosphorylation can be inhibited by the compound MRL24 and this appears to be sufficient to confer the insulin-sensitizing effects observed with PPARγ activation by thiazoledinedione drugs. However, Ser273 phosphorylation did not appear to affect the regulation of adipogenesis by PPARγ, demonstrating that the anti-diabetic and pro-adipogenic roles of PPARγ can be independently manipulated pharmacologically (Choi et al., 2010). Overall, the plethora of pathways, metabolites, cofactors and modifications that regulate PPARγ serves to illustrate the complexity of the adipogenic programme of gene transcription.

Additional regulation of gene expression

Alongside the identification of an increasing number of transcription factors controlling adipogenesis, several new mechanisms regulating their function have also been described recently.

Histone modification

It has been known for several years that histone acetyltransferases (HATs) and histone deacetylases (HDACs) influence adipogenic transcription factor activity. Indeed, the selective recruitment of different HATs and HDACs by PPARγ permits this transcription factor to have divergent effects on different promoters (Guan et al., 2005).

More recently, methyltransferases have also been implicated in the regulation of adipogenesis. For example, Pax-transactivation-domain-interacting protein β (PTIPβ, officially known as PAXIP1) regulates the expression of both C/EBPα and PPARγ by controlling recruitment of the histone 3 lysine 4 (H3K4) methyltransferase MLL4, as well as DNA polymerase II, to their promoters (Cho et al., 2009). In addition, the lysine-specific histone demethylase 1A (KDM1A, also known as LSD1) and the H3K9 methyltransferase SET domain, bifurcated 1 (SETDB1) exhibit opposing effects by promoting and inhibiting adipogenesis, respectively (Musri et al., 2010). It has been proposed that SETDB1 maintains the promoter for the gene encoding C/EBPα in a silent state, but that recruitment of LSD1 increases upon differentiation, permitting induction of C/EBPα expression (Musri et al., 2010).

More broadly, the integration of genome-wide analyses of chromatin modification, structure, mRNA expression and transcription factor binding has powerfully illustrated the dynamic remodeling of chromatin and its influence on adipogenic gene expression, both at specific loci and in a more general context (Mikkelsen et al., 2010; Steger et al., 2010).

MicroRNAs

MicroRNAs (miRNAs) provide an additional newly discovered mechanism for controlling adipogenic gene expression. These small noncoding RNAs are processed from longer precursor primary transcripts (pri-miRNA) by the enzymes DGCR8 (DiGeorge syndrome critical region gene 8, also known as PASHA) and DROSHA (also known as ribonuclease 3). The miRNAs associate with the RNA-induced silencing complex (RISC) and direct the degradation of target mRNA sequences or impair their translation. A study of miRNA expression during human MSC differentiation detailed miRNAs induced during adipogenesis (Oskowitz et al., 2008). This study also demonstrated that knockdown of either DICER1 or DROSHA, both enzymes required for functional miRNA generation, inhibits adipogenesis. Several miRNAs were shown to inhibit the expression of leukaemia inhibitory factor (LIF) (Oskowitz et al., 2008), a cytokine associated with maintaining an uncommitted state in stem cells. Hence, the miRNA-mediated reduction on LIF could facilitate adipogenesis. Specific miRNAs, including miR-130, miR-27 (Lin et al., 2009) and miR-378 (Gerin et al., 2010), can regulate the expression of genes controlling adipogenesis and lipogenesis. Furthermore, individual miRNAs can affect multiple targets and several miRNAs can function synergistically (Singh et al., 2008). This provides the potential for miRNAs to regulate multiple targets in a concerted manner to modulate both adipocyte development and function.

Protein modification by ubiquitin

Phosphorylation has been long appreciated as a means to regulate adipogenic transcription factors post-translationally. However, the role of ubiquitin modification has only been appreciated more recently. As with phosphorylation, ubiquitin modification can have multiple effects, depending on the residues targeted and the proteins affected (Cohen and Tcherpakov, 2010). Perhaps the best understood role for ubiquitylation is in targeting proteins for degradation and recycling. This has recently been shown for several adipocyte transcription factors, such as SREBP1c (Sundqvist et al., 2005), peroxisome proliferator-activated receptor γ, coactivator 1α (PGC1α) (Trausch-Azar et al., 2010) and C/EBPα. In the case of C/EBPα, this occurs through the action of the ubiquitin ligase FBXW7 (for F-box- and WD-repeat-domain-containing 7), which targets

C/EBPα for proteasome-mediated degredation (Bengoechea-Alonso and Ericsson, 2010). Expression of FBXW7 is reduced during adipogenesis, allowing its substrates to accumulate and adipogenesis to proceed. It seems probable that future studies will demonstrate a more widespread and complex involvement of ubiquitylation in adipocyte differentiation.

Additional cellular processes influencing adipogenesis

Role of the unfolded protein response

The unfolded protein response (UPR) is activated in response to stress caused by accumulation of unfolded proteins in the endoplasmic reticulum (ER) and has recently been shown to have an important role in adipocyte development.

One arm of the UPR involves the PKR-like ER kinase (PERK), which is activated by the accumulation of unfolded proteins in the ER lumen and triggers signals that slow protein synthesis and increase the expression of chaperone proteins. During differentiation of mouse embryonic fibroblasts and 3T3-L1 cells into adipocytes, PERK deficiency reduces the expression of lipogenic genes and attenuates lipid accumulation (Bobrovnikova-Marjon et al., 2008).

X-box-binding protein 1 (XBP1) is a key component of a second arm of the UPR that involves the mRNA splicing enzyme inositol-requiring 1 (IRE1, also known as ERN1), and XBP1 has recently been identified as a direct target of C/EBPβ during adipogenesis. Upon activation of the UPR, *XBP1* mRNA undergoes unconventional post-transcriptional splicing by IRE1. In turn, the spliced form of XBP1 (XBP1s) then binds and activates the promoter in the gene encoding C/EBPα (Sha et al., 2009). Interestingly, a pathophysiological role for ER stress pathways has previously been demonstrated in adipose and other insulin-sensitive tissues in metabolic disease (Hotamisligil, 2010). Thus, whereas a modest physiological ER stress response is essential for normal adipocyte development and function, hyperactivation might be a detrimental component of chronic metabolic disease.

The influence of oxidative stress

Oxidative stress and the generation of reactive oxygen species (ROS) influences the function of several proteins involved in adipogenesis. ROS can originate from intracellular sources, most notably the mitochondria, or exogenous sources (Gummersbach et al., 2009). Numerous pathways and molecules are regulated by ROS including the hypoxia-inducible factor HIF1, which can inhibit PPARγ (Gummersbach et al., 2009). ROS have been proposed to facilitate the early mitotic clonal expansion phase of adipogenesis in culture (Lee et al., 2009). Moreover, the thioredoxin-interacting protein (TXNIP) has been shown recently to influence adipocyte development in vivo. Loss of TXNIP, which inhibits the antioxidant protein thioredoxin, increases adipogenesis in culture and adiposity in vivo (Chutkow et al., 2010). This leads to improved insulin sensitivity through increased PPARγ expression and activity.

Autophagy and adipogenesis

Increased autophagosome levels in differentiating adipocytes suggested a potential role for autophagy in adipogenesis. Subsequent studies have demonstrated that loss of *Atg5* or *Atg7* in mice, two key autophagy genes, results in impaired white adipose tissue development in vitro and in vivo (Singh et al., 2009; Zhang, Y. et al., 2009). In each case, reduced adipocyte size and decreased lipid storage is accompanied by increased mitochondrial number. *Atg5*- and *Atg7*-knockout mice are euglycaemic and insulin sensitive, with increased fatty-acid β-oxidation. This suggests that depots that normally comprise white adipose tissue have taken on a phenotype that more strongly resembles brown adipose tissue (Singh et al., 2009; Zhang, Y. et al., 2009). These findings are particularly noteworthy given that so-called ‘browning’ of white adipose tissue is an area of intense interest as a possible therapy for obesity and metabolic disease.

Circadian rhythm influences adipogenesis

Several molecules that are involved in the regulation of circadian rhythm have also been shown to influence adipogenesis, including nocturnin (Kawai et al., 2010), PER2 (Grimaldi et al., 2010) and RevERBα, a target of the complex of CLOCK (for circadian locomotor output cycles kaput) and BMAL1 (Wang and Lazar, 2008). Whereas PER2 inhibits PPARγ, the cytoplasmic protein nocturnin facilitates the translocation of PPARγ to the nucleus for ligand activation in response to various stimuli, including a high-fat diet and insulin (Kawai and Rosen, 2010b). These studies suggest that components of this system in adipocytes might contribute to the increase in adiposity and metabolic disease that is linked to disrupted circadian rhythm (Bass and Takahashi, 2010).

Lipid biosynthesis and the developing adipocyte

Lipid storage and subsequent release is a defining feature of adipocytes, and there is tight inter-regulation of adipogenic transcription and lipogenesis in the developing fat cell. This is exemplified by the enzymes glycerol-3-phosphate acyltransferase 3 (GPAT3), AGPAT2 and lipin 1, which have key roles in lipogenesis by catalysing the conversion of glycerol 3-phosphate into lysophosphatidic acid (LPA), LPA into phosphatidic acid (PA), and PA into diacyglycerol (DAG), respectively. These species are key intermediates for both triglyceride (TG) and phospholipid synthesis. However, loss of GPAT3 or AGPAT2 expression also inhibits adipogenic gene expression at an early stage (Gale et al., 2006; Shan et al., 2010). Lipin 1 can also influence adipogenic transcription (Takeuchi and Reue, 2009) and can bind to and activate PPARγ during adipogenesis (Koh et al., 2008). In mature adipocytes lipin 1 also appears to act as a co-repressor of nuclear factor of activated T cells, cytoplasmic (NFATC) facilitating the inhibition of target genes such as PPARγ, TNFα and FABP4 (Kim et al., 2010).

The Berardinelli–Seip congenital lipodystrophy 2 (BSCL2, also known as seipin) protein also links lipid biosynthesis with adipogenesis. Disruption of BSCL2 causes severe generalized lipodystrophy in humans (Capeau et al., 2010; Rochford, 2010). BSCL2 has been implicated in lipid-droplet fusion or biogenesis and has an essential cell-autonomous role in adipogenesis (Payne et al., 2008; Szymanski et al., 2007). However, the precise molecular mechanisms involved in both processes remain unclear.

Disruption of caveolin 1, a caveolar protein with multiple roles in cellular lipid uptake and transport, also causes severe lipodystrophy in humans (Le Lay et al., 2009; Rochford, 2010). However, caveolin-1-null preadipocytes appear to differentiate relatively normally in culture (Le Lay et al., 2009). Moreover, DGAT (Harris et al., 2011) and the droplet protein cell-death-inducing DFFA-like effector c (CIDEC, also known as FSP27) (Keller et al., 2008) provide further examples of proteins that are important for lipid droplet formation but not differentiation in adipocytes. Thus, the processes of lipid synthesis and/or storage and transcriptional regulation during adipogenesis, are linked but not inseparable.

Perspectives

Although the studies reviewed here continue to increase our understanding of adipogenesis, many questions remain. Are different populations of stem cells responsible for adipocyte development at different developmental stages or in disease states? What triggers adipogenesis in vivo during physiological or pathophysiological expansion? As yet, there is little information about what

might control the death or turnover of adipocytes in vivo. Moreover, most studies have broadly classified adipose tissue as subcutaneous or visceral and a more sophisticated understanding of the adipocytes in different depots and their precursors is clearly warranted.

A considerable number of molecules or pathways that have been identified from cellular models of adipogenesis have yet to be validated in vivo or in human cells. The ability of adipose tissue to influence whole-body metabolism makes it attractive for pharmacological therapy. However, selecting and targeting the most appropriate pathways remains challenging. Recent progress suggests that unexpected pathways, molecules and mechanisms controlling the formation of adipocytes have yet to be uncovered.

The authors' work is supported by the UK Medical Research Council [New Investigator Research Grant number GO800203 (to J.J.R.), Program Grant number G09000554 (to S.O'R.)]; the Cambridge National Institutes of Health Research Comprehensive Biomedical Research Centre [grant number CG50826 METABOLISM (C.E.L.); the Medical Research Council Centre for Obesity and Related Medical Diseases [grant number GO600717] and the Wellcome Trust [grant number 078986/Z/06/Z (to S.O'R.)].

Individual poster panels are available as JPEG files at
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