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Insight Into the Tumor Suppressor Function of CBP Through the Viral Oncoprotein Tax

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CREB binding protein (CBP) is a cellular coactivator protein that regulates essentially all known pathways of gene expression. The transcriptional coactivator properties of CBP are utilized by at least 25 different transcription factors representing nearly all known classes of DNA binding proteins. Once bound to their target genes, these transcription factors are believed to tether CBP to the promoter, leading to activated transcription. CBP functions to stimulate transcription through direct recruitment of the general transcription machinery as well as acetylation of both histone and transcription factor substrates. Recent observations indicate that a critical dosage of CBP is required for normal development and tumor suppression, and that perturbations in CBP concentrations may disrupt cellular homeostasis. Furthermore, there is accumulating evidence that CBP deregulation plays a direct role in hematopoietic malignancies. However, the molecular events linking CBP deregulation and malignant transformation are unclear. Further insight into the function of CBP, and its role as a tumor suppressor, can be gained through recent studies of the human T-cell leukemia virus, type I (HTLV-I) Tax oncoprotein. Tax is known to utilize CBP to stimulate transcription from the viral promoter. However, recent data suggest that as a consequence of the Tax–CBP interaction, many cellular transcription factor pathways may be deregulated. Tax disruption of CBP function may play a key role in transformation of the HTLV-I-infected cell. Thus, Tax derailment of CBP may lend important information about the tumor suppressor properties of CBP and serve as a model for the role of CBP in hematopoietic malignancies.

CREB binding protein (CBP) Tax oncoprotein Tumor suppression

CREB binding protein (CBP) is a very large, highly conserved coactivator protein that serves as a central mediator of gene expression in metazoans. CBP, and its sister protein p300, controls essentially all known pathways of gene expression, including signal-dependent and -independent activation, programs of differentiation, and modulation of cell death. Although CBP was originally named following its identification as a coactivator for the transcriptionally poised, phosphorylated form of CREB, the acronym is a misnomer, as CBP is utilized by numerous cellular transcription factors (38,69). To date, over 25 cellular transcription factors have been demonstrated to interact with CBP, with some transcription factors binding at multiple locations on the protein. In addition, many viral activator proteins have evolved strategies to take advantage of CBP's coactivator properties (4,17,37). Transcription factor binding to CBP is believed to recruit the coactivator to target promoters, leading to activated transcription.

The transcriptional coactivator properties of CBP appear to be twofold. First, there is evidence that CBP is an intrinsic component of the RNA polymerase II holoenzyme (50), with recruitment of CBP leading directly to an increase in the rate of preinitiation complex assembly (90). In this capacity, it appears that transcription factor recruitment of CBP concomitantly brings RNA polymerase to the target promoter. There is also evidence that, subsequent to promoter association, CBP may directly recruit, or stabilize, components of the general transcription machinery, including TFIIB and TBP (16,38). Second, there is a significant body of accumulating evidence showing that CBP is involved in both nucleosome

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and transcription factor acetylation. This activity is an intrinsic property of CBP, as well as P/CAF, an ancillary protein present in the coactivator complex (6,52,88).

At present, the nucleosome acetyltransferase activity of CBP is the most well-characterized functional activity of the coactivator. CBP has been shown to directly acetylate lysine residues present within the amino-terminal tails of all four core histones (68). Acetylation occurs on the histone tails both free in solution and assembled in the mononucleosome core particle (52). While it is well established that histone H3 and H4 acetylation is enriched in transcriptionally active chromosomal regions, acetylation of the histone tails has only subtle effects on nucleosome structure and stability. However, the tails appear to play a significant role in chromatin compaction and higher ordered structure (3,5,19,22,28,43,45,84,85). Furthermore, acetylation appears to increase the accessibility of the nucleosomal DNA to transcription factor binding, a critical step in gene activation (40,81). Although P/CAF may facilitate nucleosome acetylation by CBP, it is unclear whether this "associated" HAT works in concert with CBP or provides other functions important to recognition of chromatin substrates.

Although the evidence for histone acetylation by CBP is strong, direct evidence demonstrating gene-specific activation following histone acetylation in the vicinity of the target promoter is just beginning to emerge. In a recent study by Parekh and Maniatis (54), the authors found that transcriptional activation of the interferon-β gene correlated with a dramatic increase in the hyperacetylation of the histone H3 and H4 tails, specifically within the vicinity of the interferon-β promoter. Unfortunately, the molecular events linking histone acetylation and gene activation remain vague. Whether the histone acetyltransferase activity of CBP is typically targeted to specific promoters, or functions more regionally, is not well understood.

Nucleosomes were originally identified as the primary targets of the CBP acetyltransferase activity. However, several recent studies indicate that transcription factors also serve as acetylation substrates. For example, CBP (and p300) has been shown to acetylate lysine residues in the transcription factors p53, GATA-1, and c-Myb. In all cases, the acetylation enhances the DNA binding activity of the proteins, leading to increased transcription (10,26,78). CBP also acetylates TFIIE and TFIIF, members of the general transcription machinery (30). These observations underscore the complex and pleiotropic nature of the acetylation activity of CBP, and its central role in gene regulation.

CBP and p300 appear to be functionally homologous and have generally overlapping expression patterns. However, the expression of each protein appears to be developmentally regulated, with distinct patterns of expression in distinct cell types. While both proteins are required for normal development in the mouse, a recent study suggests that each protein has a discrete role in cellular differentiation and embryogenesis (56). Furthermore, their specific coactivator functions appear to be gene-dosage sensitive, as haploinsufficiency of either CBP or p300 produces abnormalities in the developing mouse embryo (77, 89). In further support of this, gene-dosage insufficiency of CBP underlies Rubinstein-Taybi syndrome (RTS), a developmental disorder in humans characterized by craniofacial abnormalities and mental retardation (57,77). CBP haploinsufficiency is also associated with a variety of additional disorders in mice, including defects in hematopoiesis and vasculo-angiogenesis, as well as an increased incidence of malignancies (36,53). Finally, embryos nullizygous for either the CBP or p300 gene die at approximately 10 days postconception, further validating an essential role for both proteins in development. These observations suggest that a critical dosage of CBP is required for normal development and tumor suppression, and that perturbations in CBP concentrations may disrupt cellular homeostasis. Furthermore, these studies indicate that CBP and p300 have overlapping, yet distinct, functions in the development of multicellular organisms.

A ROLE FOR CBP IN HEMATOPOIETIC MALIGNANCIES

The tissue-specific transcription factors c-Myb and GATA-1 participate in hematopoiesis, with each protein having opposing roles in the differentiation process (83). It is interesting that both proteins utilize CBP to carry out their transcriptional activation function (8,15), with competition for limiting CBP possibly playing a role in regulating the progression from primitive progenitor cells to terminally differentiated lymphocytes (74). These observations suggest that CBP has a central role in differentiation of cells in the hematopoietic lineage. Furthermore, defects in primitive hematopoiesis were observed in the mice nullizygous for the CBP gene (53,89). Although about 50% of the mice heterozygous for the CBP gene were born alive, they exhibited hematopoietic defects, including dramatic splenomegaly and diminished numbers of all hematopoietic subpopulations (36). Significantly, as the $CBP^{-/+}$ mice aged, a notable percentage (39%) developed malignancies of hemato-

poietic origin, including primary myelogenous leukemia and multiple plasmacytomas. Some of the hematopoietic malignancies were evident at necropsy, while others became evident following transplantation of cells from the $CBP^{-/+}$ mice into sublethally irradiated mice. Interestingly, these malignancies were unique to mice with CBP haploinsufficiency, as they were not detected in the $p300^{-/+}$ mice, or in the wild-type controls. The observation of hematopoietic malignancies in these mice is consistent with the increased incidence of malignancies observed in RTS patients (47). Although the malignancies observed in RTS patients frequently appear in neural tissues, there is also evidence suggesting a specific increase in the incidence of leukemias (70). These data provide the first strong evidence that CBP functions as a tumor suppressor, and that disruption of the full complement of CBP renders the cell susceptible to differentiation defects and malignant transformation.

The molecular basis for the tumor suppressor function of CBP is unknown; however, several reports suggest a strong link between abnormal acetylase function of CBP and human leukemias. For example, translocation of the MOZ gene to the largely intact CBP loci is associated with a distinct subtype of acute myeloid leukemia (9,12). This malignancy has a poor prognosis, and is typically observed in children under the age of 17. It is interesting to note that MOZ is also believed to carry acetyltransferase activity, and that the acetyltransferase activities of both proteins are likely retained in the chimeric gene product that is generated following the translocation (64). In-frame translocations of the CBP gene to several other loci have also been strongly linked with acute myeloid leukemia and treatment-related leukemias (1,65,72,75). For example, the recurring translocation t(11;16)(q23;p13.3) has been documented in cases of acute leukemia that occur following chemotherapy with drugs targeting DNA topoisomerase II. In this translocation, the MLL gene is fused in-frame to the CBP gene, and the chimeric protein product retains the histone acetyltransferase domain of CBP. The protein product is believed to cause leukemia by promoting aberrant chromatin structure of the gene targets of MLL. Interestingly, a translocation involving p300 has recently been associated with a case of acute myeloid leukemia (29), suggesting that translocations leading to dysregulation of either p300 or CBP serve as a molecular trigger for leukemogenesis. Whether the translocation events result in aberrant acetylation through a gain of function or a loss of function mechanism is not known. Taken together with the observation of increased leukemogenesis in the $CBP^{-/+}$ mice, the available data suggest that inappropriate CBP acetylation function is the underlying molecular defect that leads to malignant transformation. Whether gene-specific chromatin acetylation is altered, or global changes in chromatin condensation occur, is currently not known.

THE HTLV-I TAX PROTEIN

Further insight into the function of CBP and its role as a tumor suppressor can be gained through recent studies of the human T-cell leukemia virus, type I (HTLV-I) Tax oncoprotein. Tax is known to bind to CBP and utilize the coactivator properties of CBP to stimulate transcription from the viral promoter. However, accumulating evidence suggests that as a consequence of the Tax–CBP interaction, the coactivator properties of CBP may be deregulated, initiating a pathway towards transformation of the HTLV-I-infected cell. Thus, Tax derailment of CBP may reveal important information about the tumor suppressor properties of CBP and serve as a model for the role of CBP in hematopoietic malignancies.

It is estimated that up to 20 million people worldwide are infected with HTLV-I. Although the vast majority of infected individuals remain asymptomatic throughout their lives, fewer than 5% develop an aggressive leukemia that is refractory to chemotherapy, and therefore invariably fatal. HTLV-I represents the first pathogenic human retrovirus isolated and characterized. It was originally discovered in 1980 in a T-lymphoblast cell line derived from a patient incorrectly diagnosed with cutaneous T-cell lymphoma (mycosis fungoides) (60). Since that time, HTLV-I has become well established as the etiologic agent of adult T-cell leukemia (ATL), a distinct disease entity (82). ATL is characterized clinically by skin lesions (due to infiltrating leukemic cells), lytic bone lesions, and greater than 5% abnormal T cells (with lobular or flower-like nuclei). Features of the leukemic cells include the CD4+ phenotype, and monoclonal or oligoclonal integration of the HTLV-I provirus. The observation that only a small percentage of HTLV-I-infected individuals develop ATL, following a latency period of several decades, indicates that the virus is necessary, but not sufficient, for malignant transformation (34,49). Transformation by HTLV-I is therefore a statistically rare event, as over a billion T cells carry the provirus at any given time during the lifetime of the infected individual [(18), M. Matsuoka, personal communication].

A single HTLV-I-encoded protein, called Tax, is strongly implicated in the etiology of ATL. Tax is clearly established as an oncoprotein, as it promotes transformation of cells both in vitro and in vivo (23–25,51,61,76,86). Tax is a regulatory protein produced

by the virus to achieve high-level expression of the HTLV-I genome. Following infection of the T cell, the virus is believed to primarily exhibit low levels of gene expression. During the intermittent transition to high levels of viral gene expression, Tax protein levels increase significantly, promoting a dramatic increase in RNA polymerase II transcription of the viral genome.

To stimulate HTLV-I transcription, Tax binds to specific DNA sequences located within three conserved enhancer elements in the transcriptional control region of the virus. These elements, called viral CREs, also serve as binding sites for the cellular transcription factor CREB. To assemble the transcriptionally competent activator proteins on the viral CRE, Tax participates in both protein–protein interactions with CREB and protein–minor groove DNA interactions with GC-rich sequences in the viral CRE (35, 41,42,44). These elaborate interactions promote the assembly of a very stable ternary complex on the HTLV-I promoter. The formation of this complex is critical, yet appears insufficient, for the strong transcriptional activation associated with Tax. The DNA-bound ternary complex appears to function primarily as a binding site for the recruitment of CBP (21, 27,37,87). Once anchored at the HTLV-I promoter, CBP promotes the strong transcriptional activation that leads to high levels of viral replication.

Tax recruitment of CBP to the HTLV-I promoter is dependent upon CREB, and largely independent of the phosphorylation state of CREB (21,37,39). In support of this, the entire amino-terminus of CREB, including the PKA-phosphorylation domain, has been shown to be dispensable for CBP recruitment (13, 21,39). Efficient CBP recruitment appears to also require assembly of the Tax–CREB complex on the HTLV-I promoter DNA, as specific sequences in the viral CRE elements have been shown to be critical for coactivator binding (21,37,42). Although there is strong evidence indicating that Tax and CBP interact in solution, the high affinity of CBP for the Tax-containing ternary complex suggests efficient recruitment of CBP to assembled complexes on the HTLV-I proviral DNA (21,46,87). Once associated with the HTLV-I promoter DNA, CBP strongly activates transcription of the viral genome, presumably through chromatin remodeling and stabilization of the general transcription machinery (31,33).

THE TAX–CBP INTERACTION: IMPLICATIONS FOR LEUKEMOGENESIS

To recruit CBP to the transcriptionally poised HTLV-I promoter, Tax specifically interacts with a small domain of CBP called KIX (21,37). The KIX domain, located approximately between amino acids 588 and 683, folds into three α-helicies, which come together to form a hydrophobic core structure (62). This region of the coactivator is also recognized by several cellular transcription factors, including phosphorylated CREB, c-Jun, c-Myb, and p53 (7,15,55, 79). The KIX domain likely represents a single protein-docking site for the numerous transcription factors that interact with this region.

The observation that several transcription factors bind to a common region of CBP suggests that their binding sites may be mutually exclusive, creating competition for the limiting amounts of CBP in the cell. Several recent studies indicate that the Tax binding site on KIX significantly overlaps with the binding sites for c-Myb, c-Jun, and p53 (14,79,80,87). Not unexpectedly, Tax directly competes with these cellular transcription factors for binding to KIX. This coactivator competition has been shown to result in Tax repression of transcription mediated through these cellular transcription factors (14,73,79,80). Competition between Tax and cellular transcription factors for CBP may result in global changes in cellular gene expression in the infected cell, and may be relevant in HTLV-I-dependent malignant transformation. The extent of transcription factor competition would likely depend upon several factors, including the relative abundance and CBP binding affinity of each transcription factor, and the concentration of available CBP in the cell.

The evidence showing that Tax and p53 compete for CBP utilization may be a particularly significant event in the progression toward HTLV-I-associated adult T-cell leukemia. Cells taken from ATL patients are characterized by chromosomal instability and karyotypic abnormalities; however, p53 mutations in these cells are relatively rare (11,20,63). Thus, functional inactivation of p53 may be necessary for the development of genetic mutations and for the ensuing transformation process. Several studies have demonstrated that the transcription function of p53 in HTLV-I-infected T cells is blocked (2,11,20,59). This effect has been shown to be specifically mediated by Tax (2,48,59,67). As a result, HTLV-I-infected cells appear to be refractory to classical p53 stimuli, such as gamma irradiation (11,32,58,59,66). The observation that Tax can block p53 binding to CBP may account for Tax repression of p53 transcription function (79). This interference would thus allow the accumulation of mutations and chromosomal instability observed in the HTLV-I-infected T cell. Perhaps the intermittent disruption of p53 function over the lifetime of the infected cell might permit the slow accumulation of mutations. Tax protein levels are believed to intermit-

tently reach high levels in the infected cell (71), and only during these times would p53 function be compromised. This scenario is consistent with the observed long latency of disease onset, and statistically rare transformation event in HTLV-I-infected cells.

The very strong correlation between abnormal CBP function and hematopoietic malignancies forms the basis for the hypothesis that the physical interaction between CBP and Tax plays a causal role in HTLV-I-associated leukemogenesis. Because of the pleiotropic role of CBP in cellular gene expression, it is likely that Tax binding to CBP promotes aberrant gene expression in the HTLV-I-infected cell. This may occur as a consequence of inappropriate coactivator competition, leading to transcriptional repression of certain target genes. Alternatively, Tax binding to CBP may promote alterations in either the local or global acetylation state of chromatin. It is interesting to speculate that Tax binding to CBP mimics the deregulation that is achieved following chromosomal translocations involving CBP. In both scenarios, CBP may remain partially functional; however, its histone acetyltransferase activity is misdirected. This misdirection appears to be a critical initiating event in the pathway towards malignant transformation.

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