

SP Transcription Family Involve In Tooth Development ?

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Abstract

Specificity Protein (SP) family members are tissue specific transcription factors. They regulate a wide range of cellular function including cells growth, apoptosis, differentiation and tumor formation. This family composed of more than 25 member proteins, which contain a DNA-binding domain very well conserve between all members with three tandem zinc fingers of the C₂H₂ type in their Cterminal region. Recently, it has reported in mammalian genome, there are nine Sp genes (Sp1-Sp9). Some previous study reported Sp3 knockout mice have enamel/dentin layer defect. Sp4 mRNA express in E13- E16 of WT mouse incisor. Sp7 mRNA express in at 15, 17 days of post coitum and P1 (postnatal day 1). Sp6 has another name epiprofin, I also worked with this genes. *Sp6* mRNA expressed in early stage of tooth development to the secretory stage of ameloblast. It also reported *Sp6* weakly expressed in mesenchymal odontoblast of the incisor. *Sp6* deficient mice reported delay tooth development. SP family members play an important role in tooth development.

Keyword: SP family, transcription factor, tooth development

SP Transcription Family Terlibat dalam Perkembangan Gigi?

Abstrak

Specificity Protein (SP) merupakan faktor transkripsi pada jaringan spesifik. Protein ini mengatur berbagai fungsi sel termasuk pertumbuhan, apoptosis, diferensiasi dan pembentukan tumor. Keluarga protein ini terdiri dari lebih dari 25 anggota, yang mengandung domain pengikat DNA yang sangat mirip di setiap anggota pada tiga tandem zinc fingers dari tipe C₂H₂ di bagian C-terminal. Saat ini telah dilaporkan terdapat sembilan gen Sp (Sp1-Sp9) dalam genom mamalia. Beberapa penelitian sebelumnya melaporkan Sp3 tikus K menyebabkan kerusakan pada lapisan email/dentin. mRNA Sp4 terlihat pada E13-E16 WT gigi incisivus tikus. Sp7 mRNA terlihat pada hari ke 15, 17 pascacoitum dan P1 (pascakelahiran hari pertama). Sp6 memiliki nama lain yaitu

epiprofin, saya juga bekerja dengan gen ini. Sp6 mRNA terlihat pada tahap awal perkembangan gigi ke tahap keluar nya

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gigi dari ameloblast. Juga dilaporkan Sp6 terlihat agak lemah di odontoblast mesenchymal pada gigi incisivus. Defisiensi gen Sp6 pada tikus dilaporkan bahwa terjadi penundaan pertumbuhan gigi. SP memainkan peran penting dalam perkembangan gigi.

Kata kunci: keluarga SP, factor transkripsi, perkembangan gigi

Introduction

Regulation of transcription is an important to explore the question of how DNA sequence information is used appropriately by mammalian cells. Using an array of biomolecular tools, we can identify all the genes that encode transcription factor belonging the certain class and also study their biological function ¹. The SP/KLF transcription factor family contains over 25 members sharing a DNA-binding domain composed of three zinc fingers motif of the C₂H₂ type at the C-terminus and binds to GGGCGG motifs or related GC-rich sequence. This family comprises of nine members (Sp1-Sp9) in mammals ¹⁻²

. Each members are located adjacent to a HOX gene cluster ³.

A number of transcription factors control tooth development in order to form unique structures specialized for tooth function especially for shapes and sizes. The developing tooth is a good model for

studying the aspects of molecular and genetic on mammalian tooth development ³. During tooth development epithelial and mesenchyme interaction is thought very important. Early signals for tooth development arise in the oral ectoderm, appearing as thickening of the dental lamina. The dental lamina invaginates into the underlying neural crest-derived mesenchyme to form the tooth bud. The dental epithelial cells proliferate to form a double layer cap that is called the enamel organ. After the cap stage, the tooth germ progresses to the bell and late bell stages before the tooth erupts into the oral cavity. All these stages are regulated not only by cytokines, such as bone morphogenetic proteins (BMPs), sonic hedgehogs (Shhs), fibroblast growth factors (FGFs), and *wingless* (Wnts), but also by extracellular matrices. The deletion of these gene functions results in the arrest of tooth development ⁴⁻⁷.

The SP-Family

The first identified member of this family is termed SP1, for Specificity Protein, in the 21bp repeats of the simian virus (SV40) early promoter. DNA binding domain of SP1 is composed of three zinc fingers of the classical Cys2–His2 type. The first four members of the Sp-family (Sp1-4) are more

closely related to each other than to Sp5-8. Sp 1-4 contain an N-terminal activation domain and a C-terminal DNA binding domain. Sp5-8 proteins are shorter, lacking the N-terminal activation domain. This may decrease transcriptional activation potential. The overview of each Sp-family domain is performing in the figure 1.

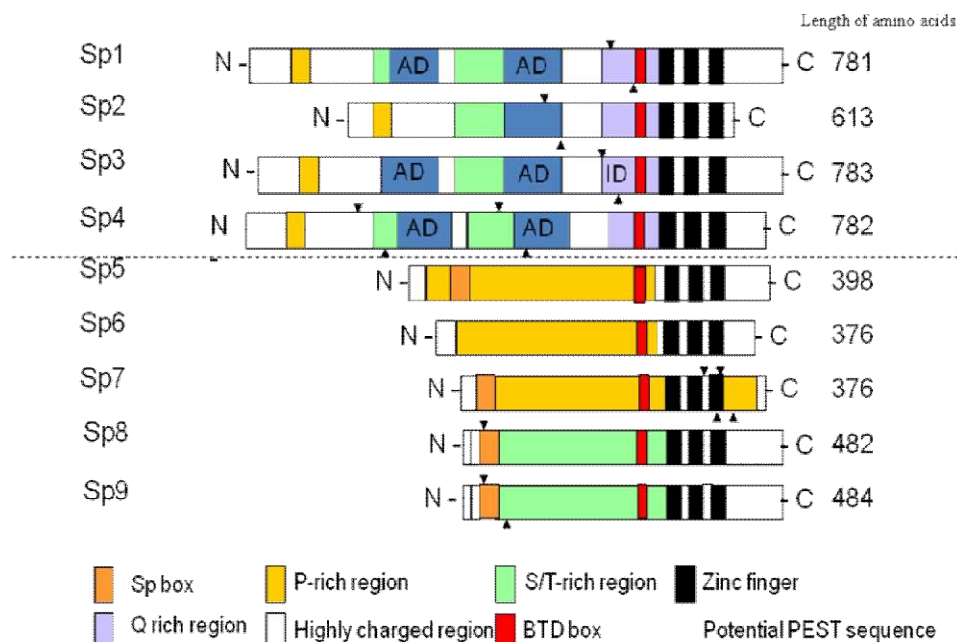


Figure 1. The domain structure of Sp-family transcription factors
(Modified from Bowman P. and Philipsen S., 2002)⁸

At C-terminal, three black boxes are C2H2 type zinc finger motifs for DNA binding. This domain is a common feature of Spfamily. At N-terminal is a transcriptional regulatory domain. The red box is buttonhead box, it may contribute to transactivation³

Regulation of Sp transcription factors in tooth development

Both of *Sp1* and *Sp3* have been reported to exhibit ubiquitous expression and dental epithelium. *Sp2* expression has been observed in a number of cell lines, whereas *Sp4* expression, currently reported expressed in CNS, liver, lung, kidney,

heart, gonads, intestine and also in dental papilla and dental sac^{3,9}

. *Sp7* was observed play roles as a

bone specific transcription factor required for osteoblast differentiation and bone formation⁽¹⁰⁾. *Sp5*, *Sp8*, and *Sp9* are expressed in specific tissue and developing stages⁹. *Sp6* that correspond to epiprofin. This gene has reported by some researchers

play roles in teeth developing, caudal neuropore, limb bud, hair follicles, skin and dental epithelium¹¹. I also worked using this *Sp6* gene, our laboratory has found that *Sp6* promotes amelogenesis through inhibition of follistatin gene expression while follistatin is responsible for the formation of an enamel-free area in the mouse incisor and molar by inhibiting ameloblast differentiation¹²

. For overview of the expression pattern of Sp transcription factors,

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including the knockout mice of each members perform in Table 1.

Table 1. Expression pattern of Sp transcription factors in vertebrate embryos⁹

Factors	Expression	Chromosomal Location	Major phenotypes in knockout mice
Sp1	Ubiquitous, Dental epithelium	Human: 12q13.1 Mouse : 15	Growth retardation, prenatal lethality
Sp2	Ubiquitous	Human: 17q21.32 Mouse : 11	Growth retardation, prenatal lethality
Sp3	Ubiquitous, Dental epithelium	Human: 2q31 Mouse : 2	Growth retardation, Defect in tooth, lung, bone and hematopoietic
Sp4	CNS, liver, lung, kidney, heart, gonads, intestine, Dental papilla, and dental sac	Human: 7q15.3 Mouse : 12	Postnatal mortality, smaller body size
Sp5	Mesoderm precursors, derivatives posterior neuroectoderm,	Human: 2q31 Mouse : 2	No morphological changes enhanced frequency of taillessness
Sp6/Epiprofin	Developing teeth, caudal neuropore, limb bud, hair follicles, skin and dental epithelium	Human: 17q21.32 Mouse : 11	Enamel defect, supernumerary teeth, defective cups and root formation
Sp7/Osteorixin	Developing bone and teeth Odontoblast and dental follicle cells	Human: 12q13.13 Mouse : 15	Death at birth, Failure in ossification
Sp8	CNS, limb buds	Human: 7q15.3 Mouse : 12	Neural tube closure failure, shorter limbs

Sp9	In specific domain of CNS, limb	Human: 2q31 Mouse : 2	unknown
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Sp6in tooth development

Table 1 above showed that most of Sp-family members are correlate with tooth development. *Sp1* is expressed in dental epithelium. *Sp1* and *Sp2* knockout mice die in embryonic stage. *Sp3* is also expressed in dental epithelium. Mice lacking *Sp3* showed defect of enamel, lack amelogenin, and ameloblast, impaired ossification. *Sp4* is expressed Dental papilla, and dental sac ^{8,9}. *Sp4* and *Sp7* are expressed in dental mesenchyme ⁹. Since I was working with *Sp6* gene that we believed might play role in tooth development.

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*Sp6*mRNA is expressed tooth germ ¹³. Expression of *Sp6* is detected at the initiation stage of tooth development. *Sp6* is clearly expressed in dental epithelium of dental lamina but not expressed in dental mesenchyme (another report said that *Sp6* weakly expressed in mesenchymal odontoblast of the incisor) at early stage of tooth development. During the bud stage, *Sp6* is expressed widely in dental epithelial cells and tooth bud develops rapidly by dental epithelial cell proliferation. At the cap stage,

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dental epithelial cells determine their cell fate into several lineage such as stellate reticulum and inner and outer enamel epithelium. At the bell stage,

Sp6 is expressed in pre ameloblast and ameloblast⁹. Figure 2 is describing the expression of *Sp6* in each stage of tooth development.

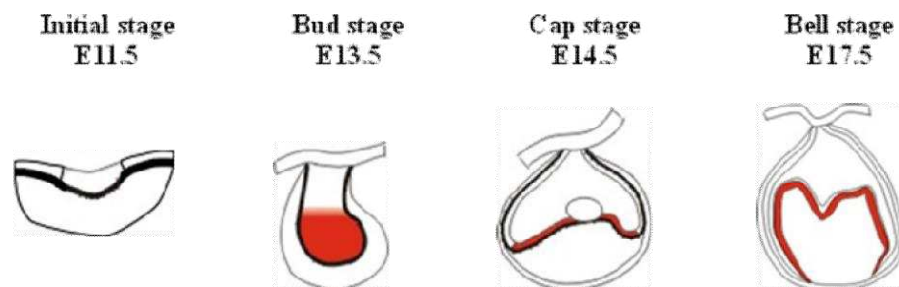
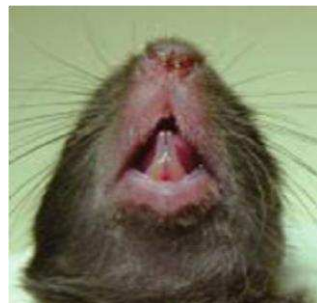


Figure 2.the expression of *Sp6* during tooth development. The meaning of the red symbol () expression *Sp6* in epithelium (<http://bite-it.helsinki.fi/>)¹⁴

As reported Nakamura et.al., 2011, in Table 1. *Sp6* knockout mice showed enamel defect, supernumerary teeth, defective cups
WT

and root formation. This result is consistence with their previous report in 2008, are showed in Figure 3, *Sp6* deficient mice.

3 weeks old



12 months old



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Figure 3. Amazing teeth phenotype in Sp6 deficient mice¹¹

The surprising/amazing phenotype of *Sp6* deficient mice. On the left side are Wild type (WT), the right side are mutant mice. At 3 weeks age, incisor and molar mutant mice were not erupted. In contrast at 12 month age mutant incisors showed multiple teeth. This result strongly suggested the involvement of *Sp6* in tooth development.

Conclusion

Tooth development is regulated by inductive interactions between the epithelium and the mesenchyme via reciprocal signalings and some cytokines are involved. Some of Sp-family have reported appear have diverse play roles in tooth development. However, the regulatory mechanism of reciprocal epithelium and mesenchyme, Sp-family, the cytokines and other signaling require further characterization.

References

1. Suske G, Bruford E, Philipsen S: Mammalian SP/KLF transcription factors: bring in the family. *Genomics* 85: 551-556, 2005
2. Jimenez-Rojas L, Ibarretxe G, Aurrekoetxea M, de-Vega S, Nakamura T, Yamada Y, Unda F: Epiprofin/ Sp6: A new player in the regulation of tooth development. *Histol Histopathol* 25: 1621-1630, 2010
3. Waby, J.S, Bingle, C.D and Corfe, B.M., Post-Translation control of Sp-family transcription factors. *Current Genomics* 9;301-311, 2008
4. Maas R, Bei M: The genetic control of early tooth development. *Crit Rev Oral Biol Med* 8: 4-39, 1997
5. Jernvall J, Thesleff I: Reiterative signaling and patterning during mammalian tooth morphogenesis. *Mech Dev* 92: 19-29, 2000
6. Thesleff I: Epithelial-mesenchymal signalling regulating tooth morphogenesis. *J Cell Sci* 116: 1647-1648, 2003
7. Wahyudi IA, Horiguchi T, Miyoshi K, Muto T, Utami TW, Hagita H, Noma T: Isolation and characterization of mouse *Specificity Protein 6* promoter. *Ind J Dent Res* 1: 13-26, 2010
8. Bouwman, P., H. Gollner, H. P. Elsasser, G. Eckhoff, A. Karis, F. Grosveld, S. Philipsen, and G. Suske. Transcription factor Sp3 is essential for post-natal survival and late tooth development. *EMBO J.* 19:655-661, 2000
9. Nakamura T, Fukumoto S, Yamada Y. Diverse function of epiprofin in tooth development. *J. Oral Biosci.* 53(1): 22-30, 2011
10. Zhang C. Transcriptional regulation of bone formation by the osteoblast-specific transcription factors Osx. *Journal of Orthopaedic surgery and Research* 5(37): 1-7, 2010

11. Nakamura T, de-Vega S, Fukumoto S, Jimenez L, Unda F, Yamada Y: Transcription factor epiprofin is essential for tooth morphogenesis by regulating epithelial cell fate and
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12. Ruspita I, Miyoshi K, Muto T, Abe K, Horiguchi T, Noma T: Sp6 downregulation of follistatin gene expression in ameloblasts. J Med Invest 55: 87-98, 2008
13. Nakamura T, Unda F, de-Vega S, Vilaxa A, Fukumoto S, Yamada KM, Yamada Y: The tooth number. J Biol Chem 283: 4825-4833, 2008
Krüppel-like factor epiprofin is expressed by epithelium of developing teeth, hair follicles, and limb buds and promotes cell proliferation. J Biol Chem 279: 626-634, 2004
14. <http://bite-it.helsinki.fi/>