Transcriptional regulation by cyclic AMP is essential for development, reproduction and survival: lessons from the transgenic mice

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A great number of hormones act at the cellular level by stimulation of the cAMP signalling pathway, after binding to their specific G protein-coupled transmembrane receptor. Alterations of the cAMP pathway have been implicated in several endocrine diseases such as acromegaly, toxic thyroid adenomas or Cushing's syndrome.

One major cellular effect of the cAMP cascade activation is stimulation of transcription after phosphorylation of nuclear factors by the cAMP-dependent kinase, PKA (Fig. 1). A conserved palindromic cAMP response element (CRE) has been identified in the promoter of various genes regulated by cAMP (i.e. somatostatin, vasoactive intestinal polypeptide, alpha chorionic gonadotrophin, enkephalin, fos, parathyroid hormone (PTH) ... genes). Three proteins have been identified that bind the CRE and are phosphorylated by PKA: CREB (CRE binding protein), CREM (CRE modulator) and ATF-1 (activating transcription factor 1) (1). While CREB and ATF-1 stimulate transcription, some isoforms of CREM can negatively regulate CRE activity. A coactivator of CREB that binds, specifically, CREB phosphorylated by PKA: CREB (CRE binding protein), CREM (CRE modulator) and ATF-1 (activating transcription factor 1) (1). While CREB and ATF-1 stimulate transcription, some isoforms of CREM can negatively regulate CRE activity. A coactivator of CREB that binds, specifically, CREB phosphorylated by PKA in response to cAMP stimulation, has been cloned and termed CREB binding protein (CBP). CBP appears to be a general transcriptional coactivator for numerous signalling pathways.

To evaluate the physiological significance of the various components regulating the CRE, a number of transgenic models have been reported and show the major role of cAMP regulated transcription. CREB null mice generated by homologous recombination die just after birth from respiratory distress (2). Analysis of these animals show that they are smaller than the controls and that they have central nervous system alterations (corpus callosum and anterior commissures reduction). It has been observed previously that mice lacking two of the three main splice product isoforms of CREB have a deficient long-term memory (3). It should be noted that in both models of CREB knockout mice (i.e. the partial and the complete models), an overexpression of CREM and ATF-1 is observed. This suggests a compensatory mechanism between the members of the CREB/CREM/ATF-1 family. The CREB -/- mice also have impaired T cell development. Interestingly, a T cell proliferative defect and a decreased interleukin-2 production are also observed in transgenic mice expressing a dominant-negative mutant of CREB under the control of the thymocyte-specific CD2 promoter (as the use of the CD2 promoter in the construction of the transgene allows specific expression of the mutant in the thymocytes) (4). In this mutant, the PKA phosphorylation site is mutated and therefore the cAMP activation of CREB is abolished. The same approach has demonstrated the major role of CREB in the development of the pituitary somatotroph. Transgenic mice expressing a similar dominant-negative mutant of CREB under the control of the growth hormone (GH) promoter are dwarf and present with pituitary hypoplasia due to a dramatic reduction in the number of GH cells (5). Targeting a dominant-negative mutant of CREB in the heart using the myocyte-specific alpha-MHC promoter leads to dilated cardiomyopathy in transgenic mice (6). Disruption of the CREM gene by homologous recombination leads to infertility in male mice due to deficient spermiogenesis (7, 8), without hormonal alterations of the gonadotroph axis. Mice homozygous for a targeted mutation of the coactivator CBP die during embryonic development and show neural tube defects (9).

Numerous transgenic mice models for the study of transcription regulation by cAMP reported to date have given insights into the major developmental role of the various CRE binding proteins and of CBP. Together with the knockout models, the use of dominant-negative mutants targeted to a given tissue allows the identification of the specific role of CRE binding proteins in each tissue and reveals tissue-specific differences for proteins that seem quite ubiquitously expressed. The CREB null mice suggest that compensation occurs in the CRE binding protein family, in keeping with the essential role of these transcription factors. Nevertheless, a specific role for each member of this family does exist. In this view the development of the ATF-1 null mice and of the double knockout mice will help to explain the function of each nuclear component of the cAMP-regulated transcription (2). The use of the conditional knockout technology which allows control of the timing and/or
the tissue of the inactivation of a given gene will undoubtedly be very useful in this field.

References