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Transcriptional Regulation of Acute Phase Protein Genes

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1. Introduction

Inflammation is an adaptive mechanism to insure restoration of tissue and cell homeostasis after injury, infection or stress. The inflammatory response leads to differential recruitment of immune cells in organs, as well as cell-specific modifications by inflammation-induced signaling pathways. All these inflammatory-specific changes establish cell- and lineage-context dependent gene expression programs characterized by gene-specific temporal regulation, resulting in waves of induced or repressed gene expression. These regulatory programs are established by the coordination of cell- and signal-specific transcription factors, co-activator or co-repressor recruitment and chromatin modifications that act through proximal promoter elements and enhancers. Here, we will review recent data uncovering the role of transcription factors in the regulation of the inflammatory response, in macrophages. With these general notions, we will discuss about the acute-phase response, as part of a repertoire of the inflammatory response, and we will review knowledge obtained in the last ten years about the regulatory transcriptional mechanisms of selected acute phase protein genes.

2. LPS/TLR4-dependent macrophage inflammatory responses are coordinated by combinations of transcription factors

Macrophages are important regulators of the inflammatory response, and sense bacterial products through Toll-like receptors (TLR). For example, TLR4 senses the presence of Gram negative bacterial lipopolysaccharide (LPS). LPS, in a complex with LPS-binding protein (LBP), is transferred by CD14 to a TLR4/MD-2 cell surface receptor. Ligand binding leads to MyD88 signaling through IRAK1/IRAK2/IRAK4 and TAK1 kinase activation, and subsequent activation of downstream signaling kinases, such as IKKs, MAPkinases ERK1/2, p38 and JNK, which affect NF-κB and AP-1 transcription factor activities. In addition, a TRIF-dependent pathway activates kinases such as TAK1 and TBK1 and IKKε non-canonical IKKs, leading respectively to NF-κB and IRF3 activation (Kumar et al., 2011). As a result, TLR4 activation induces acute inflammation in macrophages, characterized by the expression of a series of genes, such as cytokines, chemokines and antibacterial peptides, among others. These genes are temporally regulated, with early expressed or primary response genes, and late expressed or secondary response genes. In contrast to primary

response genes, secondary response genes need new protein synthesis to establish full expression patterns.

This complex regulation depends on an array of transcription factors that may be divided in four classes (Medzhitov and Horng, 2009) (Table 1). The first two classes of transcription factors are ubiquitous stress sensors that respond to external stress signals. Class I includes constitutively expressed transcription factors, such as NF-κB and IRF3, activated by signal-dependent post-translational modifications that affect their activation properties and nuclear localization. For example, cytoplasmic NF-κB is rapidly translocated to the nucleus after LPS stimulation, and is involved in the induction of primary genes. Other transcription factors of this class include latent nuclear AP-1 transcription factors, such as c-Jun phosphorylated rapidly after LPS stimulation. Class II transcription factors, including C/EBP and AP-1 transcription factor family members, need new protein synthesis for LPS-dependent stimulation. In addition to inducing secondary late gene expression, these transcription factors play a role in determining waves of time-dependent levels of gene expression. In macrophages, CCAAT/enhancer-binding protein δ (C/EBPδ) expression is increased late after LPS induction (see below).

The two last classes comprise tissue-restricted and cell-lineage transcription factors. The third category includes the macrophage-differentiation transcription factors PU.1 and C/EBPβ. Transcription factors of this class establish inducible cell-specific responses to stress and inflammation, by generating macrophage-specific chromatin domain modifications. The fourth category includes metabolic sensors of the nuclear receptor family, such as peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXR), activated respectively by fatty acids and cholesterol metabolites (Glass and Saijo, 2010). These ligand-dependent transcription factors are anti-inflammatory and link metabolism and tissue inflammation.

Recent findings have uncovered a general view of the various regulatory mechanisms establishing differential gene-specific patterns of primary and secondary gene expression after LPS stimulation in macrophages. These studies have determined the role of transcription factors, chromatin modifications and structure in gene regulation from transcription start sites and proximal promoter elements, or from enhancers, with microarray data generating genome-wide expression patterns, global chromatin immunoprecipitation experiments (ChIP-on-ChIP), real-time PCR analysis and massively parallel sequencing.

	Macrophage IR	Acute Phase Response
signal	LPS	IL-1, IL-6, TNF
class I	NF-κB, IRF3, AP1	STAT3, NF-κB, AP1
class II	C/EBPδ, ATF3, AP1	C/EBPβ, C/EBPδ, AP1
class III	PU.1, C/EBPβ, RUNX1, BCL-6	HNF1, HNF4α, GATA4
class IV	PPARγ, LXR	PPARα, PPARδ, PPARγ, LXR, LRH1

Table 1. Transcription factors involved in macrophage inflammatory response (IR) or acute phase response according to their classes.

3. Stress sensor transcriptional regulatory networks control LPS/TLR4-dependent macrophage inflammatory responses

LPS-dependent macrophage-specific primary and secondary gene expression depends on regulatory networks implicating the transcription factors NF-κB, C/EBPδ and ATF3, a

member of the CREB/ATF family of transcription factors (Gilchrist et al., 2006; Litvak et al., 2009) (Figure 1). Indeed, transcriptomic analysis has defined clusters of early, intermediate and late patterns of gene expression in response to LPS. Included in the early phase cluster is ATF3. Promoter analysis has uncovered the juxtaposition of NF-κB and ATF3 DNA-binding sites, in a subset of promoters, including Il6 and Nos2. Chromatin immunoprecipitation experiments have shown that LPS-induced chromatin acetylation allows NF-κB recruitment at the Il6 promoter, and subsequent activation. ATF3 then binds to the promoter, and by recruiting histone deacetylase activities, inhibits transcription. Thus, ATF3 acts as a transcriptional repressor in a NF-κB-dependent negative feedback loop. The same group observed that LPS induced C/EBPδ promoter NF-κB binding after 1 hour, and ATF3 binding after four hours. Chromatin immunoprecipitation experiments showed that C/EBPδ and ATF3 bound the Il6 promoter later than NF-κB. Mathematical modeling of this regulatory network indicated that, while NF-κB initiates and ATF3 attenuates C/EBPδ and Il6 expression, C/EBPδ synergizes only with NF-κB to insure maximal Il6 transcription. This transcriptional network may be maintained by C/EBPδ's ability to induce its own expression by autoregulation. It has been proposed that C/EBPδ acts as an amplifier of the LPS response, distinguishing transient from persistent TLR4 signals and enabling the innate immune system to detect the duration of the inflammatory response. Thus, regulatory networks implicating combinatorial gene controls with subsets of transcription factors, such as C/EBPδ and ATF3, specify the proper NF-κB regulatory yield to unique gene subsets.

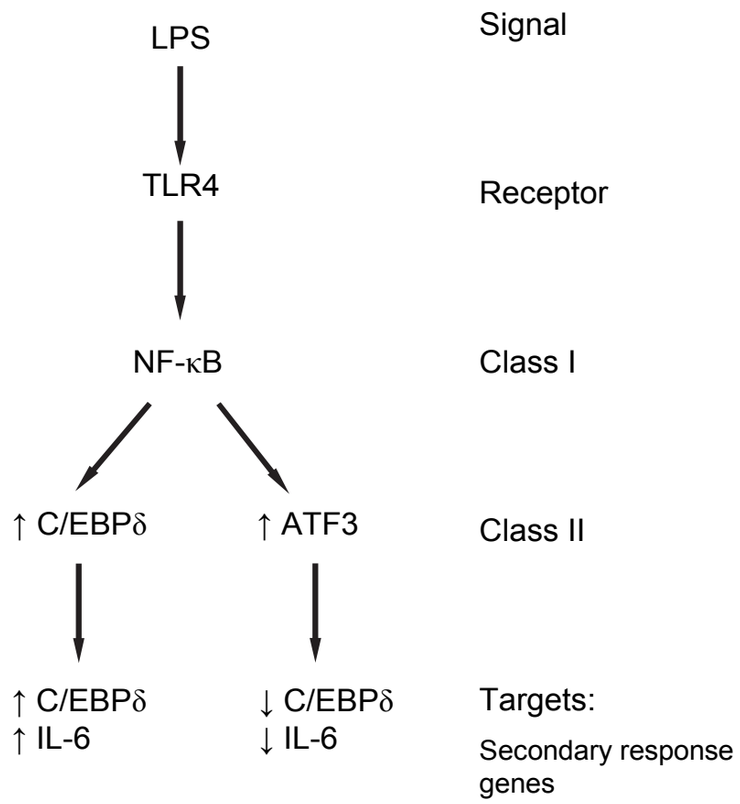


Fig. 1. Transcriptional network regulating LPS/TLR4-dependent secondary gene expression.

4. Distinct proximal promoter elements and chromatin modifications regulate LPS/TLR4-dependent macrophage inflammatory responses

Promoter, as well as chromatin structure, differentiates LPS-dependent macrophage-specific primary and secondary gene expression. Inflammatory gene expression has been divided in three classes, namely early primary, late primary and secondary response genes, depending on expression kinetics, the secondary gene expression being dependent on new protein synthesis. Ramirez-Carrozzi et al. (2006) have shown different chromatin remodeling requirements between these three classes. Both ATP-dependent remodeling complexes SWI/SNF and Mi-2/NURD were involved. SWI/SNF contains ATPase subunits BRG1 or BRM, and the Mi-2/NURD complex contains the Mi-2α or Mi-2β ATPase subunit associated with histone deacetylases, among others (Hargreaves and Crabtree, 2011). While constitutively associated BRG1 and Mi-2β complexes correlate with primary response gene accessible chromatin structure, both BRG1 and Mi-2β-containing complexes are recruited in an LPS-dependent manner to late primary and secondary gene promoters. As opposed to primary gene activation, secondary gene expression requires BRG1/BRM-containing SWI/SNF complexes for activation. In addition, Mi-2β recruitment depends on prior chromatin remodeling by SWI/SNF. While SWI/SNF-dependent remodeling positively regulates secondary gene expression, Mi-2β-mediated chromatin alterations inhibit late primary as well as secondary gene LPS-dependent induction.

These data suggest that basic promoter element signatures may be differently decoded in order to establish contrasting chromatin remodeling requirements. Indeed, genome-wide analysis has uncovered two promoter classes based on normalized CpG dinucleotide content between observed and expected ratios (Saxonov et al., 2006). While CpG is underrepresented in the genome, CpG islands, originally discovered in housekeeping gene promoters, occur at or near transcription start sites. Indeed, 72% of human gene promoters are characterized with high CpG concentrations, and 28% with low CpG content. In unstimulated cells, one class of primary response genes is characterized by CpG-island promoters and SWI/SNF independence, with constitutively active chromatin demonstrating reduced histone H3 levels, but high basal levels of acetylated H3K9/K14 (H3K9ac, H3K14ac) and trimethylated H3K4 (H3K4me3) positive regulatory marks and increased presence of RNA polymerase II and TATA-binding protein (Ramirez-Carrozzi et al., 2009). It is proposed that nucleosome destabilization on CpG-island promoters could result from the binding of transcription factors, such as the GC-rich DNA-binding Sp1 transcription factor (Wierstra, 2008). Thus, high CpG-containing promoters display reduced nucleosome stability that favor increased basal chromatin availability and facilitate further induction. Indeed, these genes are favored targets of TNFα-mediated induction. A subset of non-CpG primary response genes and secondary response genes are characterized by low CpG content in their promoter. Non-CpG primary response gene promoters form stable nucleosomes and require for their induction, recruitment of SWI-SNF activity and IRF3 activation through TLR4 signaling. These promoters, as well as secondary response gene promoters, are not associated with active chromatin or RNA polymerase II before induction. Thus, the correlation between CpG content of primary and secondary response gene promoters with basal levels of RNA polymerase II, as well as H3K4me3 and H3ac modifications, suggests that chromatin's transcriptional potential may depend in part on variations of CpG proportions. In addition, promoter structure may preferentially target gene expression to specific signaling pathways. Of note, two acute-phase protein genes,

namely Lcn2 and Saa3, display properties of non-CpG island promoters, with SWI/SNF-dependent LPS activation (Ramirez-Carrozzi et al., 2009).

While the transcriptional initiation phase depends on Ser5 TFIIH-dependent phosphorylation of the C-terminal domain (CTD) of the recruited polymerase, the elongation phase occurs after Ser2 phosphorylation by the P-TEFb cyclin T1/cdk9 complex (Sims et al., 2004). Short RNAs are produced by the initiating RNA polymerase II because of transcriptional pausing before elongation (Fuda et al., 2009). Hargreaves et al. (2009) have determined the transcriptional state of RNA polymerase II complexes recruited to primary response gene promoters. Indeed, at the basal state, there is enrichment for the Ser5-phosphorylated form of RNA polymerase II associated with transcriptional initiation (Sims et al., 2004). The Ser2-phosphorylated form, associated with transcriptional elongation, is only induced after LPS stimulation and recruitment of the Ser2 P-TEFb phosphorylation complex (Hargreaves et al., 2009). Basal RNA polymerase II recruitment is insured by the Sp1 transcription factor which binds GC-rich DNA elements more frequently found in GC-rich promoter sequences (Li and Davie, 2010). Interestingly, only full-length unspliced precursor transcripts are detected at the basal state, suggesting that the RNA polymerase II Ser5-phosphorylated form is competent for full transcription, but not for RNA processing. Thus, continuous basal primary response gene expression insures a permissive chromatin environment. LPS stimulation leads to recruitment of the Brd4 bromodomain-containing protein and its interacting P-TEFb partner (Yang et al., 2005), through binding to co-activator PCAF- or GCN5-generated H4K5/K8/K12 acetylated marks. This results in Ser2 RNA polymerase II phosphorylation and productive transcriptional processing. In addition to Brd4/P-TEFb, NF-κB, while not implicated in transcriptional events related to initiation, is required for effective elongation of primary response gene transcripts. Basal expression of primary response genes is further regulated by HDAC-containing co-repressor complexes NCoR and CoREST (Cunliffe, 2008). Indeed, NCoR, CoREST, HDAC1 and HDAC3 are present at the basal state, and keep H4K5/K8/K12 in an unacetylated state, therefore inhibiting P-TEFb recruitment and subsequent productive elongation. Upon LPS stimulation, co-repressors are removed. NF-κB p50/p50 dimers, which do not transactivate, are present on primary response gene promoters, in the absence of the NF-κB p65 transactivating partner, and may assure a H4K5/K8/K12 unacetylated state by recruiting co-repressor complexes at non-induced promoters (Hargreaves et al., 2009). Thus, primed CpG-rich primary response genes, with basal active chromatin, Sp1 and co-repressor recruitment, among others, are ubiquitously regulated by multiple signals. In contrast, GC-poor primary and secondary response genes require further chromatin modifications, including SWI/SNF-dependent remodeling, to insure inflammatory gene expression. A summary of the different modifications associated with inflammatory primary response genes is presented in Table 2.

5. Distal enhancer elements and chromatin modifications differentially regulate LPS/TLR4-dependent macrophage inflammatory responses

In addition to proximal sequences, distal elements, such as enhancers, are important to establish proper inflammatory gene-specific and cell-specific regulation. Enhancer-specific signature elements, namely high levels of the H3K4 monomethylated mark as opposed to the trimethylated mark (Heintzman et al., 2007), and bound acetyltransferase coregulator p300, have allowed genome-wide enhancer identification (Heintzman et al., 2009; Visel et

		primary response gene protein synthesis not required SWI/SNF independent GC rich promoters	
		- LPS	+ LPS
Chromatin modification	H3K9Ac	+	+
	H3K4me3	+	+
	H4K5/K8/K12Ac		+
Transcription factors	Sp1	+	+
	NF-κB		+
	C/EBPβ	+	+
Coactivator	p300/CBP	+	+
	PCAF/Gcn5		+
Corepressor	HDAC1	+	
	HDAC3	+	
	NCoR	+	
	CoREST	+	
Pol II phosphorylated	ser 5	+	+
	ser 2		+
Elongation regulator	P-TEFb		+
	Brd 4		+
Pol II status	Initiation/paused	+	
	elongating		+
Transcripts	full lenght unspliced	+	
	mature processed		+
SWI/SNF remodeling complexes	Mi2-beta (CHD4)	+	+
	BRG	+	+

+ indicates high levels detected on promoters, based on Hargreaves et al. (2009) and Ramirez-Carrozzi et al. (2006).

Table 2. Basal and LPS-induced chromatin modifications of primary response gene promoters.

al., 2009). Ghisletti et al. (2010) have used LPS-stimulated p300 chromatin binding in order to isolate and characterize enhancer regions, in macrophages, by chromatin immunoprecipitation experiments followed by high-throughput sequencing (ChIP-seq). Enhancers are associated with known LPS-induced primary and secondary response genes, among others. While binding site motifs for inflammatory transcription factors such as NF-κB, AP-1 and IRFs are enriched in these inflammatory enhancers, the most enriched transcription factor is PU.1, a cell-lineage-restricted transcription factor required for macrophage differentiation (Friedman, 2007). Enhancer elements are characterized by constitutive PU.1 binding, nucleosome depletion, high H3K4me1, low H3K4me3 and LPS-

inducible p300 and NF-κB recruitment (Ghisletti et al., 2010). Nucleosome alterations as well as positioning of the H3K4me1 modification require PU.1 recruitment to the enhancers (Heinz et al., 2010). Thus, PU.1 binding in collaboration with other cell-lineage transcription factors such as C/EBPβ, primes and marks cell-specific regulatory enhancer elements. The PU.1 macrophage-specific transcription factor targets not only cell-specific enhancers, but also inducible enhancers, in order to insure cell- and signal-specific regulation of the inflammatory response by ubiquitous stress sensors, such as NF-κB and IRFs, or by metabolic sensors, such as liver X receptors (LXR). Indeed, enhancer-specific binding of these oxysterol-inducible nuclear receptors (Rigamonti et al., 2008) requires PU.1-mediated enhancer recognition and modification as well (Heinz et al., 2010). Similar ChIP-seq experiments have uncovered B-cell lymphoma 6 (Bcl-6) as a negative regulator of TLR4/NF-κB activation of the inflammatory response in macrophages. Indeed, in addition to PU.1, both NF-κB and Bcl-6 DNA-binding sites co-localize in a large subset of LPS-inducible enhancers. Bcl-6, through HDAC3 recruitment and histone deacetylation, attenuates NF-κB- and p300 acetyltransferase-mediated transcriptional activation in response to LPS, in Bcl-6/NF-κB containing enhancers (Barish et al., 2010). Thus, lineage-specific transcription factors, through the establishment of enhancer-specific chromatin domains, allow the proper cell-specific reading of environmental and metabolic stimuli by ubiquitous transcription factors, including stress and metabolic sensors.

6. Metabolic sensors repress LPS/TLR4-dependent macrophage inflammatory responses

Co-repressor complexes negatively regulate the inflammatory response. The NCoR and SMRT co-repressors form complexes including the histone deacetylase HDAC3, transducin β-like 1 (TBL1) and TBL-related 1 (TBLR1) and G protein-pathway suppressor 2 (GPS2). The importance of NCoR in the regulation of the inflammatory response has been uncovered in NCoR-deficient macrophages displaying derepression of AP-1 and NF-κB regulated genes in response to inflammatory stimuli (Ogawa et al., 2004). NCoR and SMRT complexes are recruited to chromatin, where they establish repressive chromatin domains by mediating deacetylation of nucleosomal histones. NCoR and SMRT co-repressors do not interact directly with DNA. Recruitment of NCoR and SMRT complexes is insured by various transcription factors, including NF-κB and AP-1 subunits, ETS factors and nuclear receptors. Indeed, in addition to NF-κB p50, as discussed above, unphosphorylated c-Jun recruits NCoR while the Ets repressor TEL recruits SMRT (Ghisletti et al., 2009), thus guaranteeing specific recruitment to subsets of inflammatory gene promoters. NCoR and/or SMRT may be recruited not only to SWI/SNF-independent primary response gene promoters, such as Il1b, Tnf and Cxcl2, but also to SWI/SNF-dependent primary and secondary response gene promoters, such as Nos2, Ccl2 and Mmp13 (Hargreaves et al., 2009; Ghisletti et al., 2009). In order to achieve TLR4-dependent gene activation, NCoR and SMRT complexes must be removed and replaced by co-activators. A common nuclear receptor and signal-dependent transcription factor derepression pathway involves the activation of NCoR/SMRT subunits TBL1 and TBLR1, which act as recruiters of ubiquitin-conjugating enzymes, such as the UbcH5 E2 ligase. This leads to NCoR/SMRT ubiquitylation and ensuing disposal by the 19S proteasome complex (Ogawa et al., 2004; Perissi et al., 2004). Recent analysis of Nos2 activation by LPS in macrophages suggests that c-Jun phosphorylation is central to insure

NCoR promoter discharge (Huang et al., 2009). Indeed, LPS treatment leads to recruitment of NF-κB p65 to a NF-κB DNA-binding site near the AP-1 element. NF-κB p65 recruits the inhibitor of κB kinase IKKε (Nomura et al., 2000) which phosphorylates c-Jun and triggers NCoR removal (Huang et al., 2009). In addition to Nos2, other composite NF-κB- and AP-1-containing promoters are regulated by NF-κB p65/IKKε-dependent c-Jun phosphorylation, such as Cxcl2, Cxcl9, Cxcl10 and Ccl4 (Huang et al., 2009).

Peroxysome proliferator-activated receptors (PPARs) and liver X receptors ((LXRs) are nuclear receptors forming dimers with retinoid X receptors (RXRs). These metabolic sensors bind specific hormone responsive elements, and ligand binding leads to transcriptional activation (Glass and Saijo, 2010). In addition, PPARs and LXRs repress inflammatory gene expression by a mechanism of transrepression. Indeed, PPARγ and LXR ligands inhibit TLR4/LPS-mediated inflammatory gene expression by counteracting NCoR disposal. PPARγ agonists stimulate PPARγ sumoylation by the SUMO E3 ligase PIAS1, which adds SUMO1. Sumoylated PPARγ binds NCoR and inhibits NCoR removal normally induced in response to TLR4/LPS signaling (Pascual et al., 2005). Likewise, LXR agonists stimulate LXR sumoylation by HDAC4, which acts as a SUMO E3 ligase adding SUMO2/3. As for PPARγ, sumoylated LXRs bind NCoR and inhibit NCoR removal induced by TLR4/LPS signaling (Ghisletti et al., 2007). Thus, NCoR and SMRT complexes integrate both cell-extrinsic and –intrinsic signals, resulting in stress and metabolic activation or repression of specific inflammatory response gene expression programs.

7. The acute phase-response and acute phase proteins

Tissue injury, trauma or infection lead to complex and systemic reactions referred to as the acute-phase reaction (APR) (Epstein, 1999). The APR is part of a repertoire of cell responses to inflammation, characterized by increased or decreased plasma concentrations of acute phase proteins (APPs). These plasma proteins, mostly synthesized by the liver, participate in blood coagulation, maintenance of homeostasis, defense against infection, transport of nutrients, metabolite and hormone transport, among others. Marked changes in APP gene expression vary from 0.5-fold to 1000-fold, with either rapid or slow expression kinetics, and depend on signals generated at the site of injury or distributed via the bloodstream to remote sites. Indeed, cytokines produced locally or by circulating activated mononuclear cells in response to inflammatory stimuli elicit the diverse effects characteristic of the APR: regulating and amplifying the immune response, restoring homeostasis or inducing chronic tissue injury. Mediators of APP gene expression include pro-inflammatory cytokines such as IL-6, IL-1β and TNFα, glucocorticoids and growth factors. APPs are divided as positive and negative APPs, respectively increasing or decreasing during the APR. Positive APPs include CRP, HP, AGT, ORM, SAA, LBP, FBG, VTN, among others. ALB and TRR are examples of negative APPs (Epstein, 1999; Gruys et al., 2005; Khan and Khan, 2010).

Hepatocytes are considered as the primary cell type expressing APPs. However, APP production is induced after lipopolysaccharide- or cytokine-mediated systemic inflammation in other cell types, including intestinal epithelial cells, adipocytes, endothelial cells, fibroblasts and monocytes. Thus, local APP production may be important. Of note, APP expression is increased in various chronic inflammatory diseases, such as atherosclerosis (Packard and Libby, 2008). Obesity, through the formation of stressed fat tissue, contributes to both local and systemic inflammation by releasing pro-inflammatory

cytokines, such as TNFα and IL-1, and APPs, such as HP and CRP. These APPs are useful as inflammatory biomarkers for these conditions (Rocha and Libby, 2009).

Depending on their cytokine responsiveness, class I APPs are induced by IL-1β and IL-6, while class II APPs are expressed in response to IL-6. Pro-inflammatory signaling converges on APP gene regulatory regions, by activating various classes of transcription factors acting as stress sensors. The IL-1 pathway shares many signal transduction components with TLR pathways. IL-1 binding to the IL-1 receptor leads to the association of the IL-1 receptor accessory protein. This complex leads to MyD88 signaling through IRAK1/IRAK2/IRAK4 and TAK1 kinase activation, and subsequent activation of downstream signaling kinases, such as IKKs, MAPkinases ERK1/2, p38 and JNK, which affect NF-κB, AP-1 and C/EBP transcription factor activities (Weber et al., 2010). The IL-6 pathway is activated by IL-6 binding to the IL-6 receptor, followed by induced recruitment of gp130. This complex activates Janus kinase 1 (JAK1)/STAT3 and ERK1/2 kinase signaling pathways. JAK1-dependent STAT3 tyrosine phosphorylation leads to STAT3 dimerization, nuclear translocation and regulation of genes with STAT3-responsive promoter elements (Murray, 2007). ERK1/2 signaling activates AP-1, C/EBPβ and ELK1 that again, target specific promoter elements (Kamimura et al., 2003).

From a selected list of 28 human APPs (Epstein, 1999), we have found that 27 APP gene promoters displayed low CpG content, under normalized CpG values of 0.35, as assessed by Saxonov et al. (2006): CRP, HP, FGG, A2M, SAA1, ORM, TTR, FGG, CP, SERPINE1, SERPING1, SERPINA1, SERPINC1, SERPINA3, APCS, KNG1, LCN2, ALB, CFP, C3, TF, C9, IL1RN, CSF3, MBL2, IGF1, VTN. This observation suggests that most APP genes may be considered as late primary or secondary response genes, that RNA polymerase II pre-loading, as found for primary response genes, may not be the norm, and that chromatin modifications including remodeling, may be important for APP gene induction during the APR.

In the next section, we will review some examples of APP gene regulation mostly in hepatocytes. We will discuss the role of Class I constitutively expressed (NF-κB, STAT3) and Class II regulated (C/EBP, AP-1) stress-induced transcription factors, as well as tissue-restricted and cell lineage-specific Class III transcription factors (GATA4, HNF-1α, HNF4α) and Class IV metabolic sensors (PPARs, LXR) (Table 1).

8. Stress sensors and APP gene regulation

8.1 CRP promoter structure and APP gene regulation

Plasma C-reactive protein levels (CRP) are induced more than 1000-fold in response to APR (Mortensen, 2001). Human CRP synergistic induction in response to IL-1β and IL-6 depends on a combination of transcription factors, including STAT3, C/EBP family members and NF-κB. The proximal 300 bp promoter element binds C/EBPβ and C/EBPδ at two sites. The more proximal site is a composite C/EBP site with a non-consensus NF-κB site. While C/EBPβ binding in vitro is not efficient, NF-κB p50 binds to the non-consensus NF-κB site, increases C/EBPβ binding and transcriptional activation by cytokines (Cha-Molstad et al., 2000; Agrawal et al., 2001; Agrawal et al., 2003a; Agrawal et al., 2003b; Cha-Molstad et al., 2007). This site is essential for CRP expression. In the absence of C/EBPβ, this element is bound by a negative regulator of C/EBP activities, namely C/EBPζ (Oyadomari and Mori, 2004), and by RBP-Jκ, a transcriptional repressor of Notch signaling (Sanalkumar et al., 2010), which insures C/EBPζ binding to the C/EBP site (Singh et al., 2007). Cytokine

stimulation leads to a replacement of the repressor complex by the p50/C/EBP positive regulatory complex. An upstream element consisting of an overlapping NF-κB/OCT-1 DNA-binding site has also been uncovered (Voleti and Agrawal, 2005). OCT-1 binding is increased in response to transient NF-κB p50-p50 dimer levels, resulting in CRP repression. Cytokine stimulation leads to a switch to NF-κB p50-p65 dimers which replace OCT-1, and in conjunction with C/EBPs, mediate CRP transcriptional activation. Chromatin immunoprecipitation (ChIP) assays show that cytokine treatment increases binding of C/EBPβ, STAT3, NF-κB p50, c-Rel and TBP to the CRP promoter, while low levels of these transcription factors are present on the unstimulated CRP promoter (Young et al., 2008). C/EBPβ recruitment appeared after 2 hours, in contrast to later induced recruitment for STAT3 and NF-κB p50. Of note, no expression of CRP was observed in basal conditions, suggesting that pre-bound transcription factors are not sufficient to insure basal transcription. Thus, APP regulation depends on the promoter structure, which acts as a platform characterized by specific transcription factor DNA-binding site arrangements, allowing the exact response to inflammatory stimuli.

8.2 STAT3 and APP gene regulation

STAT3 is the major class I stress sensor induced in response to IL-6. STAT3 mouse knockout results in decreased inducible expression of APP genes, including serum amyloid A (SAA) and γ-fibrinogen (γ-FBG) (Alonzi et al., 2001). STAT3 transcriptional activity is regulated by posttranscriptional modifications altering STAT3 localization and interactions with co-activators or co-repressors. Recent data have uncovered the role of STAT3 in the regulation of APP expression. IL-6 is a major regulator of the acute-phase protein γ-FBG (Duan and Simpson-Haidaris, 2003, 2006). Hou et al. (2007) have found that IL-6-inducible γ-FBG expression mediated by STAT3 involves the formation of a stable enhanceosome including STAT3, p300, and phosphorylation of RNA polymerase II on Ser2 of the C-terminal domain. The γ-FBG promoter contains three IL-6 response elements. IL-6-induced Tyr-phosphorylated and acetylated nuclear STAT3 interacts with the TEFb complex composed of CDK9 and cyclin T1, as determined by co-immunoprecipitation. Although the STAT3 N-terminal region is sufficient for TEFb complex formation, both N- and C-terminal domains participate in complex formation. CDK9 silencing decreases IL-6-induced γ-FBG expression. In addition, ChIP experiments show that STAT3, CDK9, RNA polymerase II and its phosphorylated form are recruited rapidly to the γ-FBG promoter. Inhibition of CDK9 activity reduces both basal and IL-6-inducible phosphoSer2 CTD RNA polymerase II formation. Thus, activated STAT3 interacts with TEFb, and recruits TEFb to the γ-FBG promoter. TEFb phosphorylates recruited RNA polymerase II, and renders RNA polymerase II competent for transcriptional elongation. In addition, the p300 bromodomain mediates p300 interaction with the acetylated STAT3 N-terminal domain. This strengthened interaction between p300 and acetylSTAT3, stimulated by IL-6, further stabilizes the recruitment of other transcription factors, including RNA polymerase II, to insure correct initiation and elongation (Hou et al., 2008). Thus, STAT3 induces APP gene regulation, in part by recruiting competent RNA polymerase II forms for transcriptional initiation and elongation,

IL-6-mediated angiotensinogen (AGT) gene expression in hepatocytes is regulated by IL-6 at the transcriptional level (Brasier et al., 1999). The proximal AGT promoter contains distinct elements binding STAT3 (Sherman and Brasier, 2001). Using an acetyl-lysine antibody, it was found that IL-6 treatment of hepatocytes leads to STAT3 acetylation, and that the p300

acetyltransferase mediates this acetylation (Ray et al., 2005). Proteomic analysis uncovered STAT3 N-terminal lysines 49 and 87 as being acetylated. While mutation of STAT3 K49 and K87 does not alter IL-6-mediated STAT3 translocation, the double mutant acts as a dominant-negative inhibitor of endogenous STAT3 transactivation and AGT expression in response to IL-6. Mutation of the acetylated lysines, while not affecting DNA-binding ability, decreases STAT3 interaction with the p300 co-activator, thereby leading to decreased transcriptional activation. ChIP assays show that, at the basal state, the AGT promoter is occupied by unacetylated STAT3 and p300, and displays acetylated H3 modifications. Recruitment of STAT3 and its acetylated forms to the AGT promoter is increased after IL-6 treatment, correlating with a slight increase in p300 engagement. Induction of an APR in mice by LPS injection induces STAT3 acetylation in liver nuclear extracts. Treatment with the HDAC inhibitor Trichostatin A increases STAT3-dependent AGT expression in the absence of IL-6 (Ray et al., 2002). It was found by co-immunoprecipitation that histone deacetylase HDAC1, HDAC2, HDAC4 and HDAC5 interact with STAT3, and that HDAC overexpression inhibits IL-6 mediated AGT transcriptional activity. Thus, HDACs associate with STAT3 and inhibit IL-6 signaling and hepatic APR. While the HDAC1 C-terminal domain is necessary to repress IL-6-induced STAT3 signaling, the STAT3 N-acetylated domain is required for HDAC1 interaction. HDAC1 overexpression in hepatocytes reduces nuclear STAT3 amounts after IL-6 treatment while HDAC1 silencing increases STAT3 nuclear accumulation. HDAC1 knockdown augments IL-6 stimulated AGT expression. This suggests that HDAC1 may be required to insure proper STAT3 cytoplasmic-nuclear distribution and to restore non-induced expression levels after inflammation (Ray et al., 2008).

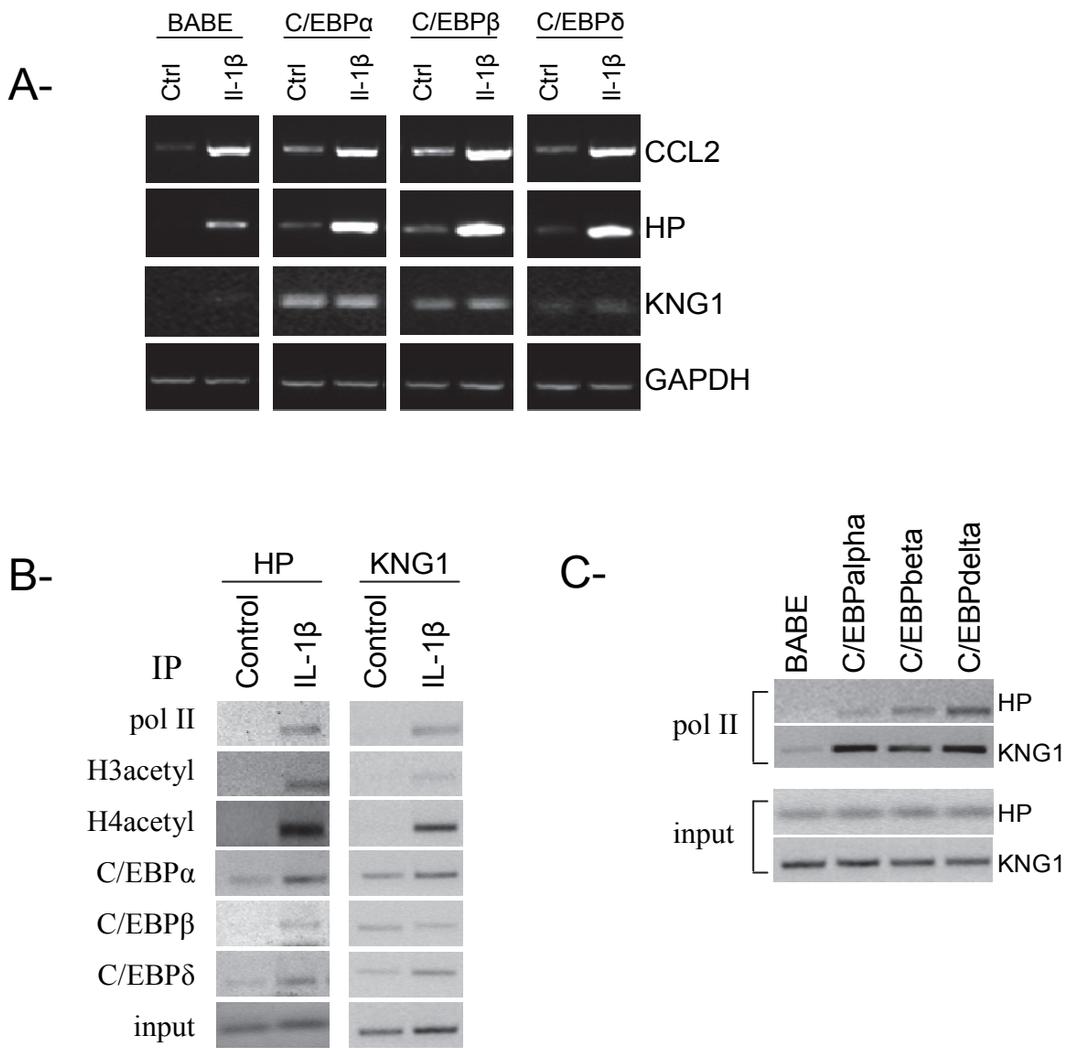
It has been recently shown that STAT3 activates apurinic/apyrimidinic endonuclease 1 (APE/Ref-1), involved in base-excision repair (Izumi et al., 2003). This activation may protect against Fas-induced liver injury (Haga et al., 2003). It was found that IL-6 induces a nuclear STAT3-APE1 complex (Ray et al., 2010). Indeed, co-immunoprecipitation studies show that APE1 interacts with the acetylated STAT3 N-terminus, leading to increased transactivation of the STAT3-containing AGT promoter, in response to IL-6. RNAi knockdown experiments show that APE1 enables IL-6-mediated STAT3 DNA-binding. APE1 knockdown in hepatocytes decreases CRP and SAA APP gene expression in response to IL-6. This is confirmed in APE1 heterozygous knockout mice in which liver LPS-induced expression of α-acid glycoprotein (ORM) is decreased. Finally, ChIP assays show that APE1 is important for γ-FBG promoter enhanceosome formation, as shown by a decrease in STAT3, p300 and phosphorylated RNA polymerase II when APE1 levels are decreased by shRNAs. Thus, APE1 may represent a novel co-activator of APP gene expression and APR, as p300 and TEF-b, through STAT3-mediated activation.

In addition to STAT3-mediated activation of APP genes, STAT3 synergizes with NF-κB to attain full APP gene expression. Indeed, although there is no consensus STAT3 DNA-binding in the SAA1 and SAA2 promoters, IL-1 and IL-6 stimulation of HepG2 cells leads to the formation of a complex between NF-κB p65 and STAT3, as assessed by co-immunoprecipitation. STAT3 interacts with a non-consensus STAT3 site in a NF-κB-STAT3 composite element (Hagihara et al., 2005). This synergistic element requires the co-activator p300. IL-1 and IL-6 treatment leads to NF-κB p65, STAT3 and p300 recruitment to the SAA1 promoter. Thus, protein interactions with members of different stress sensor categories are involved in mediating transcriptional synergy.

A2M is regulated by IL-6 through STAT3. STAT3 cooperates with the glucocorticoid receptor (GR) induced by dexamethasone (Dex) for full A2M induction in rat hepatocytes. While there is no GR DNA-binding site, the A2M proximal promoter contains DNA-binding sites for STAT3, AP-1 and OCT-1 (Zhang and Darnell, 2001). GR binds both STAT3 and c-Jun (Lerner et al., 2003). IL-6 and Dex synergize for full transcriptional activation. Double immunoprecipitation ChIP assays have been used to assess the sequential recruitment of transcription factors to the A2M promoter and their role in enhanceosome formation. At the basal state, both OCT-1 and c-Jun are constitutively bound. Dex-activated GR is first recruited by c-Jun interaction. Then, IL-6 dependent STAT3 is recruited, leading to histone acetylation and RNA polymerase II recruitment, rendering the gene transcriptionnally active. While IL-6 signaling alone, through STAT3 recruitment is sufficient to insure RNA polymerase II recruitment and low levels of A2M expression, both IL-6 and Dex are more effective to recruit RNA polymerase II and achieve maximal transcription.

8.3 C/EBPs and APP gene regulation in intestinal epithelial cells

C/EBP isoforms regulate APP gene expression in intestinal epithelial cells (IEC). Indeed, APP transcriptional response to glucocorticoids, cAMP, TGFβ and IL-1β is mediated in part by C/EBP isoforms (Boudreau et al., 1998; Pelletier et al., 1998; Yu et al., 1999; Désilets et al., 2000). C/EBP isoform overexpression increases IL-1β-mediated induction of the APP gene haptoglobin (HP), and C/EBPs are the major regulator of HP expression in IEC (Gheorghiu er al., 2001). We have found that a functional interaction between C/EBPδ and the p300 co-activator is necessary for HP IL-1β-mediated transactivation (Svotelis et al., 2005). In addition, we have shown that C/EBPδ interacts with HDAC1 and HDAC3. HDAC1 interaction necessitates both N-terminal transactivation and C-terminal DNA-binding domain. HDAC1 represses C/EBPδ-dependent HP transactivation. ChIP assays show that, at the basal state, the HP promoter is characterized by the presence of HDAC1, with low levels of C/EBPβ and C/EBPδ. HDAC1 recruitment is inhibited by IL-1β, and this correlates with increased occupation by C/EBPβ and C/EBPδ, and increased H3 and H4 acetylation (Turgeon et al., 2008). To determine whether C/EBP isoforms are sufficient to establish a proper chromatin environment for transcription, we have studied HP and T-kininogen (KNG1) expression in IECs. IL-1β treatment leads to late HP and KNG1 expression, as assessed by semi-quantitative RT-PCR after 24 h (Fig. 2A). Kinetics of expression suggests that both HP and KNG1 are secondary response genes (Désilets et al., 2000; Turgeon et al., 2008; Rousseau et al., 2008). C/EBP isoform overexpression increases both basal and IL-1β-mediated HP and KNG1 expression (Figure 2A). ChIP experiments show that HP and KNG1 promoter sequences in non-stimulated control cells are not associated with RNA polymerase II binding or H3/H4 acetylation, but with low levels of C/EBP isoforms. In contrast, IL-1β treatment leads to increased RNA polymerase II and C/EBP isoform recruitment after 4 hours, correlating with increased H3/H4 acetylation (Figure 2B). In the absence of IL-1β, C/EBP isoform overexpression is sufficient to induce RNA polymerase II recruitment to both promoters (Figure 2C). This suggests that C/EBP isoform overexpression leads to chromatin changes compatible with RNA polymerase II recruitment and transcriptional activity. Whether recruitment of co-activators, such as p300 and CBP (Kovacs et al., 2003; Svotelis et al., 2005), and/or of remodeling SWI/SNF complexes (Kowenz-Leutz et al., 2010) are required, needs to be addressed. Thus, C/EBPs are a major regulator of APP inflammatory secondary responses in IECs.



A) Rat intestinal epithelial IEC-6 cells stably transfected with C/EBP isoforms α, β and δ were treated for 24 h with IL-1β. Expression levels of APP genes Chemokine ligand 2 (CCL2), Haptoglobin (HP) and T-Kininogen 1 (KNG1) were evaluated by semi-quantitative RT-PCR. HP and KNG1 proximal promoter modifications were assessed by chromatin immunoprecipitation with IEC-6 cells treated for 4 h with IL-1β (B) or with IEC-6 cells stably transfected with C/EBP isoforms α, β and δ (C).

Fig. 2. Regulation of APP gene expression by C/EBP isoforms involves chromatin remodeling.

9. Cell lineage-specific transcription factors and APP gene regulation

9.1 HNF-1α and APP gene regulation

Liver-specific gene expression is regulated by tissue-restricted transcription factors, including hepatocyte nuclear factor 1 (HNF-1α and HNF-1β) and hepatocyte nuclear factor 4α (HNF4α) (Nagaki and Moriwaki, 2008). The POU homeodomain-containing transcription factor HNF-1α regulates bile acid, cholesterol and lipoprotein metabolism as well as glucose

and fatty acid metabolism (Shih et al., 2001; Armendariz and Krauss, 2009). In addition, HNF-1α activates numerous APP genes, including SERPINA1, ALB, TRR, CRP, FBG, LBP and VTN. Indeed, expression of these APP genes is reduced in HNF-1α knockout mice (Armendariz and Krauss, 2009).

CRP proximal promoter binds the HNF-1α transcription factor. While HNF-1α is required but not sufficient for CRP expression (Toniatti et al., 1990), HNF-1α, along with a complex composed of STAT3 and c-Fos, regulates cytokine-dependent CRP expression synergistically (Nishikawa et al., 2008). Indeed, c-Fos is recruited to the CRP promoter in the late induction phase of IL-1β and IL-6 stimulation. Since there is no AP-1 site found on the CRP promoter, it is proposed that c-Fos may bridge STAT3 and HNF-1α transcription factors bound to their respective site. A similar interaction between HNF-1α, IL-6-induced STAT3 and AP-1 regulates the expression of the HNF-1α-regulated APP gene α-FBG (Hu et al., 1995; Leu et al., 2001). Interestingly, unlike the CRP promoter which contains a STAT3 DNA-binding element, STAT3 does not bind the α-FBG proximal promoter (Liu and Fuller, 1995), suggesting that HNF-1α may act as a STAT3 recruiter. HNF-1α plays also an important role in IL-6-induced AGT expression (Jain et al., 2007). Of the three putative STAT3 DNA-binding sites identified (Sherman and Brasier, 2001), the most proximal site indeed binds STAT3, and when mutated, decreases IL-6-mediated AGT transactivation, while a secondary STAT3 DNA-binding site binds HNF-1α instead. ChIP assays indicate that, indeed, HNF-1α occupies the AGT promoter and that IL-6 treatment increases HNF-1α recruitment. While HNF-1α positively regulates AGT expression in the absence of IL-6, mutation of the HNF-1α DNA-binding site reduces IL-6 induced promoter activity. STAT3 or HNF-1α reduction by siRNAs inhibits AGT promoter activity as well as AGT endogenous protein levels. These results suggest that, in addition to the STAT3 DNA-binding site, the HNF-1α DNA-binding site acts as an IL-6 inducible element, playing an important role in both basal as well as IL-6 induced AGT expression.

9.2 HNF4α and APP gene regulation

The nuclear hormone receptor HNF4α is one of the major modulator of hepatocyte differentiation and regulates the expression of a number of liver-specific transcription factors, including C/EBPs and HNF-1α (Nagaki and Moriwaki, 2008). HNF4α regulates APP gene targets. Indeed, basal human AGT expression is regulated by HNF4α through two responsive sites (Yanai et al., 1999; Oishi et al., 2010). In addition, the HNF4α-regulated TTR and SERPINA1 genes are respectively downregulated and upregulated in response to cytokines (Wang and Burke, 2007). HNF4α DNA-binding activity decreases following cytokine IL-1β, IL-6 and TNFα treatment, leading to decreased HNF4α-dependent transcriptional activation (Li et al., 2002). In addition, ChIP assays demonstrate diminished HNF4α recruitment to the TTR promoter in response to cytokines, and a lesser decrease at the SERPINA1 promoter. HNF4α knockdown with shRNAs reduces SERPINA1 and TTR basal mRNA levels, and cancels the cytokine-dependent increase or decrease of SERPINA1 and TTR expression respectively. This is specific for HNF4α-regulated APP genes since cytokine-dependent expression of SAA, which is devoid of an HNF4α DNA-binding site, is not altered. It is proposed that cytokine-induced phosphorylation of HNF4α modulates HNF4α DNA-binding ability.

Recruitment of the peroxysome-proliferator-activated receptor-γ co-activator 1α (PGC-1α) may be important to modulate the action of HNF4α. In contrast to the p300 co-activator,

PGC-1α increases the HNF4α-dependent transactivation of TTR and SERPINA1, while HNF4α silencing impairs PGC-1α co-activation (Wang and Burke, 2008). Interestingly, PGC-1α overexpression cancels cytokine-mediated HNF4α DNA-binding capacity. ChIP assays indicate that, as for HNF4α, cytokine treatment reduces PGC-1α recruitment. Thus, HNF4α may control a subset of APP genes in response to inflammatory stimuli.

The TTR proximal promoter contains, in addition to HNF4α, DNA-binding sites for tissue-restricted transcription factors HNF-1α and HNF-3/HNF-6 (Wang and Burke, 2010). Mutation of the HNF4α DNA-binding site decreases the TTR transcriptional response induced not only by HNF4α, but also by HNF-1α and HNF-6. Mutation of the respective HNF DNA-binding sites reduces their specific binding, without affecting other HNF binding in vitro. However, cytokine treatment decreases HNF4α, but also HNF-1α and HNF-6 recruitment to the TTR proximal promoter, as assessed by ChIP assays. This indicates that HNF4α may serve as an interacting element organizing interactions between HNFs, to insure basal expression levels.

HNF4α may also regulate the inflammatory response in liver by regulating tissue-restricted transcription factors involved in inflammation. One of these transcription factors is CREB3L3 (CREBH). CREB3L3 is a membrane-bound transcription factor related to ATF6, an endoplasmic reticulum (ER) transmembrane transcription factor normally retained in the ER through interaction with the BIP/GRP78 chaperone, but released and cleaved after accumulation of misfolded proteins. Activated ATF6 then induces the expression of unfolded protein response (UPR) genes, to insure homeostasis (Inagi, 2010). CREB3L3 is a liver-specific bZIP-containing transcription factor of the cyclic-AMP response element binding protein (CREB/ATF) family. ER stress induces a cleaved form of CREB3L3 that translocates to the nucleus and mediates UPR gene expression in response to ER stress. Interestingly, CREB3L3 knockdown in mice reduces the expression of APP genes, such as CRP, serum amyloid P (SAP) and SAA3. In addition, serum SAP and CRP levels are reduced in IL-6/IL-1β or LPS stimulated CREB3L3 knockout mice, as compared to wild-type mice. Pro-inflammatory cytokines and LPS induce CREB3L3 cleavage during APR activation. CREB3L3 and ATF6 form heterodimers and synergistically activate the expression of target genes, including a subset of APR genes, in response to ER stress. Indeed, CREB3L3 responsive elements have been found in the CRP and SAP promoter regions (Zhang et al., 2006). One major regulator of CREB3L3 expression is HNF4α. Indeed, CREB3L3 is a direct target of HNF4α transcriptional activity, and HNF4α binds the CREB3L3 promoter, as determined by ChIP assays. While mice with liver CREB3L3 targeted deletion do not show hepatocyte differentiation defects, loss of CREB3L3 results in reduced expression of APP genes induced by tunicamycin, an UPR inducer. Thus, CREB3L3 controls APP gene expression induced by ER stress. In addition, a cell-lineage specific transcription factor, namely HNF4α, may link both APR and ER stress response, by insuring liver-specific CREB3L3 expression (Luebke-Wheeler et al., 2008).

9.3 GATA4 and APP gene regulation

GATA4 is a zinc-finger-containing transcription factor whose expression is restricted to certain tissues, such as heart and intestine (Viger et al., 2008). IEC-expressed GATA4 is required to maintain proximal-to-distal identities along the gastrointestinal tract (Bosse et al., 2006). We have found that IEC-restricted GATA4 modulates C/EBP-dependent transcriptional activation of APP genes (Rousseau et al., 2008). Indeed, GATA4 represses

C/EBP isoform activation of the KNG1 and HP promoters. GATA4 interacts with the C/EBPδ C-terminal DNA-binding domain. GATA4 overexpression leads to decreases in C/EBPβ and C/EBPδ basal as well as IL-1β-induced protein levels. This results in decreased IL-1β-dependent induction of KNG1. This correlates with decreased IL-1β-dependent C/EBPδ recruitment and H4 acetylation, as assessed by ChIP assays. Thus, the lineage-specific transcription factor GATA4 may insure specific regulation of APP genes in IECs.

10. Metabolic sensors and APP gene regulation

Nuclear receptors have been shown to play a regulatory role in APP gene expression. For example, the nuclear receptor liver receptor homolog 1 (LRH-1) regulates bile acid biosynthesis and cholesterol homeostasis (Fayard et al., 2004). LRH-1 inhibits IL-1β- and IL-6-mediated induction of the APP genes HP, SAA, FBG and CRP. LRH-1 negatively regulates specifically C/EBP activation by IL-1β and IL-6, without affecting STAT3 and NF-κB transactivation. Indeed, mutation of the HP C/EBP DNA-binding site decreases basal expression levels, as well as IL-1β and IL-6 induction levels, and abolishes LRH-1 negative repression. LRH-1 reduces C/EBPβ DNA-binding capacity. Increased LPS-stimulated APP plasma gene concentrations are reduced in heterozygous LRH-1 mice, as compared to wild-type mice. These results indicate that LRH-1 regulates the hepatic APR at least in part by down-regulating C/EBP-mediated transcriptional activation (Venteclef et al., 2006).

The oxysterol receptors LXRα and LXRβ play similar roles in CRP regulation in hepatocytes (Blaschke et al., 2006). Indeed, LXR agonists inhibit IL-1β and IL-6-mediated CRP induction. A portion of the promoter including a C/EBP DNA-binding site is necessary. The N-CoR co-repressor complex, with the histone deacetylase HDAC3, is necessary to mediate LXR negative regulation. Indeed, ligand-activated LXR prevents cytokine-induced removal of N-CoR on the CRP promoter, as assessed by ChIP assays. In vivo, LXR agonists inhibit the LPS-induced hepatocyte APR, as assessed by reduction of CRP and SAP mRNA levels specifically in wild-type mice, as opposed to LXRα/LXRβ knockout mice. Thus, both LRH-1 and LXR nuclear hormone receptors regulate negatively APP gene expression in hepatocytes.

Recent data suggest that LXRβ is the main LXR subtype regulating APP gene expression (Venteclef et al., 2010). Ligand-activated LRH-1 and LXR inhibit HP, SAA and SERPINE1 expression by preventing NcoR complex removal. ChIP experiments indicate that components of the NcoR complex, but not of the SMRT co-repressor complex, are present on the non-stimulated HP promoter, namely HDAC3, GPS2 and TBLR1. HP transrepression is dependent on sumoylation of both LRH-1 and LXRβ receptors. Indeed, an increased hepatic APR is observed in SUMO-1 knockout mice. ChIP experiments have been done with liver extracts of control as well as LXR knockout mice treated with agonists before LPS induction. Results show that while N-CoR and GPS2 recruitment is decreased by LPS treatment, LXR agonists prevent N-CoR and GPS2 removal, and increase HDAC4, LXR and SUMO-2/3 recruitment to the HP promoter. In contrast, LRH-1 transrepression depends on SUMO-1. Thus, LRH-1 and LXR repress APP gene expression by ligand- and SUMO-dependent nuclear receptor interactions with N-CoR/GPS2-containing co-repressor complexes, resulting in inhibition of complex removal after cytokine induction. Ligand activation leads to increased SUMOylated nuclear receptors, either through stabilization of LRH-1 SUMOylated levels, or through induction of specific LXRβ SUMOylation. These modified

nuclear receptors interact with GPS2, associate with the N-CoR complex and prevent its disposal following the inflammatory response.
Another nuclear receptor, namely PPARδ, is involved in negative regulation of IL-6 mediated APR in hepatocytes (Kino et al., 2007). Indeed, treatment of liver cells with PPARδ agonists inhibits IL-6 induction of A2M, ORM, CRP, FBG and SERPINA3. PPARδ depletion by siRNAs, but not that of PPARα or PPARγ, attenuates agonist-dependent suppression. ChIP experiments suggest that PPARδ agonist treatment inhibits IL-6-dependent STAT3 recruitment to the SERPINA3 promoter. Thus, both C/EBP and STAT3 recruitment is altered by nuclear agonist treatment, respectively by LRH-1 (Venteclef et al., 2006) and PPARδ (Kino et al., 2007), explaining in part the nuclear receptor-dependent regulation of hepatocyte APP expression during the inflammatory response.

11. Conclusion

APP genes form a subset of inflammatory genes, with promoters associated with low CpG content, and rather late response expression patterns. Most APPs are considered late primary or secondary response genes. In response to stimulus from IL-1β and IL-6, among others, proximal promoters, with specific transcription factors, such as STAT3, AP-1 and C/EBPs, form an enhanceosome, through DNA-protein and protein-protein interactions. Tissue-restricted transcription factors, such as HNF-1α, HNF4α or GATA4 are involved in establishing proper tissue-specific inflammatory responses. Transcriptional activation depends on co-activator complexes with chromatin and transcription factor modifying activities, such as p300, and on chromatin remodeling complexes, such as SWI/SNF. Transcriptional repression depends on co-repressor complexes, like NCoR and SMRT complexes, with chromatin modifying activities as well. In addition, metabolic sensors, such as PPARs, LXRs and LRH-1, through the induction of post-translational modifications, such as sumoylation, may cancel APP induction by inflammatory signaling pathways. In contrast to primary response genes, much remains to be done to understand the mechanisms behind specific late primary and secondary APP gene regulation. Basal as well as signal-specific chromatin modifications (methylation and acetylation of various lysines on histones), RNA polymerase II status and presence of remodeling complexes remain to be determined. What is the temporal activation of these modifications during APR induction? How are these modifications established? How do tissue-specific transcription factors affect chromatin structure before and after the APR? What is the basis of the APR tissue-specific response? What is the promoter specificity of co-repressor complexes with HDAC3 activity (NCoR, SMRT) versus HDAC1/HDAC2 activity (NURD, CoREST)? What is the exact role of the various stress sensors in establishing proper chromatin structure? In addition to binding to proximal promoter sequences, do tissue-specific transcription factors, such as HNF-1α and HNF4α, mediate part of the inflammatory response through the establishment of enhancer-specific chromatin domains, like PU.1 in macrophages?

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13. References

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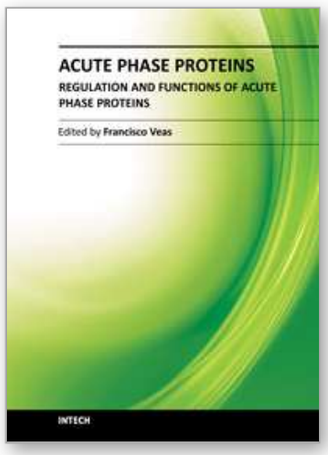
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