Minireview

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 273, No. 46, Issue of November 13, pp. 30057–30060, 1998

The Role of *C/EBP* Genes in Adipocyte Differentiation*

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One of the central problems facing higher animals is that cells require a continuous source of energy; however, it is impractical for organisms to meet this need by supplying a constant external source of calories. Two specialized tissues, brown and white adipose tissues, have evolved to meet the ongoing requirement for energy. White adipose tissue is able to store excess calories in the form of triacylglycerol. When cells require energy, such as during periods of fasting, these needs are largely met by fatty acids and glycerol formed from lipolysis of stored triacylglycerol. Brown adipose tissues use stored triacylglycerols to maintain body temperature. In particular, these cells convert energy from fatty acid metabolism to heat through the action of uncoupling protein 1 (UCP1),[1] a mitochondrial protein found only in brown adipose tissue. Brown adipocytes contain less triacylglycerol and many more mitochondria than white adipocytes, resulting in their characteristic color. Humans and rats develop brown adipose tissue depots prenatally, and although these depots largely disappear in humans during childhood, some brown adipocytes likely remain interspersed in white adipose tissue throughout adulthood (1).

In view of the prevalence of obesity and obesity-related diseases, such as type II diabetes, it is important to understand how white and brown adipose tissues develop and how the activities of these tissues are regulated. Many factors are important for normal adipocyte development and function. In this minireview, we explore the role of one family of transcription factors, the CCAAT/enhancer-binding proteins (C/EBPs), in inducing preadipocyte differentiation and in modulating gene expression in the fully differentiated adipocyte. Analyses of cultured cell lines, and more recently, genetically altered mice have contributed significantly to our understanding of the way in which adipose-specific gene expression is directed by C/EBPs. These models have also elucidated some of the molecular mechanisms that regulate the expression of the *C/EBP* genes themselves.

Adipocyte Development in Cultured Cells

Preadipocyte Cell Models—A variety of pluripotent and preadipocyte cell lines that have been developed from mouse embryonic tissue are useful for analysis of the adipocyte differentiation program (reviewed in Ref. 2). NIH 3T3 and C3H10T1/2 are two well characterized pluripotent cell lines, which are maintained as fibroblast-like cells, but which are capable of differentiation into multiple cell types (*e.g.* myocytes, adipocytes, or chondrocytes (2)). Two widely studied models, 3T3-L1 and 3T3-F442A, are already committed to the adipocyte lineage and are thus considered preadipocyte cell lines. Analyses of the differentiation program in these cell lines have shown that C/EBP and PPAR transcription factors work sequentially and cooperatively to stimulate the genetic events that result in differentiation.[2] The molecular events associated with preadipocyte differentiation have been most thoroughly studied in 3T3-L1 cells, because they differentiate in a synchronous manner in response to dexamethasone (DEX), methylisobutylxanthine (MIX), insulin, and fetal bovine serum (Fig. 1 and see Ref. 5). This differentiation scheme routinely results in >90% of preadipocytes accumulating triacylglycerol 5 days after differentiation is initiated.

Differentiation of brown adipocytes in culture has been investigated using two systems: primary brown preadipocytes (6) and HIB-1B cells, which were derived from SV40-induced brown fat tumors (7) and which express the brown adipocyte marker, UCP1. The roles of C/EBPs in differentiation of brown adipocytes have not been explored. However, it is likely that C/EBPs are involved, because *C/EBPα* and *C/EBPβ* are expressed in these cell lines and C/EBPs induce UCP1 promoter activity. In addition, analysis of animals with targeted deletions of *C/EBP* genes suggests that C/EBPs regulate brown adipocyte development *in vivo* (8).

Role of C/EBPs in the Preadipocyte Differentiation Program—C/EBPs appear to have diverse roles in regulation of preadipocyte differentiation. After treatment of preadipocytes with inducers of differentiation, a rapid and transient increase in transcription and expression of *C/EBPβ* and *C/EBPδ* is observed (Fig. 1). Differentiating preadipocytes undergo approximately two rounds of cell division after differentiation is induced; cell proliferation ceases coincident with the transcriptional activation of *C/EBPα* (Fig. 1). Induction of *C/EBPα* is followed by transcriptional activation of many genes encoding proteins involved in creating the adipocyte phenotype (Fig. 1). (For a more complete listing of genes induced or repressed during the differentiation process see Refs. 2 and 5.) *C/EBPζ* (*CHOP* or *gadd153*) is expressed at relatively low levels in confluent preadipocytes and is suppressed throughout the period of clonal expansion that precedes adipogenesis. On the 4th day of differentiation, *C/EBPζ* is induced and remains elevated thereafter (Fig. 1).

The coordinate activation of *C/EBP*s and adipocyte markers provides correlative evidence for the hypothesis that induction of *C/EBPβ* and *C/EBPδ* increases expression of *C/EBPα*, which, in turn, activates expression of adipocyte genes and thus stimulates the differentiation process. The positive actions of C/EBPα, C/EBPβ, and C/EBPδ on differentiation may be susceptible to counter-regulation by expression of C/EBPζ, which acts as a dominant-negative for C/EBPs by forming heterodimers that do not bind DNA at the consensus sites for C/EBPα, -β, and -δ. In addition, C/EBPα and C/EBPζ, two factors with antimitotic activity, may regulate preadipocyte cell devision during differentiation because clonal expansion is preceded by repression of C/EBPζ, and clonal arrest is correlated with induction of C/EBPα (reviewed in Ref. 5).

C/EBPβ and C/EBPδ—C/EBPβ and C/EBPδ are the first transcription factors induced following exposure of preadipocytes to differentiation medium and were thus postulated to be involved in directing the differentiation process. In accord with this notion, expression of either C/EBPβ or C/EBPδ in preadipocytes accelerates the rate of *C/EBPα* induction and adipogenesis in response to hormonal inducers, indicating that both factors are stimulatory to adipogenesis (9). In addition, embryonic fibroblasts from mice lacking both *C/EBPβ* and *C/EBPδ* expression are unable to differen-

* This minireview will be reprinted in the 1998 Minireview Compendium, which will be available in December, 1998. This is the third article of five in the "Biological Role of the Isoforms of C/EBP Minireview Series." This work was supported in part by National Institutes of Health Grants RO1-DK45285 and RO1-DK53405 (to G. J. D.) and RO1-DK51563 (to O. A. M.) and by Juvenile Diabetes Foundation International Grant 197039 (to O. A. M.).

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‖ Supported by a predoctoral fellowship from the Natural Sciences and Engineering Research Council of Canada.

[1] The abbreviations used are: UCP1, uncoupling protein 1; C/EBP, CCAAT/enhancer-binding protein; PPAR, peroxisome proliferator-activated receptor; PEPCK, phosphoenolpyruvate carboxykinase; UTR, untranslated region; USF, upstream stimulatory factor; GLUT4, insulin-responsive glucose transporter; SCD1, stearoyl-CoA desaturase I; 422/aP2, adipocyte lipid-binding protein; DEX, dexamethasone; MIX, methylisobutylxanthine; FAS, fatty acid synthase; LPL, lipoprotein lipase.

[2] A detailed account of the important role of PPARγ in preadipocyte differentiation is outside the purview of this paper; however, it has been reviewed elsewhere (3, 4).

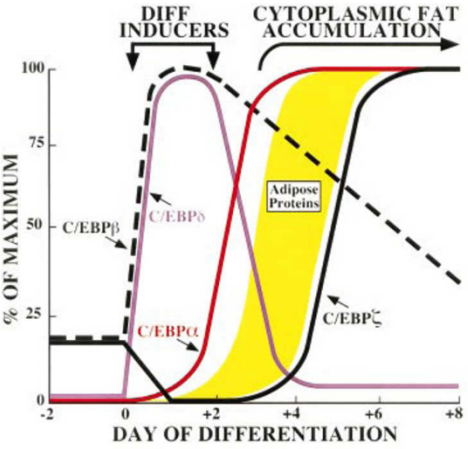

FIG. 1. **Patterns of *C/EBP* gene expression in differentiating 3T3-L1 cells.** *Curves* represent percentage of maximum expression for each gene. Figure is modified from Vasseur-Cognet and Lane (35).

tiate in response to hormonal stimulation (8). These cells fail to express C/EBPα and PPARγ or adipocyte markers such as 422/aP2 and PEPCK, suggesting that the absence of both C/EBPβ and C/EBPδ blocks adipogenesis. However, ectopic expression of C/EBPβ, but not C/EBPδ, in 3T3-L1 preadipocytes is sufficient to cause differentiation in the absence of DEX and MIX (9). Taken together, these data suggest that, although C/EBPδ stimulates differentiation, its role may be minor, whereas C/EBPβ is an integral part of the genetic cascade that causes adipogenesis (Table I).

In addition to its involvement in the sequence of genetic events leading to preadipocyte differentiation, C/EBPβ may play a more global role in adipocyte development by causing pluripotent cells to become committed to the adipocyte lineage. Although introduction of *C/EBP*β into pluripotent NIH 3T3 cells does not cause spontaneous differentiation, *C/EBP*β (but not *C/EBP*α or *C/EBP*δ) confers the ability of these cells to be differentiated into adipocytes by hormonal inducers (9, 10). Interestingly, expression of *C/EBP*β in these cells causes preadipocyte differentiation without induction of *C/EBP*α, perhaps indicating that C/EBPβ can functionally replace C/EBPα or that C/EBPα is not required for adipogenesis in these cells. These experiments using cultured pluripotent and preadipocyte cell lines suggest that C/EBPβ plays a dual role as a stimulator of cell determination as well as differentiation (Table I).

C/EBPα—Work from a number of investigators has solidified the correlative link between expression of *C/EBP*α and that of adipose-specific genes. For example, promoters from adipocyte genes such as *GLUT4*, *SCD1*, *leptin* (11), and *422/aP2* are transactivated by C/EBPs, including C/EBPα (reviewed in Ref. 5). To show that expression of *C/EBP*α is necessary for preadipocyte differentiation, Lin and Lane (12) blocked its expression through the introduction of antisense RNA into 3T3-L1 preadipocytes. In the absence of C/EBPα, adipose-specific genes were not expressed and triacylglycerol accumulation was not detected. Also, the conditional expression of *C/EBP*α in stably transfected clones of 3T3-L1 preadipocytes was sufficient to bring about differentiation as measured by the cytoplasmic accumulation of lipid and the expression of *422/aP2*, *GLUT4*, and endogenous *C/EBP*α (13). These studies demonstrate that expression of C/EBPα is both necessary and sufficient for differentiation of 3T3-L1 preadipocytes to adipocytes (Table I).

C/EBPζ—Although it cannot form homodimers, C/EBPζ avidly forms heterodimers with other C/EBP members (14). Because these heterodimers cannot bind traditional C/EBP-binding sites, C/EBPζ acts as a dominant-negative C/EBP (14). Consistent with this role as a sequestrant of C/EBP, enforced expression of C/EBPζ inhibits adipogenesis in 3T3-L1 preadipocytes (Table I (15)). It is possible that C/EBPζ also has positive effects on gene expression; C/EBPβ-C/EBPζ heterodimers bind to a novel DNA sequence and thus may redirect C/EBPs from classic C/EBP-binding sites to different elements in other promoters (16). Consistent with this hypothesis, the N terminus of C/EBPζ is capable of transactivation when tethered to DNA by a heterologous DNA-binding domain (17). However, to date, genes induced by C/EBPζ have not been identified.

C/EBPζ causes growth arrest in a variety of cell types when it is induced by stresses such as DNA damage (18). The role of C/EBPζ in preadipocyte differentiation is not well characterized, but when induced by unfavorable conditions, C/EBPζ may inhibit differentiation (19). Moreover, its suppression may be required for the clonal expansion of preadipocytes after induction of differentiation.

Transcriptional Regulation of the C/EBP Genes—Although the promoters for *C/EBP*α, *C/EBP*β, *C/EBP*δ, and *C/EBP*ζ have been cloned, only the regulation of the *C/EBP*α promoter has been characterized during preadipocyte differentiation. Within the mouse *C/EBP*α promoter is a C/EBP consensus site that could permit autoregulation by direct binding of C/EBPα as well as activation by other C/EBP family members (20). In addition, C/EBPα promotes USF binding at an E-box site, thus regulating its own expression through an indirect mechanism (21). Autoactivation of *C/EBP*α may be more complex *in vivo*, where *C/EBP*α expression is dependent upon the full complement of regulatory regions. When the *C/EBP*α gene is disrupted by insertion of *neo*, the *C/EBP*α*-neo* fusion transcript is expressed at near physiological levels, indicating that transcription of *C/EBP*α is not wholly dependent upon autoactivation (22). Another important regulator of *C/EBP*α transcription has recently been reported (23). The observation that AP-2α acts as a transcriptional repressor of *C/EBP*α has elucidated a possible mechanism for tissue-specific gene expression of *C/EBP*α and suggests that AP-2α is an inhibitor of adipose differentiation.

Translational Regulation of C/EBPs—Another mode of regulation that may be important for expression of C/EBPs is the use of alternative translational start sites. Both C/EBPα and C/EBPβ are translated from multiple in frame AUG sites giving rise to, for C/EBPα, proteins of 42, 40 and 30 kDa, and for C/EBPβ, proteins of 35, 32, and 20 kDa. Although both p42C/EBPα and p30C/EBPα transactivate C/EBPα-responsive promoters, p42C/EBPα appears to be a more potent transcription factor and is more capable of inducing adipogenesis and blocking mitosis (24, 25). In contrast, p20C/EBPβ (liver inhibitory protein) functions as a dominant-negative inhibitor of p32C/EBPβ (liver activator protein) and other C/EBPs. The ratio of p42C/EBPα to p30C/EBPα (and liver activator protein to liver inhibitory protein) changes over the course of adipocyte differentiation, suggesting that alternative translation may be a regulated process and could theoretically play a role in the control of adipogenesis (24, 26). In addition, a short open reading frame in the 5′-UTR of p42C/EBPα and p32C/EBPβ mRNA suppresses their translation and although not examined in preadipocytes may present another mechanism for regulating *C/EBP* gene expression (27).

Post-translational Regulation of C/EBPs—In fully differentiated adipocytes, post-translational regulation of C/EBP activity may be as important as regulation of *C/EBP* expression. Some of this regulation most certainly involves phosphorylation of C/EBPs, which has been reported for C/EBPα (28), C/EBPβ (29, 30), and C/EBPζ (17). C/EBPα is phosphorylated on as many as six sites in fully differentiated adipocytes (28). Two of these sites are dephosphorylated in response to treatment with insulin or IGF-1 and may therefore be especially important for the regulation of C/EBPα activity. Like C/EBPα, C/EBPβ is also phosphorylated in a regulated manner, and this process has been studied in a variety of cell types, particularly hepatocytes (see second minireview by Poli (36)). Regarding its phosphorylation in preadipocytes, one study indicates that C/EBPβ is serine-phosphorylated in response to increases in cAMP (30). This phosphorylation likely regulates, at least in part, the C/EBPβ-mediated increases in transcription of the gene for acetyl-CoA carboxylase. Finally, C/EBPζ phosphorylation has important consequences for adipocyte differentiation. C/EBPζ is phosphorylated by mitogen-activated protein kinase at serines 78 and 81 in the transactivation domain, and this phosphorylation is required for the full inhibitory effect of C/EBPζ on adipogenesis (17). Determining the sites and functions of phosphorylation will be important for our understanding of C/EBP functions during preadipocyte differentiation and in fully differentiated adipocytes.

Importance of Cell Culture Models of Preadipocytes and Adipocytes—From studies of cells undergoing differentiation *in vitro*, it

TABLE I
Summary of C/EBPs in development of adipocytes in culture and in vivo

	Cell culture models, white preadipocytes	Knockout mouse models[a]	
		White adipose tissue	Brown adipose tissue
C/EBPα			
Determination[b]	Not required (9, 10)	Unknown	Not required (31)
Differentiation[c]	Necessary and sufficient (12, 13)	Important: ↓↓lipid accumulation (22, 31)	Important: ↓lipid accumulation and ↓UCP1 but normal expression of 422/aP2, GLUT4, FAS (22, 31)
C/EBPβ			
Determination	Sufficient (9, 10)	Not required (8)	Not required (8)
Differentiation	Sufficient (9, 10)	Not required: normal lipid accumulation and expression of 422/aP2, adipsin, C/EBPα, LPL, PPARγ (8)	Involved: ↓lipid accumulation and ↓UCP1 but normal expression of 422/aP2, C/EBPα, PPARγ, LPL (8)
C/EBPδ			
Determination	Not required (9, 10)	Not required (8)	Not required (8)
Differentiation	Not sufficient but accelerates (9)	Not required; normal lipid accumulation and expression of 422/aP2, adipsin, C/EBPα, LPL, PPARγ (8)	Involved: ↓UCP1 but normal lipid accumulation and expression of 422/aP2, C/EBPα, PPARγ, LPL (8)
C/EBPβ and C/EBPδ			
Determination		Important: ↓↓mass (8)	Not required (8)
Differentiation	Necessary (8)	Not required: normal lipid accumulation and expression of 422/aP2, adipsin, C/EBPα, LPL, PPARγ (8)	Important: ↓↓UCP1 and ↓↓lipid accumulation but normal expression of 422/aP2, C/EBPα, PPARγ, LPL (8)
C/EBPζ			
Differentiation	Represses (15)		

[a] ↓ and ↓↓ indicate decreased expression.
[b] Defined as commitment to the adipocyte lineage in cultured cells and the presence of the tissue type *in vivo*.
[c] Defined as accumulating lipid and expressing adipocyte markers.

has been possible to identify C/EBP and other proteins as transcriptional regulators of adipocyte differentiation. Experiments performed using cultured fibroblasts and preadipocytes suggest that deletion of *C/EBPα* or *C/EBPβ in vivo* would have profound effects on adipose tissue development. As we shall see, this prediction is only partially correct.

Adipocyte Development in Vivo

Although mammals require adipose tissues to store energy for metabolic or thermogenic needs, the point in development at which fully differentiated white and brown adipocytes form varies greatly among species. In the mouse, despite considerable expression by preadipose tissue of genes normally expressed in adipocytes (*GLUT4*, *422/aP2*, *SCD1*), little or no lipid accumulation is observed at the time of birth. Rather, the characteristic morphology of adipocytes develops in the first 24 h after birth (31). Rat adipocytes appear earlier in development, with the expression of adipose-specific genes late in gestation and accumulation of triacylglycerol in brown adipocytes prior to parturition (32). Human adipocytes are observed earlier still, with brown and white adipocytes forming in the second trimester of gestation (33). Expression of C/EBPs has not been examined during development of human adipose tissues. However, analyses of mRNA from brown adipose tissue during the final days of fetal development of the rat and mouse indicate that *C/EBP*s are already expressed (8, 32), suggesting that C/EBPs may direct differentiation of preadipocytes, as they do in cultured cells. To address the importance of C/EBP over the course of development *in vivo,* animals deficient in expression of either *C/EBPα*, *C/EBPβ*, *C/EBPδ*, or both *C/EBPβ* and *C/EBPδ* have been created (8, 22, 31, 34). Analyses of these animal models have begun to clarify the roles of C/EBPs in adipocyte development and function.

Deletion of the Gene for C/EBPα—The phenotype of mice homozygous for a deletion in the gene for *C/EBPα* (*C/EBPα−/−*) is complex, with defects in glycogen storage and failure to activate gluconeogenic pathways at birth (22, 31). The mutant homozygotes die 7–8 h postpartum because of extreme hypoglycemia. With administration of glucose, a small percentage of *C/EBPα−/−* mice survives for periods of up to 36 h (Table I). Analysis of these surviving animals demonstrates the important role of C/EBPα for lipid accumulation (Table I). White adipocytes in wild type mice have large cytoplasmic lipid droplets 32 h after birth. In contrast, preadipose sites in *C/EBPα−/−* mice do not have cells containing lipid droplets in skin, the inguinal site, or in the interscapular region at this time. Interscapular brown adipose tissue is present in newborn animals of both genotypes. However, brown adipocytes from *C/EBPα−/−* knockout mice also show defects in lipid accumulation. *C/EBPα−/−* mice do not accumulate lipid in brown adipose tissue within 24–32 h, despite normal expression of adipocyte markers (FAS, *GLUT4*, and *422/aP2*). Besides impaired lipid storage, brown adipocytes from *C/EBPα−/−* mice show altered expression of *UCP1*, which is virtually absent at birth and remains markedly reduced at 7 h. These findings provide evidence that *C/EBPα* is important for the differentiation of adipose tissue.

Inactivation of the Genes for C/EBPβ—Although C/EBPβ deficiency has many consequences including defects in immune and liver function and female infertility (see Ref. 36), there is little effect on white adipocyte development or function. Adipocytes from *C/EBPβ* homozygous mutants are normal in size and morphology and in their expression of adipocyte markers (*422/aP2*, *adipsin*, *C/EBPα*, *PPARγ*, and *LPL*). The finding that C/EBPβ is not required for development of white adipose tissue is surprising in view of the important role of C/EBPβ in cultured adipocytes, where its expression can cause cell determination and differentiation (Table I). This disparity suggests that although C/EBPβ may be sufficient in cultured cells, it is not necessary for differentiation of white adipose tissue *in vivo*. In brown adipose tissue, the absence of C/EBPβ leads to reduced lipid accumulation and a reduction in *UCP1* expression. Although brown adipose tissue function is abnormal, commitment to the brown adipose lineage is not altered, provided other C/EBP family members are normally expressed (8).

Inactivation of the Gene for C/EBPδ—*C/EBPδ*-deficient mice are similar to wild type littermates in appearance and survival rates and show no gross abnormalities in white or brown adipose (8). It appears that the role of C/EBPδ in adipocyte differentiation is minor, because its absence does not impede the accumulation of lipid or the expression of adipocyte markers (*LPL*, *PEPCK*, *C/EBPα*, and *PPARγ*, Table I). This conjecture is consistent with findings using cultured cells, where expression of *C/EBPδ* is insufficient to induce adipogenesis, although it assists in differentiation by accelerating hormonally induced adipogenesis (Table I). Similarly, C/EBPδ may assist in the differentiation of brown adipose tissue. Although brown adipocytes from *C/EBPδ−/−* mice accumulate fat normally, these cells tend to have lower UCP1 expression. As with the *C/EBPβ−/−* mice, brown adipocyte function may be somewhat impaired in C/EBPδ-deficient mice (Table I), but C/EBPδ is not required for determination of this tissue type.

Inactivation of the Genes for Both C/EBPβ and *C/EBPδ*—Although the absence of C/EBPβ or C/EBPδ individually in adipose tissues results in an unremarkable phenotype, loss of both has

deleterious consequences (Table I). *C/EBPβ*(−/−)δ(−/−) mice have extremely high rates of mortality. Only 15% of these mice survive their 1st day, and by 4 weeks less than 4% remain (8). The importance of C/EBPβ and C/EBPδ for white adipose tissue was examined in this small fraction of surviving mice by comparing the epididymal adipose tissue mass from wild type and mutant animals. At 8 weeks, epididymal adipose mass in the doubly deficient animals was only 30% of that in wild type controls. Yet, individual fat cells within this tissue were normal in size and morphology, suggesting that the decrease in epididymal adipose mass was because of a decrease in fat cell number. This finding implies that C/EBPβ and C/EBPδ are important in determination of the adipocyte lineage, because in their absence, considerably fewer cells become committed to adipocyte development (Table I). Once cells are determined to become adipocytes, however, their differentiation does not appear to be impaired by the absence of C/EBPβ and C/EBPδ. At 8 weeks, the expression of *422/aP2*, *C/EBPα*, *PPARγ*, *adipsin*, and *LPL* is normal in *C/EBPβ*(−/−)δ(−/−) mice (8). C/EBPβ and C/EBPδ may be more important for differentiation of brown rather than of white adipose tissues. Brown adipocytes from *C/EBPβ*(−/−)δ(−/−) mice contain virtually no lipid droplets at 20 h after birth, and the expression of *UPC1* in these mice is less than 10% of that of wild type controls. This severe phenotype suggests that terminal differentiation of brown adipocytes is blocked in *C/EBPβ*(−/−)δ(−/−) mice (Table I).

Perspectives—Analysis of cultured cell lines has led to a model in which C/EBPs play integral roles in determination and differentiation of preadipocytes. In this paradigm of white adipocyte development, C/EBPβ commits cells to the preadipocyte lineage; C/EBPβ and C/EBPδ initiate the differentiation cascade; C/EBPβ and C/EBPα stimulate differentiation; and under unfavorable conditions, C/EBPζ represses differentiation (Table I). The validity of this model is largely supported by findings from animals deficient for various C/EBPs, which suggest that C/EBPβ and C/EBPδ are important for determination to the preadipocyte lineage and that C/EBPα is important for differentiation to the adipocyte phenotype. Further, these genetically deficient mice provide evidence for the importance of C/EBPα, C/EBPβ, and C/EBPδ for normal lipid accumulation and expression of UCP1 in brown adipose tissue.

Unfortunately, the requirement for C/EBPs in other tissues, particularly liver, complicates analysis of adipose tissues, because most *C/EBP* knockout mice die early in life from metabolic disorders unrelated to fat development. This limitation underscores the importance of creating additional models with which to study the function of C/EBPs in adipocyte development. For example, animals in which C/EBPs are deficient only in adipose tissue, so-called tissue-specific knockouts, will be useful for delineating the importance of C/EBPs in adipose tissue development, without the metabolic aberrations and early death associated with C/EBP deficiencies in liver and other tissues. In addition, development of conditional adipose-specific knockouts will facilitate the study of C/EBP-regulated gene expression in mature adipose tissues. Finally, another substantial advance will be development of "knock-in" animals, where one *C/EBP* gene is replaced by another such that, for instance, activation of the *C/EBPα* promoter results in expression of *C/EBPβ*. Experiments with these "knock-in" animals will help distinguish between differences in the functions of individual C/EBPs and differences because of the timing of their expression.

The complexity of dimer formation among C/EBP transcription factors and the potential for these dimers to physically and functionally interact with other proteins, such as NFκb, Sp1, p300, and cell cycle-related proteins Rb and p21, compound the challenge of understanding C/EBPs and their mechanisms of action. In addition, C/EBPs function within the context of other factors, such as PPARγ, that can act independently or synergistically with C/EBPs to regulate adipocyte differentiation. The ultimate goal of research efforts will be to integrate work on C/EBPs and other factors into a comprehensive model of white and brown adipose tissue development that will ultimately elucidate targets for therapeutic management of obesity and type II diabetes.

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