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CREB: the Mediator of Long Term Memory. ZUO Wei, SHEN Zheng (*Psychology Department, Peking University, Beijing* 100871, China).

Abstract As a translator factor, CREB takes part in the transformation process from short term memory to long term memory, which has been evidenced in several different kinds of animals. In addition, its two forms as both activator and inhibitor with high conservation in their gene structures can mediate this transformation process in a more precise manner. Researches having been conducted so far and the recent progressed in this field were reviewed; the issues to be researched and addressed in future were also pointed out.

Key words CREB, long-term memory, gene expression, protein synthesis

骨形态发生蛋白的受体及其信号传递过程*

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摘要 近年来已克隆出几种Ⅰ型和Ⅱ型 BMP 受体. BMP 受体属于 TGFβ 受体超家族的成员, 具有丝氨酸/苏氨酸蛋白激酶活性. Ⅰ型与Ⅱ型 BMP 受体均可与 BMP 配基结合, 但若执行传递信号功能, 两受体需首先形成复合物. 删除突变和基因剔除研究证明, ⅠA 型 BMP 受体对动物的中胚层发育至关重要. 而ⅠB 型 BMP 受体在软骨细胞形成、成骨细胞分化以及程序化细胞死亡方面起主要作用. BMP 受体信号传递分子 Smad 1 和 Smad 5 也已被克隆和鉴定, 它们在 BMP 受体介导的功能中起重要作用.

关键词 骨形态发生蛋白 (BMP), 受体, 丝氨酸/苏氨酸蛋白激酶, 信号传递
学科分类号 R34, R341

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近年来，随着对骨形态发生蛋白（BMP）生理功能研究的深入，对BMP受体及其信号传递途径的研究也取得了突破性的进展.

1 BMP受体的结构与功能

BMP受体属于转化生长因子β（transforming growth factor β, TGF β）受体超家族的成员，是膜蛋白受体，受体分子由细胞外区，跨膜区和细胞内区组成，具有丝氨酸/苏氨酸蛋白激酶结构，以及与TGFβ受体类似的信号传递机制. 利用已知Ⅰ型受体间分子同源性的特点，用简并PCR技术，几个不同的实验室先后于1994年克隆出Ⅰ型BMP受体[1~3]. 已发现的Ⅰ型BMP受体包括ⅠA和ⅠB两个亚型. Ⅱ型受体间分子同源性较低，难以用简并PCR的方法克隆，而基于Ⅰ型和Ⅱ型受体可相互作用形成杂聚体（heteromer）的机制，利用双杂交（two-hydrid）技术，继而成功地克隆出了Ⅱ型BMP受体[4,5]. BMP的信号传递是由Ⅰ型和Ⅱ型BMP受体共同介导的.

将蛋白激酶缺陷的ⅠA和Ⅱ型BMP受体mRNA注射到非洲爪蟾蜍（Xenopus）的胚胎中，可阻断腹侧中胚层（ventral mesoderm）的形成[6]. 过量表达删除蛋白激酶的Ⅰ型BMP受体可与内源性的Ⅱ型BMP受体结合，并因其缺乏蛋白激酶活性，而无信号传递功能. 但这一结合使内源性Ⅰ型受体无法与Ⅱ型受体结合，故阻断了BMP受体的信号传递过程. 用基因剔除（gene knock-out）技术产生的无ⅠA型BMP受体的小鼠，同样发现有中胚层形成障碍[7]. 将无蛋白激酶活性的ⅠB型BMP受体转染到鸡胚足趾部，可大大减低趾间细胞凋亡（apoptosis）[8]，表明ⅠB型BMP受体对于此部位的程序化细胞死亡起重要作用. 此外，将去除蛋白激酶的ⅠB和Ⅱ型BMP受体转染到鸡胚的足趾部，可造成局部骨缺损和抑制软骨形成[9].

已有实验证明，成骨细胞和脂肪细胞是由共同的前体细胞分化而来的. 将缺失蛋白激酶的ⅠB型BMP受体的cDNA转染成骨细胞的前体细胞，可阻断这一细胞向成骨细胞分化，并使其转化为脂肪细胞. 相反，若将有活性的ⅠB型BMP受体的cDNA转染前体细胞，可促使其向成骨细胞分化[10]. 这一发现表明，ⅠB型BMP受体对成骨细胞的定向分化起决定性作用.

2 BMP受体的信号传递

从TGFβ受体功能的研究中已知，Ⅰ型TGFβ受体不直接与TGFβ配基结合，Ⅱ型TGFβ受体首先与TGFβ配基结合，然后吸引Ⅰ型受体，与其形成杂聚体. 目前广为认可的受体模型是四聚体（tetramer）模型，即两个Ⅰ型受体的同二聚体（homodimer）和两个Ⅱ型受体的二聚体一起组成四聚体，共同将信号传入细胞内. Ⅱ型受体处于自动磷酸化状态，当与配基结合后，其蛋白激酶活性催化Ⅰ型受体GS区的丝氨酸和苏氨酸残基磷酸化，磷酸化的Ⅰ型受体可进一步磷酸化下游分子，将信号传入细胞[11]. BMP受体的信号传递过程与TGFβ受体类似，所不同的是Ⅰ型BMP受体可直接与BMP配基结合，但这一结合的亲和力很弱，在Ⅱ型受体同时存在的情况下，BMP配基对受体的亲和力大大增强，细胞对BMP的反应也随之增加[4,9]. Ⅰ型受体的GS区位于跨膜区与蛋白激酶区之间，含有具有特征性的保守的SGSGSG序列，GS区内有7个丝氨酸和苏氨酸残基，在受体激活过程中，可被Ⅱ型受体磷酸化[11]. 若将GS区的倒数第二个氨基酸残基——谷氨酰胺转换成天门冬氨酸，可使Ⅰ型BMP受体转变为具有基本活性的Ⅰ型受体（constitutively active BMP R-Ⅰ）. 如将这种Ⅰ型受体的cDNA转染至靶细胞内，可在不需要BMP配基的情况下，启动信号传递过程，诱发细胞反应[12].

除了Ⅰ型和Ⅱ型BMP受体的相互作用外，BMP受体与Activin（TGFβ超家族的另一成员）受体间有交叉作用. Ⅰ型Activin受体可与Ⅱ型BMP受体形成复合物，Ⅰ型BMP受体也可与Ⅱ型Activin受体形成复合物，传导BMP的信号[13]. BMP受体与TGFβ受体间无交叉作用.

近年来，在研究果蝇（*Drosophila*）的BMP2和BMP4的同源蛋白-DPP（decapentaplegic）的信号传递机制中发现果蝇基因Mad（mother against DPP）可作为DPP信号传递的下游分子，参与DPP的信号传递. 人的Mad基因的同源蛋白，Smad1至Smad7的基因已被先后克隆[12,14~17]. 实验结果表明，Smad1和Smad5参与BMP的信号传递[12,17]，Smad2和Smad3参与Activin和TGFβ的信号传递[14~16]. Smad4（DPC4）可与Smad1，Smad2和Smad5在细胞内形成复合物，参与和调节TGFβ，Activin和BMP的信号传递[18]. Smad6和Smad7可与TGFβ受体或ⅠB型BMP受体结合但不被其磷酸化，因而可抑制TGFβ或BMP受体的信号传递[19,20]. 有活性的Ⅰ型BMP受体可与

Smad1 或 Smad5 结合，并磷酸化 Smad1 或 Smad5 蛋白质羧基端的丝氨酸，激活的 Smad1 或 Smad5 蛋白可由细胞浆转入细胞核[12]，或直接作用于下游靶基因，或与其他转录调节因子一起作用于下游靶基因. 在 Activin 的信号传递过程中，已经发现 Smad2、Smad4 转移到细胞核后可与转录因子 (FAST-1) 共同作用于下游靶基因[16]. 将突变后的 Smad5 的 cDNA 转染至 C2C12 前体细胞可抑制 BMP2 对这一细胞向成骨细胞分化的调节作用. 正常情况下，BMP2 可诱导这一前体细胞向成熟的成骨细胞分化[17]. 这一实验结果进一步证实了 Smad5 可作为 BMP 信号传递的下游分子参与 BMP 对成骨细胞分化的调节作用.

随着 BMP 受体的克隆、受体功能研究的进展以及 BMP 受体信号传递下游分子的发现，极大地丰富了人们对 BMP 作用机制的了解，促进了人们对胚胎发育，骨形成及骨细胞分化以及程序化细胞死亡的机制等方面的认识.

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Bone Morphogenetic Protein Receptor and Signal Transduction.

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Abstract Recently, several bone morphogenetic protein (BMP) receptors (I A, I B and II) have been cloned and characterized. BMP receptors belong to the TGFβ receptors family of serine/threonine kinases. Both type I and type II BMP receptors bind BMP ligands, in order to elicit a signal, heteromeric complexes of type I and type II receptors are required. Using truncated and constitutively active BMP receptors, it has been shown that type I A BMP receptor plays important role in mesoderm formation *in vivo*. Type I B BMP receptor plays major roles in chondrogenesis, osteoblast differentiation and programmed cell death *in vivo* and *in vitro*. BMP receptor signaling molecules Smad1 and Smad5 are also cloned and characterized. They also play important roles in BMP receptor mediated function.

Key words bone morphogenetic protein (BMP), receptor, serine/threonine kinase, signal transduction