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The SIE, SRE, CRE, and FAP-1 Four Intracellular Signal Pathways Between Stimulus and the Expression of c-fos Promoter

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ABSTRACT

c-fos gene has a close relationship with the osteoblasts. Mechanical signal effect on osteoblasts would change the expression level of c-fos. Authors introduce the signal pathways of four *cis*-response elements on the promoter of c-fos, that is, CRE (cAMP responsive element), FAP-1 (Fbs-AP-1 site), SRE (serum response element), and SIE (sis-inducible element), as the regulatory mechanism for c-fos gene expression following various stimuli. J. Cell. Biochem. 106: 764–768, 2009.

KEY WORDS: SIGNAL TRANSDUCTION PATHWAY; C-FOS GENE; RESPONSE ELEMENT; OSTEOBLASTS

Besides c-jun, myb, myc, ets, and ski, c-fos is also one of the hundred members in the family of immediate early genes (IEGs) which are considered to be the link between acute activity-dependent events and the long-term expression of gene, and which change the structure and function of a cell by coding the intra-nuclear protein and regulating the downstream gene expression [Deleu et al., 1999]. The length of human c-fos gene is 9 kb, including four exons and three introns, located at 14q of the chromosome. Encoding a 2.2 kb of mature mRNA, c-fos gene 3 product c-Fos is composed of 380 amino acids with a molecular weight of 55 kDa, sites in nucleus, is a nuclear phosphorylated protein. c-fos is a key regulatory factor for bone cell's growth and differentiation and has much effect on osteoblasts and osteoclasts during the normal development and bone diseases [Miyauchi et al., 1994; Olena, 1995; David, 1997; Papachristou et al., 2003]. The overexpression of c-fos gene in the transgenic mice would result in tumors of osteoblasts or cartilage cells [David, 1997]. On the contrary, the missing of c-Fos in transgenic mice, which completely blocks the differentiation of osteoclast will lead to bone sclerosis [Matsuo et al., 1999]. Researches in recent years show that among the IEGs family, c-fos gene has a close relationship with the osteoblasts [Laura et al., 1995; David, 1997; Nina et al., 1997; Jane et al., 1999; Sato et al., 1999; Bowler et al., 2001; Sze et al., 2004; Jun et al., 2006; Elisabetta et al., 2008; Jinbin et al., 2008; Schwartz et al., 2008; Yung et al., 2008].

REACTION OF C-FOS GENE TO STIMULI IN OSSEOUS CELL

Research has confirmed that some of the bone cells can perceive biophysical conditions such as mechanical and electrical signals and transfer them into a corresponding change in bone structure after processing and integration [Joseph et al., 1994; Sato et al., 1999; Turner and Akhter, 1999; Jun et al., 2006; Schwartz et al., 2008; Yung et al., 2008]. A study on the in vitro cultivation of cell strain found that an increase in mRNA levels of c-fos can be induced by tension, centrifugal force, vibration force, and so on significantly in a short term, and there would be a recovery to a normal level after a few hours. While Kostenuik [Kostenuik et al., 1997] once raised the hind limb of SD rats, non-weight-bearing, collected the tibia bone marrow stromal cells for cell culture 5 days later, and then after the cultivation of 10, 15, 20, 28 days analyzed the c-fos gene, ALP, and osteocalcin mRNA expression level.

It was found that c-fos mRNA expression level reduced by 50% than in the control group, ALP increased to 61%, osteocalcin reduced by 35%, which inferred that non-weight-bearing bone would inhibit the proliferation and differentiation of the in vitro bone cell. On hanging the rat by the tail for 2 weeks, there was significant inhibition of the c-fos gene expression and bone mineral density (BMD) increased in the region under the periosteum [Matsumoto et al., 1998]. On allowing the hind limbs to be

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mechanical-weight-bearing, c-fos gene expression of periosteal cell showed an instantaneous increase in less than 2 h. These studies suggested that c-fos can be used as a marker for bone cells reacting to some mechanical and other stimuli.

MECHANISM OF C-FOS GENE EXPRESSION CAUSED BY STIMULUS

Regulatory mechanism for c-fos gene expression is far from clear. Several parts in the DNA sequence have been found in the c-fos gene as the adjustment components taking part in regulation either in the physical condition or when the cells are exposed to various stimuli [Sato et al., 1999; Bowler et al., 2001; Jun et al., 2006; Schwartz et al., 2008; Yung et al., 2008]. They are the four *cis*-response elements [Joseph et al., 1994; Melissa, 2002; Hideki et al., 2007] on the promoter of c-fos, that is, CRE (cAMP responsive element), FAP-1 (Fbs-AP-1 site), SRE (serum response element), and SIE (sis-inducible element). We present them in the following to study the intracellular signaling pathways leading to c-fos gene expression caused by outside stimulus.

REGULATORY MECHANISM OF SIE RESPONSE ELEMENT

SIE sites at the 5′-end of the promoter, −348, have a basic sequence of TI'CCCGTCAA. It combines signal transducer and transcription activator. Studies found outside stimulus, such as colony stimulating factor (CSF-1), platelet-derived growth factor (PDGF) and so on, can stimulate c-fos gene transcription. They submit signal from outside into inside of cell by the composite JAKs–STAT pathway. Then the Tyr at the C end of STAT is phosphorylated and activated by JAK; this is very important which can dimerize STAT1 and STAT3. SIE combines with STAT1 and STAT3 complex [Benbassat et al., 1999] to induce c-fos gene expression. Other research holds that it is only STAT3, instead of STAT1, that gathers to SIE and activates c-fos transcription [Edwa et al., 2003].

REGULATORY MECHANISM OF SRE

SRE is just adjacent to FAP-1, −319; its basic sequence is GGATGTCCATATYAGGACATCT. It has a 10 bp of core sequence as CCATATTAGG, also known as the CArG box; E-box-binding sequence: CATCTG; C/EBP-binding sequence: TI'AGGACAT; as well as the Ets-binding sequence: GGA. It is a same type of dimer, serum response factor (SRF) and triple composite factor (ternary complex factor, TCF) that binds with it. SRF can identify CArG box on SRE. TCF, which is a subfamily member of the Ets-structure domain transcription factor family, at least three compositions, Elk-1, SAP-1, SAP-2/ERP/Net, does not automatically bind with SRE and so as to combine with DNA effectively without the assistance of SRF [Ramirez et al., 1997].

RTK-Ras-MAPK Signal Pathway. During the course of the outside stimulation signal submission to the nucleus, tyrosine kinase receptor (RTK)-Ras-MAPK is the most important signal pathway [Dunn et al., 2005]. Extracellular signal binds with Ras protein to form complex under the membrane through the "joint proteins," such as growth factor receptor binding protein 2 (Grb_2), SOS (son of sevenless), and so on. Ras protein is a representative of GTP-binding protein family, reputed as a "molecular switch," exchanging circularly from activity GTP-binding type to non-activity GDP-binding type as one of the key regulatory moleculars for cell proliferation and differentiation. Ras interacts with serine/threonine protein kinase Rafl by GTP-dependent mode and activates it by entering into the MAPK pathway. MAPK pathway contains a series of cascading events involving three key kinases: Raf (MAPK kinase kinase, MAPKKK), MEK (MAPK kinase, MAPKK), and MAPK (also known as the extracellular signal-regulated kinase, ERK). C-Raf-1 is an important effector in the downstream of Ras, bear the work of MAPK kinase kinase (MAPKKK/MEKK) as a bridge of Ras signal entering into MAPK signal pathway. Activated c-Raf-1 brings a selected phosphorylation and activation of MAPKK (MEK1 and MEK2, dual-specificity kinase, activates ERK subfamily of MAPK) which would make some ERK1 and ERK2 shift from cytoplasm to the nucleus and affect the nuclear material Elk-1 to promote the transcription of c-fos [Chen et al., 2004; Sze et al., 2004; Reuter et al., 2000].

Rho GTPase Signal Pathway. A study found that the mutation of c-fos promoter cannot combine with TCF to start the RTK-Ras-MAPK pathway, but it is still able to respond to stimulation signal from the serum. Research further shows that there is still another pathway different from the RTK-Ras-MAPK pathway which regulates the activity of SRE through SRF and known as Rho GTPase (Cdc42, Racl, and RhoA) signal pathway being a member of the Ras super-family including the three members. Activated Rho family member can regulate the activities of different transcription factors. Transcription activity of SRF is regulated by RhoA, Racl, and Cdc42Hs using two independent mechanisms that promote the activation of transcription factor NF-κB through the transfer of intracytoplasmic RelA/p50 and P50/p65 dimers to the nucleus [Reuter et al., 2000]. This path is different from Ras/Raf pathway. For example, Rac1 phosphorylates GDP/GTP exchange (activating IkBβ) and specifically activates the NF-κB depending on Vav and casein protein. Cdc42Hs catalyzes GDP/GTP exchange and specifically activates the NF-κB depending on Dbl. RhoA and Cdc42Hs specifically activate the NF-κB through catalyzed by Ost (activates neither IKBα nor IKBβ). It is inferred that there exists a JNK/SAPK pathway [Papachristou et al., 2003; Yung et al., 2008] in series for that wild-type MEKK1 can activate IKBα enzyme complex, while Rac1 and Cdc42Hs induce the present negative MEKK1 to inhibit the activity of NF-κB [Ysadora et al., 2008]. Moreover, activated Rac1, Cdc42Hs, and RhoA enhance the activity of ERK2 with the cooperation of Raf, and after a series of kinase activity level amplification, RhoA can activate ERK6 (P38γ) to constitute a new signal pathway by RhoA, PKN, MKK3/MKK6, and ERK6 (P38γ) [Marinissen et al., 2001; Yung et al., 2008].

REGULATORY MECHANISM OF CRE

CRE is at the 3-end of the promoter, −63; its basic sequence is TGACGTCA, mainly binding the cAMP response element binding protein (CREB) family member. CREB has two forms: transcription active dimer and non-transcription active monomer. CBEB activity adjustment mechanism is realized by the phosphorylation of the site

points (Ser98, Ser129, Ser133, Ser142), in which, Ser133 is the key site to activate; its phosphorus acidification can be a variety of catalytic protein kinases, including Ca^{2+}/CaM-dependent protein kinase, cAMP-dependent protein kinase, etc. [Cammarano and Minden, 2001; Servillo et al., 2002; Hideki et al., 2007].

Ca^{2+}/CaM-Dependent Protein Kinase. The multi-functional Ca^{2+}/CaM-dependent protein kinase (CaMK) is the Ser/Thr type protein kinase family, including I, II, IV, V subtypes, in which both CaMK II and IV have nuclear activity to identify the Ca^{2+} signal frequency, magnitude, and duration, and to control the gene expression through phosphorylation of the key site of nuclear transcription factor [Brigitte et al., 2000; Servillo et al., 2002].

Ca^{2+} signal that activates c-fos gene expression has a specific characteristic of the space. Studies have shown that nuclear Ca^{2+} signal activates the c-fos transcription through CRE, but the cytoplasm Ca^{2+} signal controls gene expression through a different mechanism, including stimulating the interaction between the transcription factor and the other *cis*-response element SRE on the c-fos promoter [Zayzafoon et al., 2005]. And the nuclear Ca^{2+} signal activates the CRE-dependent c-fos transcription is a course that needs a multi-step process; recent studies have revealed that the co-activated CREB-binding protein (CBP), containing a transcription activation area of signal regulation, is the target protein of signaling pathway activated by the nuclear Ca^{2+} [Maturana et al., 2002]. Nuclear Ca^{2+} signal activates the transcription of CBP after phosphorylated by CaMK IV; phosphorylated CBP combines with phosphorylated CREB by mutual activation, by which the specific sequence of the transcription exciter is connected to the transcription machinery, and then affects the transcription of the c-fos after the gathered chromatin depolymerization through its built-in or related group acetyltransferase activity.

CAMP-Dependent Protein Kinase. cAMP is a second messenger of intracellular messenger discovered earlier, which is the product of extracellular ligand after combining with its receptor through the G protein and the activated adenylyl cyclase; it continues to transmit information by a specific enzyme within cells that is cAMP-dependent protein kinase (PKA) [McGillis et al., 2002; Shimizu et al., 2004; Fitzgerald et al., 2000]. The whole PKA is constituted by four subunits (R_2C_2) in which two were of the same regulatory subunit (R) and two were of the same catalytic subunit (C). Subunit C has the catalytic activity structure district of kinase; subunit R has the site and regulation function in combination with two cAMPs. It is considered that subunit R has an inhibition to subunit C in the whole enzyme polymerized of subunits R and C, which has no catalytic activity. The combination of subunit R and cAMP leads to the dissociation of subunit R with C and the presentation of catalytic activity of subunit C. Immediately catalytic subunit C enters into the nucleus from cytoplasm, making the Ser133 phosphorylation activated in the vicinity of N-end transcription activity district of transcription factor CREB, so that the acidified CREB combines with the palindrome sequence (TGACGTCA) of the CRE so as to regulate c-fos expression.

REGULATORY MECHANISM OF FAP-1 RESPONSE ELEMENT

FAP-1 sites at the 5-end of CRE, −303, have a basic sequence of TGACTCA. This sequence having a binding site homology with activator protein-1 (AP-1) [Hideki et al., 2008], also named TPA response element (TRE), can bind with AP-1 protein family factor and CREB members under different conditions. AP-1 is referred to a class of protein family factor that can bind with AP-1-binding site, which is also called phorbol response elements (TPA responsive element, TRE) in many genes, and play an important role in cell differentiation, transcription, and apoptosis. AP-l is a series of collected protein dimers that all have "Leucine zipper" (basic region-leucine zipper, bZIP) structure including Jun (c-Jun, JunB, JunD), Fos (c-Fos, FosB, Fra-l, Fra-2), Maf (c-Maf, MafB, MafA, MafG/F/K, NrL), ATF (ATF2, LRF1/ATF3, B-ATF, JDP1, JDP2), and other subfamilies. Jun family members may be homologous polymerized with the family members or heterologous polymerized with Fos family members, with a stronger stability and activity of inducing gene transcription for a Fos heterologous dimer of AP-1 molecular than a Jun homologous dimer of AP-1 molecular [Laura et al., 1995; Jinbin et al., 2008]. A Fos family member can only bind with a Jun family member to be a AP-1 type of heterologous dimer. Then Jun–Jun and Jun–Fos dimers have a tendency to bind with FAP-1 which may be related to the role of Fos transcription of the negative feedback regulation. Phosphorylation of CREB can also be combined with FAP-1, which was studied to show a probable promoted interaction between the *cis*-response elements CRE and FAP-1 [Melissa, 2002].

Serving as the third nuclear messenger and as a molecular switch of gene transcription regulation, AP-1 family member c-fos's expression plays an important role in the coupling in information delivery cascade reaction stimulated by outside stimulating signals after osteoblasts are affected by outside mechanical stimulation. c-fos sites in many bone-specific gene promoters, such as alkaline phosphatase, human osteocalcin, osteocalcilin (which is related to bone mineralization), collagenase I (which is directly related to bone resorption), and so on [Mi et al., 1996; Nina et al., 1997; Daniella et al., 1999; Jane et al., 1999], indicate that c-fos is closely related to bone alteration and metabolism, and its expression directly affects the downstream long-term gene expression, changes cell phenotype, and produces biological effects. This would or might guide people apply the integration of such signal network to specifically regulating c-fos gene expression as well as the downstream cell reaction by some biomedical intervention.

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