DURING DEVELOPMENT, LUNG MORPHOGENESIS is initiated when the lung bud evaginates from the foregut endoderm. Subsequently, the airway tree is generated as the cells of the lung bud are induced to begin a program of repeated branching to establish airways lined with epithelium. As development proceeds, regional differentiation along the airway epithelium results in multiple subpopulations of cells with distinct functions. The cellular differentiation is accompanied by expression of differentiation markers that reflects the degree of maturation of the lung epithelium. Lung development is a multistep process, utilizing numerous transcription factors to control the cellular differentiation of multipotential progenitors (16, 29, 45, 77, 78).

Recent evidence suggests that members of the CCAAT/enhancer binding protein (C/EBP) family play important roles in lung development and lung-specific gene expression. The C/EBP transcription factors form a family within the basic region-leucine zipper (bZIP) class of transcription factors. C/EBPs are expressed in several organs and are involved in controlling differentiation-dependent gene expression. Individual members of this family have additional specific roles; some control other differentiation-dependent processes such as inhibition of proliferation, and other members are involved in regulation of inflammatory genes. In the lung, C/EBPα, -β, and -δ are expressed as well as the two ubiquitously expressed family members C/EBPγ and -ζ (58). During the last five years, the biological role of these transcription factors in lung has started to emerge, and in this review we give an overview of the current understanding of their role in the lung epithelium. In the lung, these factors play a role in inflammation, similar to other organs. However, as this has been touched on in several recent reviews (see for instance Refs. 24, 56, 58), we only briefly discuss these aspects of C/EBP function in the lung.

THE C/EBP TRANSCRIPTION FACTOR FAMILY

Structure and expression. C/EBP factors belong to the bZIP class of basic domain transcription factors (81, 82). Six members (C/EBPα–ζ) constitute the mammalian C/EBP family. Of these, C/EBPα was first identified and is the founding member. The basic region of C/EBP factors is a highly positively charged domain that directly interacts with the DNA (see Fig. 1). All members of the C/EBP family have similar basic region DNA-binding motifs except C/EBPζ (which lacks DNA-binding activity). As a consequence of the high similarity in the basic region, C/EBPα, C/EBPβ, and C/EBPδ have been shown to interact with virtually identical DNA sequences (6, 53, 80). The leucine zipper region is also conserved between the different family members, whereas the amino-terminal transactivation domain is more diverse. The leucine zipper domain is involved in homo- and heterodimerization, and all proteins in the C/EBP family have been shown to form homo- and heterodimers. Of the tissue-specific C/EBP family members, three have been demonstrated to be expressed in lung, namely C/EBPα, -β, and -δ (6, 80). Although C/EBPα and -β are expressed at highest levels in the lung, C/EBPδ expression is more restricted.
relative levels in the liver and fat, C/EBPβ is expressed at highest levels in the lung (6). C/EBP factors have been suggested to play important roles in controlling differentiation. In liver, fat, and white blood cells of the myelomonocytic lineage, C/EBP factors have been demonstrated to be important regulators of different aspects of differentiation, including proliferation, cell cycle arrest, and gene expression (reviewed in Refs. 18, 21, 22, 39, 56).

Expression pattern in lung. A similar role in lung cellular differentiation is suggested by the expression of C/EBPα in the developing lung; expression is initiated in close temporal proximity to the initiation of cellular differentiation and the appearance of differentiation markers (Ref. 40; T. Berg and M. Nord, unpublished observations; Fig. 2). In the adult lung, C/EBPα is expressed in the type II cells of the alveolar epithelium, and lower levels are also seen in the bronchiolar epithelial Clara cells, as revealed by immunohistochemical studies and studies on isolated epithelial cells (9, 40, 51, 69). C/EBPβ is expressed in type II cells of the alveolar region (61, 69), and expression is also seen in the bronchiolar epithelium (T. Berg, T. N. Cassel, and M. Nord, unpublished observations). C/EBPα shows high-level expression in the bronchiolar epithelium and lower levels in alveolar type II cells (9, 37, 61, 69). The developmental expression pattern of C/EBPβ and α has not been investigated by immunohistochemical methods, but analyses on whole embryonic lung show that these factors also increase late during development (5, 61). However, their temporal expression patterns seem to precede that of C/EBPα, similar to what has been demonstrated during adipocyte differentiation (21). An important role of C/EBPα in lung cellular differentiation is suggested by the phenotype of the C/EBPα(−/−) mouse. The phenotype is lethal, and mice die within 10 h after birth due to severe hypoglycemia (27, 76). However, a fraction of C/EBPα(−/−) mice succumbs immediately after birth from apparent respiratory distress (27). Closer examinations revealed impaired lung cellular differentiation with abnormalities in the alveolar epithelium and hyperproliferation of type II cells (27, 68). No phenotype has been reported in the C/EBPβ(−/−), C/EBPβ(+/−), or C/EBPβ(−/−)/C/EBPβ(−/−) double-knockout mice (63, 66, 70).

Role for C/EBP transcription factors in lung epithelial differentiation? Studies in transgenic and knockout mice have revealed that forkhead box transcription factors, especially FoxA2/hepatocyte nuclear factor (HNF)-3β and the homeodomain transcription factor Nkx2.1/thyroid transcription factor (TTF)-1, play major roles in cellular differentiation of the lung epithelium, as well as specifying developmental processes in the early developing lung (2, 35, 46, 47, 79, 84). This is in agreement with the expression pattern of these transcription factors. They are turned on at an early time point in lung development and are sustained in the epithelium throughout lung development (3, 38, 48; Fig. 2). As the expression of HNF-3 factors and Nkx2.1
is initiated from an early time point of lung development, additional transcription factors are likely to be important to promote the extensive cellular differentiation program that is initiated in late lung development. Several lines of reasoning support the concept that C/EBP factors could be important for cellular differentiation during late lung development; C/EBP transcription factors have been demonstrated to play important roles in cellular differentiation in a variety of different tissues including breast, adipocytes, white blood cells, and liver. Notably, a relationship between lung and liver transcriptional regulation is likely, as suggested by their shared endodermal origin, the important role of HNF-3 factors, and the expression of C/EBP factors in both organs. Moreover, C/EBP transcription factors, including C/EBPα, C/EBPβ, and C/EBPδ, are expressed in the lung, and their expression is initiated in temporal proximity to the initiation of cellular differentiation and the appearance of differentiation markers. And finally, C/EBPα(−/−) mice demonstrate morphological abnormalities with hyperproliferation of alveolar type II cells, indicating a role for C/EBPα in the control of proliferation-differentiation processes in the lung epithelium.

REGULATION OF LUNG GENE EXPRESSION

Clara cell secretory protein/secretoglobin 1a1. Clara cell secretory protein (CCSP)/secretoglobin 1a1 was the first lung-specific gene demonstrated to be regulated by C/EBP transcription factors in transcription regulation studies (9, 51). On the basis of sequences in the promoter showing similarities to consensus C/EBP-binding sites and correlating expression patterns, C/EBP regulation of the surfactant protein (SP)-A gene has also been proposed (40). CCSP is a small secretory protein abundantly expressed in the Clara cells of the bronchiolar epithelium and in similar cells in the larger airways (50). Although the exact physiological role of CCSP remains to be established, it has been suggested that CCSP plays a role in protection against oxidative stress and/or has an anti-inflammatory function (67, 83). CCSP is expressed in a differentiation-dependent pattern in the developing lung, in temporal proximity to cellular differentiation (50). Expression starts late in lung development in parallel with the appearance of Clara cells. Postnatally, the expression levels of CCSP continue to increase, and adult levels are not reached until the Clara cells are fully differentiated.

Freshly isolated primary Clara cells express high levels of CCSP. During culture in vitro, expression decreases. The expression of transcription factors such as HNF-3 and Nkx2.1, known to regulate CCSP gene expression, does not parallel the rapidly declining CCSP levels during culture in vitro. In contrast, C/EBPα expression is rapidly lost. The decrease in C/EBPα levels correlates to dedifferentiation of the cells and declining CCSP levels, suggesting a potential role of C/EBPα in the regulation of CCSP (51). In addition to C/EBPα, C/EBPδ is expressed in the bronchiolar epithelium and also in isolated Clara cells (8, 9, 37). A functional importance of both C/EBPα and C/EBPδ for CCSP gene regulation has been demonstrated in transient transfection studies in lung epithelial cell lines. These studies showed that both C/EBPα and δ promote transcription and that this occurs through interaction with two C/EBP-binding sites in the proximal promoter (Ref. 9; Fig. 3). Mutation of either C/EBP-binding site resulted in abolished or strikingly reduced C/EBPα- and C/EBPδ-mediated transactivation of the CCSP promoter, as well as impaired binding of both factors in DNase I footprint analysis. These results indicate that the two C/EBP-binding sites form a compound response element. Electrophoretic mobility shift assays showed that C/EBPα and δ can bind to both C/EBP-binding sites, whereas in DNase I footprint analyses, the interaction of C/EBPα with the proximal site was weak. To summarize, C/EBPα and C/EBPδ activate the CCSP promoter via a compound response element in the proximal promoter. This element consists of two adjacent C/EBP-binding sites (Fig. 3) that individually can bind C/EBPα and C/EBPδ with equal efficiency, but not in the context of the intact promoter. Together, this renders the C/EBP-mediated regulation of the CCSP gene a complicated process.

Combinatorial action of C/EBPs and other transcription factors. In the proximal CCSP promoter, located in a region between +1 and −130 bp of the 5′ flanking sequence, reside multiple cis-acting elements of potential importance to the promotion of the tissue and cell-specific expression of CCSP. In addition to the two adjacent C/EBP-binding sites, several functional binding sites for Nkx2.1/TTF-1 and FoxA/HNF-3 factors exist within this short region (Fig. 3). The close proximity of binding sites for multiple transcription factors suggests combinatorial action in the regulation of the CCSP gene (50). And, indeed, in studies of transient transfection, a strong synergistic transactivation was observed between C/EBPα and Nkx2.1 on the CCSP promoter. The Nkx2.1-C/EBPα synergism was specific, as other combinations of transcription factors tested resulted in levels of transactivation that were approximately additive. The synergism is mediated through interaction with elements in the proximal CCSP promoter (Fig. 3) and seems to be dependent on cooperative binding of the transcription factors to the promoter (7). These results demonstrate that C/EBPα acts on the proximal CCSP/secretoglobin 1a1 (Scgb1a1) promoter. Indicated are binding sites for transcription factors regulating the CCSP/Scgb1a1 promoter.
gether with another lung-enriched transcription factor, Nkx2.1, in the regulation of CCSP. The strong syner-
gistic activity, together with the temporal expression
patterns of CCSP, C/EBPα, and Nkx2.1, suggests that
the appearance of C/EBPα in the developing lung is a
key event to initiate high-level expression of CCSP in
late lung development (Fig. 2). With these results,
together with the studies of targeted inactivation of
C/EBPα and Nkx2.1 (27, 35), the following model con-
cerning the roles of C/EBPα and Nkx2.1 in the devel-
oping lung epithelium can be formulated: Nkx2.1
serves to specify lung epithelial cell lineage early in
lung development and thus regulates lung-specific
gene expression. C/EBPα has its main role in late
development and acts as a regulator of differen-
tiation-dependent gene expression. A gene such as CCSP,
which is specifically expressed in the lung epithelium
and exhibits a differentiation-dependent expression
pattern, would consequently be predicted to require
simultaneous presence of Nkx2.1 and C/EBPα for high-
level expression (Figs. 2 and 3). A role for C/EBPα in
late lung development is also supported by the findings
that C/EBPα expression is first detected when differen-
tiation of secretory epithelial cells is initiated: dif-
ferentiated type II cells appear in the future alveolar
epithelium, and differentiation of the bronchiolar
Clara cells starts. This is in close connection to the
onset of high-level expression of genes with a differen-
tiation-dependent expression pattern such as CCSP
(Fig. 2). However, full differentiation of Clara cells is
attained postnatally (45, 71, 72). In the postulated
model, the appearance of C/EBPα in the developing
lung epithelium is a key event to initiate expression of
differentiated gene products, in a similar fashion as
has been demonstrated in hepatocytes and adipocytes
(6, 27, 32, 59, 74, 76).

SP-A. SP-A is one of the hydrophilic surfactant pro-
teins and is expressed in the alveolar type II cells as
well as in bronchiolar Clara cells (36). SP-A expression
is initiated late in lung development and increases in
concert with the appearance of differentiated type II
cells (Fig. 2). In the adult lung, SP-A is highly
expressed in alveolar type II cells and to a lesser extent in
Clara cells (45). On the basis of sequences in the SP-A
promoter showing similarities to consensus C/EBP-
binding sites and correlations between SP-A and
C/EBPα expression, regulation of this gene by C/EBP
transcription factors has been proposed (40). And re-
cently, a functional C/EBP-binding site was demonstrat-
ed in the proximal rat SP-A gene at −180 bp
upstream of the start site of transcription (42, 61). This
element is necessary for full C/EBPα responsiveness
of the promoter, and antisense knock-down of C/EBPα
decreased expression of the endogenous SP-A gene in a
human lung cancer cell line. These results demon-
strate that C/EBPα transcription factors regulate SP-A
expression. Likewise, the expression patterns of SP-A
and C/EBPα suggest that C/EBP factors have a
role in the differentiation-dependent expression of
SP-A in the developing lung (Fig. 2). Together, these
studies suggest that C/EBPα factors are involved in the
regulation of differentiation-dependent gene expres-
sion in the alveolar epithelium as well.

SP-D. A second hydrophilic surfactant protein found
in lung lavage is SP-D. It is expressed in alveolar type
II cells, in Clara cells, and in the tracheobronchial
glands of the lung, but unlike other surfactant pro-
teins, SP-D does not localize to lamellar bodies (36).
SP-D starts being expressed late in lung development,
and expression continues to increase postnatally (Ref.
45; Fig. 2). Transfection studies in human lung cancer
cells have revealed the presence of three functional
C/EBP response elements in the promoter of the hu-
man SP-D gene (31). Two are located close together at
340 and 319 bp upstream of the start site of transcrip-
tion and the third further upstream at −432. The two
sites positioned in tandem at −340 and −319 seem not
to bind C/EBP factors simultaneously. However, these
binding sites interact with the −432 site to fully trans-
activate the SP-D promoter. The presence of several
interacting C/EBP-binding sites forms a common
theme together with the CCSP promoter, which also
contains two C/EBP-binding sites acting together.
However, in contrast to the SP-D promoter, where the
sites are separated by only 20 bp. From these results it seems that,
similar to SP-A, C/EBP factors are likely to be key
regulators underlying the developmental expression of
SP-D. In addition, both SP-A and -D are upregulated in
response to acute-phase stimuli such as instillation of
lipopolysaccharide (43). As in the liver, C/EBPβ and -δ
are increased in lung after acute-phase stimuli (1, 14).
This suggests that C/EBPβ and -δ could be involved in
mediating the acute-phase response in lung, similar to
what has been described in the liver.

CYP2B1. The P450 enzyme CYP2B1 is constitutively
expressed in the lung epithelium, both in the Clara
cells of the conducting airway epithelium and in the
alveolar type II cells. In the lung epithelium, it also
exhibits an expression pattern correlating to the exten-
sive cellular differentiation occurring around the time
of birth (Ref. 25; Fig. 2). Studies in cells of liver origin
have demonstrated that the CYP2B1 gene is transac-
tivated by C/EBPα and C/EBPβ through a C/EBP-
binding site in the proximal promoter (55), and trans-
genic studies have revealed that 1.3 kb of the 5’ flan-
k region of the CYP2B1 promoter is sufficient to
promote lung-specific expression (65). In transient
transfections in lung epithelial cells, reporter gene
activity driven by 1,350 bp of the CYP2B1 promoter
was increased by both C/EBPα and C/EBPδ, and inac-
tivation of the C/EBP-binding site caused a significant
reduction of the transactivation efficiency from both
factors (8). These results indicate that C/EBPα and
C/EBPδ are important in controlling CYP2B1 gene
expression in lung epithelial cells and show that the
proximal C/EBP-binding site confers C/EBP transac-
tivation.

In summary, the results showing C/EBP regulation of
the CCSP, SP-A and -D, and CYP2B1 genes indicate
an important role for C/EBP transcription factors in
regulating lung epithelial gene expression. All these genes show a similar differentiation-dependent expression pattern during lung development with an onset of high-level expression late in lung development (Fig. 2), suggesting that they are regulated in a similar fashion. The expression pattern of C/EBPs during lung development parallels cellular differentiation, and C/EBP expression is initiated in close proximity to the onset of high-level expression of these genes (Fig. 2). Together, this indicates that C/EBPs have a major role late in lung development as a regulator of differentiation-dependent expression of this group of genes.

**UNIQUE ROLES FOR THE DIFFERENT C/EBP FAMILY MEMBERS?**

C/EBPα. Results from targeted inactivation of the gene for C/EBPα in mice indicate a specific role for this transcription factor in regulating subsets of genes, especially in the liver, where genes involved in glucocorticoid and glycogen synthesis exhibit specific decreases (18, 76). Increased proliferation is also evident in the livers of C/EBPα(−/−) mice (27), and liver regeneration is associated with decreased C/EBPα expression. Moreover, forced expression of C/EBPα in liver cell lines inhibits proliferation. Together, this suggests a role for C/EBPα in regulating proliferation in the liver (22). In the lung, knockout of C/EBPα has revealed a critical role in regulating proliferation of the alveolar epithelium as well (27, 68). In contrast, expression of genes regulated by C/EBP factors is seemingly unaffected in the lungs of C/EBPα(−/−) mice. This is most probably explained by other C/EBPs present in lung substituting for C/EBPα in the trans-activation of target genes. An ability of C/EBPβ to substitute for C/EBPα has indeed been demonstrated (12, 18, 19). However, the idea that other C/EBPs can fully substitute for C/EBPα in transcriptional regulation in the lung is challenged by the finding of efficient synergism observed specifically between C/EBPα and Nkx2.1.

Our understanding of how C/EBPα regulates cellular proliferation was recently advanced by several studies; C/EBPα has been demonstrated to interact directly with the cyclin-dependent kinases (cdks) 2 and 4, two critical regulators of cell cycle progression (75). Interaction occurs through a short region of the C/EBPα polypeptide and prevents interaction of these kinases with their cognate cyclins. As the cyclin-cdk interaction is necessary for activity of the cdks and progression through the cell cycle, this provides a potential mechanism for the growth arrest mediated by C/EBPα. The closely related family members C/EBPβ and -δ, which are expressed in proliferating cells, do not share this cdk-interacting region. In a separate study, in vivo experiments demonstrated that C/EBPα also represses the E2F complex and that this repression is necessary for terminal differentiation of fat cells and granulocytes (57). Activation of the E2F complex is necessary for passage through the restriction point of the cell cycle and is thus central in regulation of proliferation. The E2F repression is mediated by regions of C/EBPα separate from the cdk-interacting region, suggesting the existence of two separate pathways for C/EBPα to inhibit proliferation. Notably, neither of these regions is involved in activating the conventional array of target genes for C/EBPα (44). An additional mechanism by which C/EBPs might inhibit proliferation is via transcriptional induction of the cdk inhibitor p21WAF1/Cip1. This mechanism seems to be especially important for the antiproliferative effects of glucocorticoids (10, 17). Interestingly, in human lung mesenchymal cells, this effect has recently been demonstrated to be mediated by formation of a complex between the glucocorticoid receptor and C/EBPα (62). All together, these mechanisms establish the means by which a single factor such as C/EBPα couples growth arrest to gene expression in the process referred to as differentiation and indicate that this dual activity is unique for C/EBPα (44).

The hyperproliferative nature of the alveolar epithelium in mice lacking C/EBPα indicates that C/EBPα has a central role in controlling proliferation in the lung epithelium (27, 68). Findings of dominant-negative mutations in the gene encoding C/EBPα in acute myeloid leukemias show that C/EBPα is a tumor suppressor gene (54), and recent loss, or decreased expression, of C/EBPα in lung cancers has been demonstrated (30). Decreased levels were more commonly seen in adenocarcinomas and correlated to poor differentiation and a more advanced stage of the tumors. Moreover, forced expression of C/EBPα in lung cancer cell lines reduced proliferation and induced morphological changes characteristic of differentiation. All together, this demonstrates a role for C/EBPα in regulating cellular proliferation in the lung as well. Together with the role of C/EBPα in controlling differentiation-dependent gene expression, this indicates a function for C/EBPα as a coordinating regulator of two central parts of differentiation of the lung epithelium: expression of differentiated gene products and induction of growth arrest.

C/EBPβ and -δ. Present evidence points toward a unique role for C/EBPα in regulating proliferation in addition to gene expression. Do the close relatives C/EBPβ and -δ have roles of their own in the lung? Certainly they are not vital to baseline lung function and development, as suggested by the findings in mice lacking both C/EBPβ and -δ, which exhibit no histological abnormalities of the lung (70). However, when challenged with acute-phase stimuli, C/EBPβ and -δ levels are increased in the lung (1). This is reminiscent of the liver, where C/EBPβ and -δ are both important regulators of acute-phase genes (56). Several of the acute-phase protein genes are also expressed in the lung and elevated after lung injury. In addition, collectins expressed in the lung such as SP-A and SP-D are increased after lung injury and, on the basis of this, have been suggested as lung-specific acute-phase proteins (43). As outlined above, SP-A and SP-D are regulated by C/EBP factors, and this suggests that C/EBPs regulate acute-phase proteins in the lung as
well. After lung injury, early inflammatory mediators such as IL-1β and TNF-α as well as IL-6 and the adhesion molecule ICAM-1 are elevated. Also these genes are C/EBP regulated, further adding to the group of C/EBP-regulated genes that are upregulated in lung injury (13, 24, 56). Agents apart from classical acute-phase stimuli but also causing acute-lung injury, such as oxidative stress and bleomycin, also increase the levels of C/EBPβ and -δ in the lung (1, 14, 69). This points toward a specific role for C/EBPβ and -δ in the reaction to lung injury and the subsequent activation of the innate immune system and inflammatory response.

Glucocorticoids are steroid hormones required for normal lung development. In the absence of glucocorticoid activity, mice die shortly after birth due to respiratory failure. This was clearly demonstrated in knockout mice lacking the glucocorticoid receptor. The lungs of these mice are highly immature with increased proliferation of both mesenchymal and epithelial cells (15). Treatment with glucocorticoids during embryonic development leads to enhanced lung maturation and increased expression of lung epithelial proteins exhibiting a differentiation-dependent expression pattern. Such proteins include the surfactant proteins and CCSP (11, 45). Glucocorticoids act through the glucocorticoid receptor, yet the specific molecular mechanisms for the effects of glucocorticoids on lung development are unclear. Direct effects on the lung epithelium are likely, though paracrine signaling between mesenchymal and epithelial cells has also been suggested (45). Our knowledge of this field was advanced by findings in transgenic mice harboring a mutation in the dimerization domain of the glucocorticoid receptor. This mutation prevents transcriptional regulation by DNA binding but allows regulation by protein-protein interactions. In contrast to the glucocorticoid receptor knockout mice, these mice are viable and do not suffer from respiratory problems (60). This suggests that direct transcriptional activation by the glucocorticoid receptor is of less importance during lung development and that protein-protein interactions play a more prominent role. In line with this, no functional binding sites for the glucocorticoid receptor have been demonstrated in the promoters of the glucocorticoid-regulated surfactant protein and CCSP genes (33). In summary, even though glucocorticoids have a central role in lung development, unclear issues still remain about the mechanisms of glucocorticoids signaling in the lung epithelium. Recent observations suggesting a role for C/EBPβ and -δ in glucocorticoid signaling in the lung might shed light on this. In a lung epithelial cell line, glucocorticoid stimulation of the CCSP and CYP2B1 promoters was dependent on the integrity of C/EBP-binding sites in the respective promoter. This is similar to findings in liver and adipose tissue, where glucocorticoid hormones also play an important role during cellular differentiation. In these organs, some glucocorticoid effects on gene expression are mediated via C/EBPβ and -δ (18, 28, 41). However, in contrast to these organs, glucocorticoids do not increase the protein levels of C/EBPβ and -δ in lung cells. Instead, they enhance DNA-binding activity without affecting protein levels, suggesting glucocorticoid-induced post-translational modifications that stimulate binding of C/EBPβ and -δ to their cognate binding sites in target promoters (4). Furthermore, in human fetal lung explants, glucocorticoids have been shown to increase C/EBPβ levels (5). Together, these results indicate a previously unknown role for C/EBPβ and -δ in glucocorticoid signal transduction in the lung.

How could the same factors (C/EBPβ and -δ) be involved in the response to both inflammatory stimuli and a strong anti-inflammatory agent such as glucocorticoids? The findings that C/EBPs are targets for post-translational modifications such as phosphorylation and sumoylation, which subsequently affect DNA binding and/or transactivation potential, could be part of the answer (34, 58). Posttranslational modifications have been most studied in C/EBPβ. This protein carries multiple phosphorylation sites that have been demonstrated as targets for a diverse set of signal transduction pathways. For instance, stress-activated protein kinases, such as p38, which are activated by cellular stress and involved in the acute-phase reaction, cause C/EBPβ phosphorylation on Ser105, inducing the transactivation potential (23). The same amino acid residue is also a target for PKC phosphorylation (73). Other described phosphorylation events can decrease transactivation potential, inhibit DNA binding, or affect nucleo-cytoplasmic shuttling of C/EBPβ. Also, C/EBPβ is a target for regulated phosphorylation, but this has not been studied in the same detail as for C/EBPδ (58). The ability of C/EBPβ and -δ to undergo posttranslational modifications suggests a potential scenario in which glucocorticoids cause specific post-translational modifications of C/EBPβ and -δ other than those caused by inflammatory stimuli. These events could then target C/EBPβ and -δ toward glucocorticoid-regulated lung epithelium-specific genes and away from inflammatory genes.

CONCLUSION

Even though we are far from a complete understanding, a picture is emerging in which C/EBPα has a role in directly regulating proliferation as well as differentiation-dependent gene expression. C/EBPβ and -δ have a partly overlapping role in regulating expression of differentiation markers but are also involved in responses to different stimuli such as acute lung injury and glucocorticoid hormones.

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