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## The Role of the Transcription Factor CREB in Immune Function

Andy Y. Wen,\* Kathleen M. Sakamoto,<sup>†</sup> and Lloyd S. Miller<sup>‡</sup>

CREB is a transcription factor that regulates diverse cellular responses, including proliferation, survival, and differentiation. CREB is induced by a variety of growth factors and inflammatory signals and subsequently mediates the transcription of genes containing a cAMP-responsive element. Several immune-related genes possess this cAMP-responsive element, including IL-2, IL-6, IL-10, and TNF- $\alpha$ . In addition, phosphorylated CREB has been proposed to directly inhibit NF- $\kappa$ B activation by blocking the binding of CREB binding protein to the NF- $\kappa$ B complex, thereby limiting proinflammatory responses. CREB also induces an antiapoptotic survival signal in monocytes and macrophages. In T and B cells, CREB activation promotes proliferation and survival and differentially regulates Th1, Th2, and Th17 responses. Finally, CREB activation is required for the generation and maintenance of regulatory T cells. This review summarizes current advances involving CREB in immune function—a role that is continually being defined. *The Journal of Immunology*, 2010, 185: 6413–6419.

CREB is a transcription factor that is known for its role in cell proliferation, differentiation, and survival (1–3). However, emerging evidence has revealed specific functions of CREB in immune responses, including inhibiting NF- $\kappa$ B activation, inducing macrophage survival, and promoting the proliferation, survival, and regulation of T and B lymphocytes. In this brief review, we summarize our understanding to date of how this key transcription factor plays a role in the regulation of immune responses.

### CREB

CREB is one of the best understood phosphorylation-dependent transcription factors (1–3). Several different serine-threonine kinases have been shown to promote phosphorylation of CREB

at its transcription activating site, serine 133, including 1) a cAMP-dependent protein kinase A (PKA); 2) protein kinase C (PKC; including PKC $\epsilon$ ); 3) calmodulin kinases (CaMKs; e.g., CaMK-IV) that respond to calcium fluxes from the extracellular environment or from intracellular calcium stores; and 4) pp90 ribosomal S6 kinase (pp90 RSK; also known as RSK2) (1–6). Once serine 133 of CREB is phosphorylated, CREB interacts with its coactivator protein, CREB-binding protein (CBP), or p300 to initiate transcription of CREB-responsive genes (1–3). CBP is a cofactor for many other transcription factors and helps to stimulate transcription by modulating chromatin through histone acetylation and recruiting factors required for RNA polymerization (1–3). CREB has been shown to be involved in a variety of cellular processes, including cell proliferation, survival, differentiation, adaptive responses, glucose homeostasis, spermatogenesis, circadian rhythms, and synaptic plasticity associated with memory (1–3). However, emerging evidence over the past decade has demonstrated that CREB plays an important role in immune responses.

### *The CREB family of transcription factors and their structural components*

The CREB family of transcription factors consists of cAMP-responsive activators in mammalian systems including CREB, cAMP response element modulator, and activating transcription factor 1 (1–3). The CREB family is composed of specific structural components characterized by a transactivation domain that consists of a kinase inducible domain (KID) and a constitutively active glutamine-rich domain (Q2) that synergize in response to cAMP stimulation (1–3). All CREB family members have a basic region leucine zipper dimerization domain located at the carboxy-terminal end, and they bind to DNA target sequences, such as the cAMP-responsive element (CRE), by dimerization through a leucine zipper (1–3). The target sequence CRE exists as both an eight-base-pair palindrome (5'-TGACGTCA-3') and also as a less active half-site motif (5'-CGTCA-3') (1–3). In addition, transducers of regulated CREB activity enhance CRE-dependent

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Abbreviations used in this paper: Bfl-1/A1, B cell lymphoma-2-related gene expressed in fetal liver-1/A1; CaMK, calmodulin kinase; CBP, CREB-binding protein; CRE, cAMP-responsive element; GSK-3 $\beta$ , glycogen synthase kinase-3 $\beta$ ; PAI-2, plasminogen activator inhibitor-2; PKA, protein kinase A; PKC, protein kinase C; pp90 RSK, pp90 ribosomal S6 kinase; PRR, pattern recognition receptor; Treg, regulatory T cell; TSDR, Treg-specific demethylated region.

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transcription by interacting with the transcription factor II D, which is a key general transcription factor that contains the TATA box binding protein (7). In 2004, a genome-wide analysis of rat PC12 cells (a cell line established from a rat pheochromocytoma that is a common cell type used for studies of CREB function) identified all genes that are targets of CREB, termed the *CREB regulon* (8). This analysis resulted in both the confirmation of known targets and the identification of additional targets of CREB that were grouped into the following categories: transcription factors, signaling molecules, neuron-associated molecules, metabolic factors, and factors involved in cell cycle and proliferation (8). These many and vastly different targets of CREB help to explain the numerous functional cellular processes that CREB has been shown to regulate. However, because this study was performed in a rat pheochromocytoma cell line, this list of CREB targets may not reflect the behavior of CREB in all cell types. Furthermore, CREB has been shown to induce transcription of immune-related genes that possess a CRE element, including IL-2, IL-6, IL-10, TNF- $\alpha$ , cyclooxygenase-2, and macrophage migration-inhibitory factor (2, 9, 10).

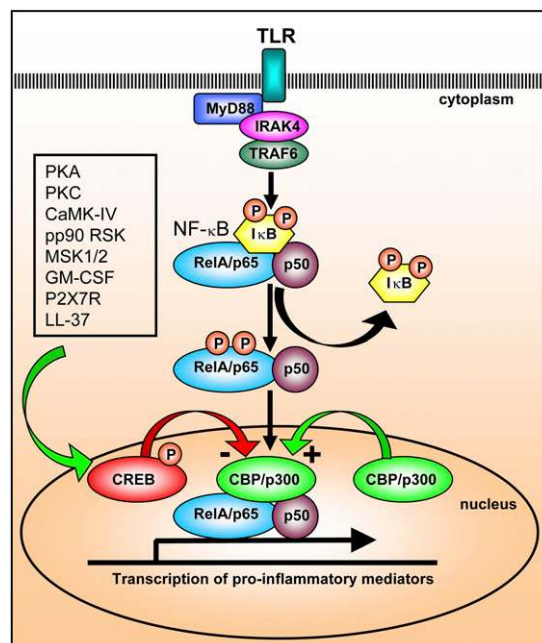
#### CREB and NF- $\kappa$ B signaling

The innate immune system uses various types of pattern recognition receptors (PRRs) to recognize components of bacteria, fungi, and viruses called *pathogen-associated molecular patterns* (11, 12). These PRRs include TLRs, nucleotide-binding oligomerization domain-like receptors, retinoic acid inducible gene I-like receptors, and C-type lectin receptors (11, 12). In particular, TLRs are PRRs that mediate cellular responses to lipopeptides (TLRs 1, 2, and 6), LPS (TLR4), flagellum (TLR5), and microbial RNA and DNA nucleotide sequences (TLRs 3, 7, 8, and 9) (11, 12). PRRs, including TLRs, initiate various signaling cascades that lead to the transcription of proinflammatory mediators that promote innate immune responses, including cytokines, chemokines, adhesion molecules, and antimicrobial peptides (11, 12). One critical pathway that is triggered by PRRs is the NF- $\kappa$ B pathway (13, 14). The NF- $\kappa$ B family of transcription factors includes RelA (p65), c-Rel, RelB, NF- $\kappa$ B1 (p50 and p105), and NF- $\kappa$ B2 (p52 and p100) (13, 14). RelA, c-Rel, and RelB contain transcriptionally active domains in their C-terminal halves and mediate the majority of NF- $\kappa$ B-mediated gene transcription, whereas p50 and p52 do not contain transactivation domains but can modulate NF- $\kappa$ B activity by forming heterodimers with RelA, c-Rel, and RelB (13, 14). Prototypical activators of NF- $\kappa$ B are TLRs, which initiate a signaling cascade beginning with TLR adapter molecules MyD88 and TRIF, resulting in NF- $\kappa$ B pathway activation and the triggering of other important signaling cascades through IFN regulatory factors and MAPKs, including ERK1/2, JNKs, and p38 isoforms (11, 12). In addition to PRRs, the NF- $\kappa$ B pathway can also be activated by proinflammatory cytokines, such as IL-1 $\beta$  and TNF- $\alpha$  (13, 14). Under resting conditions, the NF- $\kappa$ B transcription factors are sequestered in the cytoplasm associated with inhibitor molecule I $\kappa$ B, which prevents NF- $\kappa$ B activation (13, 14). When NF- $\kappa$ B is activated, a cascade of signaling events occur that ultimately lead to I $\kappa$ B degradation, which allows the release of NF- $\kappa$ B and facilitates the translocation of NF- $\kappa$ B to the nucleus, where it promotes the transcription of genes involved in proinflammatory immune responses (13, 14).

Optimal NF- $\kappa$ B activity at some target genes is mediated by direct interaction of the serine 276 of the RelA subunit of NF- $\kappa$ B with the CREB coactivators, CBP or p300 (13, 14). Furthermore, the activity of RelA is enhanced by acetylation of RelA, which can be induced by CBP/p300 (13, 14). However, the RelA component of NF- $\kappa$ B interacts with CBP/p300 at the same region as phosphorylated CREB, and it has been proposed that NF- $\kappa$ B activity is inhibited by activated CREB through competition for limiting amounts of CBP/p300 (15, 16). Thus, it could be that the balance between CREB and CBP/p300 determines whether the overall response leads to the respective inhibition (via CREB) or enhancement (via CBP/p300) of NF- $\kappa$ B activity and signaling (Fig. 1) (15, 16). However, the significance of this hypothetical competition in a physiologic setting is entirely unknown. Finally, a recent study demonstrated that the microRNA miR-34b inhibits CREB expression, providing a negative feedback mechanism to down-regulate CREB activity (17).

#### CREB promotes a survival signal in macrophages

CREB also plays a specific role in the LPS/TLR4 pathway that mediates an NF- $\kappa$ B-dependent antiapoptotic response in macrophages, which promotes macrophage survival and enhancement of immune responses (18). The LPS/TLR4 anti-apoptotic response is mediated by NF- $\kappa$ B and p38 MAPK pathways that lead to the activation of mitogen- and stress-activated protein kinases, MSK1 and MSK2, resulting in CREB phosphorylation, which in turn induces two major antiapoptotic genes,



**FIGURE 1.** Proposed model of how CREB inhibits NF- $\kappa$ B activity. NF- $\kappa$ B activity is initiated by TLRs (and other proinflammatory signals) that trigger MyD88/IRAK-4/TRAF6 activation and subsequent phosphorylation and degradation of I $\kappa$ B, allowing the active RelA (p65)/p50 NF- $\kappa$ B complex to enter the nucleus. Optimal transcriptional activity of NF- $\kappa$ B for certain target genes requires interaction of the RelA subunit with CBP or p300. Phosphorylated CREB, which occurs via activation of PKA, PKC, and others as indicated, has been shown to bind to the same region as CBP/p300, and this has been proposed as a mechanism for CREB in the inhibition of NF- $\kappa$ B activity and signaling (15, 16).

plasminogen activator inhibitor-2 (PAI-2) and B cell lymphoma-2-related gene expressed in fetal liver-1/A1 (Bfl-1/A1) (18, 19). Thus, CREB promotes an antiapoptotic survival signal in macrophages, leading to enhanced host immune responses. This action of CREB is important because certain microbes, such as *Salmonella* spp., *Shigellae* spp., and *Yersinia* spp., inhibit this survival signal and induce the apoptosis, or killing, of macrophages as a mechanism to evade host immune responses (19). Furthermore, the lethal toxin of *Bacillus anthracis* has been shown to directly inhibit the CREB-dependent macrophage antiapoptotic signal (18, 19). In addition to these findings, an adenylate cyclase gene in *Mycobacterium tuberculosis* (Rv0386) facilitated delivery of a bacteria-derived cAMP into the macrophage cytoplasm, which resulted in TNF- $\alpha$  production that depended on CREB phosphorylation (20). This CREB-mediated TNF- $\alpha$  production increased survival of *M. tuberculosis* within macrophages, representing an additional mechanism by which CREB promotes bacterial pathogenesis (20).

#### Potential factors that may inhibit NF- $\kappa$ B signaling through activation of CREB

Several different factors may inhibit NF- $\kappa$ B activity in monocytes/macrophages through the induction of CREB. For example, GM-CSF signaling results in CREB phosphorylation (21, 22). Phosphorylation of CREB in this setting involves activation of pp90 RSK through an MEK-dependent signaling pathway (21). Because GM-CSF can induce activation of CREB, this may be another mechanism whereby CREB inhibits NF- $\kappa$ B activity, thus decreasing proinflammatory responses as suggested in the proposed model (Fig. 1).

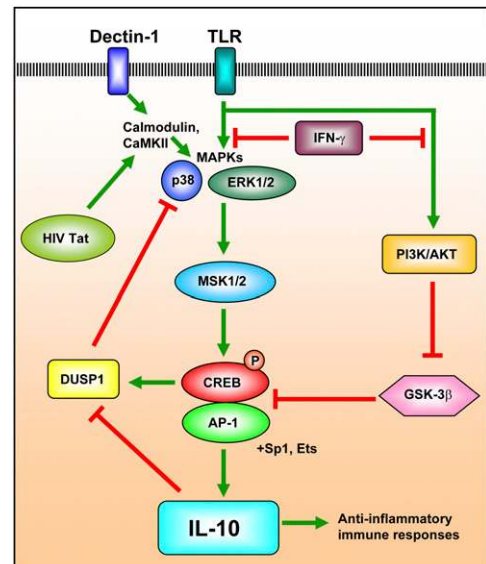
P2X7R is a ligand-gated cation channel nucleotide receptor that is present on monocytes and macrophages and is activated by extracellular ATP after tissue injury or infection (23). In particular, P2X7R triggers activation of the nucleotide-binding oligomerization domain-like receptor, nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 inflammasome, which is a cytoplasmic protein complex required to activate caspase-1 (23). Because caspase-1 cleaves pro-IL-1 $\beta$  and pro-IL-18 into their active forms, P2X7R is one of the key receptors that are important for promoting IL-1 $\beta$  and IL-18 responses (23). Upon ligand binding, P2X7R has been shown to result in the activation of CREB and other transcription factors, including MAPKs p38 and ERK1/2, and it is also involved in the production of reactive oxygen species and IL-1 isoforms as well as the creation of nonspecific cell membrane pores (24, 25). The phosphorylation and activation of CREB by P2X7R includes a CREB/CBP complex formation and is partly mediated via an extracellular calcium influx and the MEK/ERK system (24). Although the significance of the activation of CREB by the P2X7R in immune responses is not entirely clear, one study found that P2X7R stimulation decreased LPS-stimulated inducible NO synthase and cyclooxygenase-2 expression and reduced NO release in microglia in a mechanism involving activation of CREB (26). Thus, activation of CREB by P2X7R could promote CREB inhibition of NF- $\kappa$ B activity as suggested in the proposed model (Fig. 1).

The antimicrobial peptide cathelicidin (also known as LL-37) has been demonstrated to have broad-spectrum microbicidal activity while also having immunomodulatory activity, which is dependent on activation of MAPKs (ERK1/2 and p38), Elk-1, and NF- $\kappa$ B (27, 28). When PBMCs were stimu-

lated with LL-37 and IL-1 $\beta$ , there was an increase in CREB phosphorylation, suggesting that LL-37 also regulates CREB activity, potentially inducing the proposed CREB-mediated inhibition of NF- $\kappa$ B activity (Fig. 1) (28).

#### CREB induces IL-10 production

IL-10 is a potent anti-inflammatory cytokine that plays a key role in mediating a feedback inhibition loop that limits inflammation and prevents unwanted tissue damage (29). In macrophages, IL-10 is produced in response to activation of TLRs 2, 3, 4, 7, and 9 (30, 31). TLR signaling via MyD88 or TRIF results in activation of NF- $\kappa$ B and MAPK pathways (ERK1/2 and p38), which subsequently induces production of proinflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-10 (29). MAPKs activate MSK1 and MSK2 that phosphorylate the transcription factors CREB and AP-1 (e.g., c-Fos, c-Jun, JunB), which subsequently bind to the IL-10 promoter to induce transcription (Fig. 2) (32). This pathway is also required for the transcription of the dual-specificity protein phosphatase 1, which provides a negative feedback signal by inhibiting p38 (32). Thus, CREB plays an essential role in the production of IL-10, which in turn inhibits TLR-induced inflammation and prevents tissue damage (29). It should be noted that IL-10 can also regulate the pathway for TLR-induced NF- $\kappa$ B activation through the production of glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), which increases the binding of CREB and decreases the binding of CBP/p300 to the RelA subunit of NF-



**FIGURE 2.** CREB-induced IL-10 production is regulated by IFN- $\gamma$ . TLR signaling results in the activation of NF- $\kappa$ B and MAPKs (ERK1/2 and p38), which induces production of proinflammatory cytokines (e.g., TNF- $\alpha$ , IL-1 $\beta$ , IL-6) and the anti-inflammatory cytokine IL-10 (29). MAPKs activate MSK1 and MSK2 to directly phosphorylate CREB and AP-1, which bind to the IL-10 promoter and initiate transcription (32). This same pathway also induces dual-specificity protein phosphatase 1, which feeds back to inhibit p38 (32). Dectin-1, which recognizes zymosan, and the HIV-1 Tat protein also induce IL-10 production by activating CREB, Sp1, and Ets-1 through calmodulin, CaMK-II, and MAPKs (37–40). Finally, IFN- $\gamma$  inhibits IL-10 production by 1) interfering with the PI3K-AKT pathway, thereby releasing GSK-3 $\beta$ , which subsequently downregulates the activation and transcriptional activity of CREB and AP-1 proteins that induce IL-10 production; and 2) directly inhibiting MAPKs (45, 55).

$\kappa$ B (Fig. 2) (33). This mechanism utilizing GSK-3 $\beta$  is unique from other cytokines and is regulated by the constitutively active transcription factors Sp1 and Sp3 (34–36). Finally, recognition of the yeast particle zymosan by dectin-1 induces production of IL-10 by initiating CaMK-II- and Pyk2-transduced calcium signals that activate the ERK1/2 pathway and CREB in a pathway involving reactive oxygen species (37). Thus, in addition to TLRs, dectin-1 provides another mechanism that utilizes CREB to produce IL-10 (37).

#### *HIV-1 Tat induces IL-10 via CREB*

Interestingly, the HIV-1 transactivator protein Tat, which is required for viral replication and progression of HIV-1 disease, has been shown to induce IL-10 transcription in monocytes and macrophages by activating CREB, Sp1, and Ets-1 through calmodulin, CaMK-II, and MAPKs (ERK1/2 and p38) (38–40). Thus, during HIV-1 disease, Tat utilizes CREB to promote IL-10 production. Although the significance of this regarding HIV pathogenesis is not entirely clear, IL-10 can inhibit HIV-1 replication in monocytes and macrophages (41), suggesting that Tat/CREB-induced IL-10 production provides a negative feedback signal to prevent excess HIV-1 replication. In addition, because IL-10 can also prevent apoptosis of monocytes and macrophages (42), Tat/CREB-induced IL-10 may allow infected monocytes and macrophages to serve as cellular viral reservoirs.

#### *IFN- $\gamma$ regulates IL-10 production through multiple mechanisms involving CREB*

In contrast to the anti-inflammatory effects of IL-10, IFN- $\gamma$  is a potent macrophage stimulating factor that promotes various immune functions, including Ag presentation, cytokine production, and antimicrobial activity (43). In addition, IFN- $\gamma$  inhibits IL-10 production and consequently blocks the immune inhibitory actions of IL-10, resulting in an enhancement of macrophage activation and immune responses (43). In particular, IFN- $\gamma$  can downregulate the TLR-induced IL-10 inhibitory response (43). In addition, IFN- $\gamma$  can suppress IL-10 production by two distinct mechanisms: 1) IFN- $\gamma$  can interfere with the phosphoinositide 3-kinase–AKT pathway, releasing GSK-3 $\beta$ , which inhibits the activation and transcriptional activity of CREB and AP-1 proteins (including c-Fos, c-Jun, and JunB) that promote IL-10 production; and 2) IFN- $\gamma$  directly inhibits MAPKs (ERK1/2, JNK, and p38), which results in diminished CREB phosphorylation and AP-1 transcriptional activity (Fig. 2) (44, 45). Therefore, IFN- $\gamma$  can inhibit IL-10 production through a number of different mechanisms that involve CREB (29).

#### *CREB and T cells, including Th1, Th2, and Th17 cells*

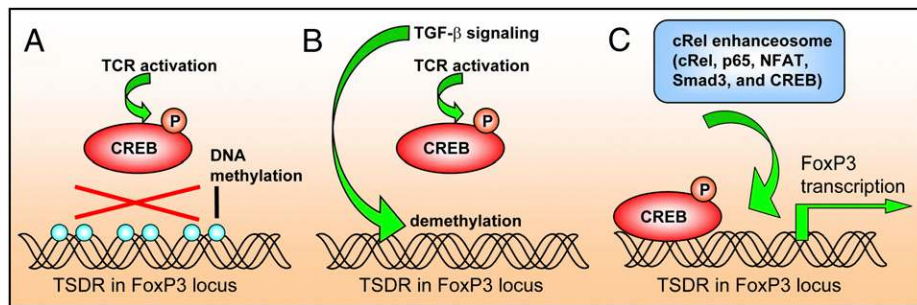
CRE elements have been identified in the promoters and enhancers of many T cell-specific genes, including TCR $\alpha$ , TCR $\beta$ , CD3 $\delta$ , CD8 $\alpha$ , IL-2, CD25/IL-2R $\alpha$ , and IL-2R $\gamma$ , suggesting that CREB plays a role in T cell function (10, 46–51). To analyze the specific function of CREB in T cells, Barton et al. (52) engineered a transgenic mouse strain expressing a dominant negative form of CREB under the control of the T cell-specific CD2 promoter. This dominant negative CREB mutation (serine 133 to alanine 133) retained DNA-binding activity but was rendered transcriptionally inactive (52). These

CREB mutant mice had normal T cell development in the thymus (52). However, activated T cells from this mouse strain had a marked defect in proliferation and IL-2 production, resulting in G1 cell-cycle arrest and apoptotic cell death (52). Another group generated a transgenic mouse strain that had the same CREB dominant-negative mutation, but under the control of the *Lck* promoter (53). In this case, T cells from this mouse strain did not have any defects in proliferation or IL-2 production, but instead had impaired Th cell function (53). Specifically, the CD4<sup>+</sup> T cells were defective in their ability to produce Th-1 (IFN- $\gamma$ ) and Th-2 (IL-4) effector cytokines, and the mice failed to produce an Ag-specific IgM and IgG humoral immune response (53). The differences in the findings between these two studies is likely explained by the differential expression of the mutant CREB by the *CD2* versus *Lck* promoters, but taken together these studies demonstrate that CREB plays a role in T cell proliferation and function. CREB activation also plays an important role in governing the cytokines produced by Th1 (IL-2 and IFN- $\gamma$ ) and Th2 cells (IL-4 and IL-13) through the regulation of IFN- $\gamma$  production. One study found that the IFN- $\gamma$  promoter is hypomethylated in Th1 cells, allowing CREB to induce IFN- $\gamma$  production and promote Th1 responses, whereas the IFN- $\gamma$  promoter is hypermethylated in Th2 cells, resulting in chromatin condensation and prevention of CREB-mediated production of IFN- $\gamma$  (54). Finally, IL-17, which is produced by Th-17 cells, downregulates CREB phosphorylation and ensuing IFN- $\gamma$  production in T cells obtained from patients with tuberculosis, suggesting that IL-17 can inhibit CREB-mediated IFN- $\gamma$  production (55).

CREB phosphorylation in T cells has been shown to involve several signaling molecules and pathways, including PKA, PKC (including PCK $\alpha$  and PKC $\theta$ ), Ras, ERK1/2 MAPKs, and pp90 RSK (10, 56, 57). In addition, the costimulatory molecule CD28 was shown to optimally activate CREB through p38 and CaMK-IV (58, 59). Although these different studies suggest that several signaling pathways lead to CREB phosphorylation in T cells, a large microarray analysis of con A/anti-CD28 stimulated T cells revealed a greater than 100-fold increase in phosphorylated CREB, which was reduced 50% when the cells were treated with a PKC inhibitor and completely blocked with a PKA inhibitor, suggesting that PKC and PKA are the major pathways that promote CREB phosphorylation (10). More recently, Kaiser et al. (60) demonstrated that MSK1/2 directly phosphorylated CREB in T cells and led to T cell proliferation and production of IL-2 in a pathway that was downstream of both ERK1/2 and p38. Collectively, CREB phosphorylation in T cells is mediated by triggering PKA and PKC, resulting in activation of MAPKs ERK1/2 and p38 and subsequent MSK1/2-mediated CREB phosphorylation that promotes T cell activation and proliferation.

#### *CREB and FoxP3 regulatory T cells*

Recently, there has been an intense interest on the role that CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells (Tregs) play in promoting peripheral tolerance and downregulating pathogenic T cell responses, including autoimmune responses and allograft rejection (61). The function of Tregs is dependent on TGF- $\beta$ -dependent expression of the transcription factor FoxP3, which is required for the development and function of Tregs (61). Emerging evidence has suggested a role for CREB, which



**FIGURE 3.** CREB promotes TGF $\beta$ -mediated generation and maintenance of FoxP3 Tregs. The TSDR in the FoxP3 locus is found methylated in conventional T cells. *A*, The methylation prevents phosphorylated CREB, which is induced by TCR activation, from binding to this region. *B*, TGF- $\beta$  induces demethylation of the TSDR. *C*, Demethylation of the TSDR allows phosphorylated CREB to bind to the FoxP3 locus to promote FoxP3 expression and the development and stabilization of Tregs (62–64). Transcription of FoxP3 also involves the formation of a “c-Rel enhanceosome”, which contains c-Rel, p65, NFAT, and Smad3 in addition to CREB (65).

is activated by TCR activation, in TGF- $\beta$ /FoxP3-dependent Treg generation and maintenance (Fig. 3). Several studies have defined a Treg-specific demethylated region (TSDR) in the FoxP3 locus, which contains a CREB-activating transcription factor site overlapping a CpG island (61–64). The CpG island is found demethylated in Tregs and methylated in conventional T cells (61–64). TGF- $\beta$ , as well as treatment with azacytidine, can induce demethylation of this locus, allowing CREB to stabilize FoxP3 expression, thus promoting and maintaining the Treg phenotype (61–64). In addition, a recent study demonstrated that transcription of FoxP3 and development of Tregs depends on the formation of the “c-Rel enhanceosome” at the FoxP3 promoter, which, in addition to

CREB, contains c-Rel, p65, NFAT, and Smad3 (65). Together, the CREB-induced generation and maintenance of Tregs represents an additional example of how CREB inhibits immune responses.

#### CREB and B cells

Previous studies in mature and immature B cells have demonstrated that BCR stimulation, which promotes B cell activation and proliferation, involved ERK1/2- and Elk-1-induced CREB phosphorylation (66). Furthermore, BCR induction of CREB phosphorylation was dependent on PKC $\delta$  and pp90 RSK signaling pathways (67). Thus, B cell activation and proliferation through the BCR involve signaling pathways

Table I. Summary of the many different roles of CREB in immune function

Role of CREB	Cell Type	Associated Factors	Overall Role in Immune Function	References
Inhibition of NF- $\kappa$ B signaling	Monocytes and endothelial cells	CREB interacts with the RelA (p65) component of NF- $\kappa$ B at the same region as CBP/p300	Anti-inflammatory (may be protective or pathogenic depending on the context)	15, 16
Antiapoptotic survival signal	Macrophages	TLR4 triggers NF- $\kappa$ B/MAPKs and MSK1/2, which activate PAI-2 and Bfl-1/A1 to phosphorylate CREB	Pathogenic (mechanism for pathogens to evade host immune responses)	18, 19
TNF- $\alpha$ -mediated survival signal	Macrophages	<i>M. tuberculosis</i> -derived adenylate cyclase (Rv0386) phosphorylates CREB	Pathogenic (promotes survival of <i>M. tuberculosis</i> in macrophages)	20
Induction of IL-10	Macrophages and myeloid dendritic cells	MAPKs (ERK1/2 and p38) trigger MSK1/2 to activate CREB	Anti-inflammatory (may be protective or pathogenic depending on the context)	29–32
Induction of IL-10	Macrophages	TLR2 activation by <i>Candida albicans</i> triggers IL-10 production	Pathogenic (promotes survival of Tregs, leading to disseminated candidiasis)	31
Induction of IL-10 by HIV-1 Tat	Macrophages	Sp1, Ets-1, calmodulin, CaMK-II, and MAPKs	Unknown, may be pathogenic (macrophages could act as cellular viral reservoirs)	38–40
Promotes T cell activation and proliferation and Th cell activity	T cells	PKA, PKC, Ras, ERK1/2, pp90 RSK and CD28 (via p38 and CaMK-IV)	May be protective or pathogenic (depending on the Ag)	52, 53, 56–59
Promotes IFN- $\gamma$ production	T cells	IFN- $\gamma$ promoter is hypomethylated in Th1 cells, allowing CREB binding	Protective (promotes Th1 responses that are protective in tuberculosis)	54, 55
Induction of FoxP3, promoting Treg generation and maintenance	T cells	TSDR in the FoxP3 locus, which allows CREB to promote FoxP3 expression	Anti-inflammatory (may be pathogenic relating to infections and tumor immunosurveillance and protective relating to autoimmunity)	61–65
Promotes B cell activation and proliferation	B cells	ERK1/2, E1K-1, PKC $\delta$ , pp90 RSK	May be protective or pathogenic (depending on the Ag)	66, 67

that include PKC $\delta$  and pp90 RSK, resulting in ERK1/2- and Elk-1-dependent activation of CREB (66, 67).

## Conclusions

CREB plays many different roles in immune function (Table I). CREB often promotes anti-inflammatory immune responses, such as through the inhibition of NF- $\kappa$ B activity, the induction of IL-10, and the generation of Tregs. These anti-inflammatory responses could be protective by inhibiting unwanted inflammation, tissue damage, and autoimmune responses, or they could be pathogenic in the context of infection and tumor immunosurveillance. However, CREB also promotes activation and proliferation of T and B cells and differentially regulates Th1, Th2, and Th17 responses. Future investigation into the role of CREB in immune function will lead to an increased understanding of how this transcription factor regulates specific immune responses. One challenge is to apply innovative technology to uncover the roles of CREB in immune responses, such as chromatin immunoprecipitation coupled to massively parallel sequencing to monitor histone modifications and nucleosome dynamics to characterize the events required for CREB binding and activation of immune-related genes (68, 69). Although CREB appears to be involved in an amazingly diverse range of processes in immune cells and other cell types, further research could reveal signaling pathways or collaborating proteins that are selectively involved in its proinflammatory or its anti-inflammatory functions. Therefore, a better understanding of the activation mechanisms and mechanisms of action of CREB in different cell types and settings could suggest therapeutic strategies for selective manipulation of immune responses.

## Disclosures

The authors have no financial conflicts of interest.

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