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 C_2H_2 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 jaringanspesifik.Protein ini mengaturberbagaifungsi seltermasuk pertumbuhansel,apoptosis,diferensiasi danpembentukan tumor.Keluarga protein initerdiri darilebih dari 25 anggota, yangmengandung domainpengikat DNA yang sangat miripdisetiap anggotapada tiga tandem zinc fingers dari tipeC_2H_2di bagian C-terminal.Saat initelahdilaporkan terdapat sembilangen Sp(Sp1-Sp9) dalam genom mamalia. Beberapapenelitian sebelumnyamelaporkanSp3tikus KOmenyebabkan kerusakan pada lapisan email/dentin.mRNASp4terlihat pada E13-E16 WTgigi incisivus tikus. Sp7mRNAterlihat pada hari ke 15, 17pascacoitumdanP1(pascakelahiran haripertama).Sp6memiliki nama lain yaitu

epiprofin, saya juga bekerja dengan gen ini.Sp6mRNAterlihat padatahap 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 trankripsi, 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 C_2H_2 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, forSpecificity Protein, in the 21bprepeats of the simian virus (SV40) early promoter. DNA binding domain of SP1 iscomposed 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.

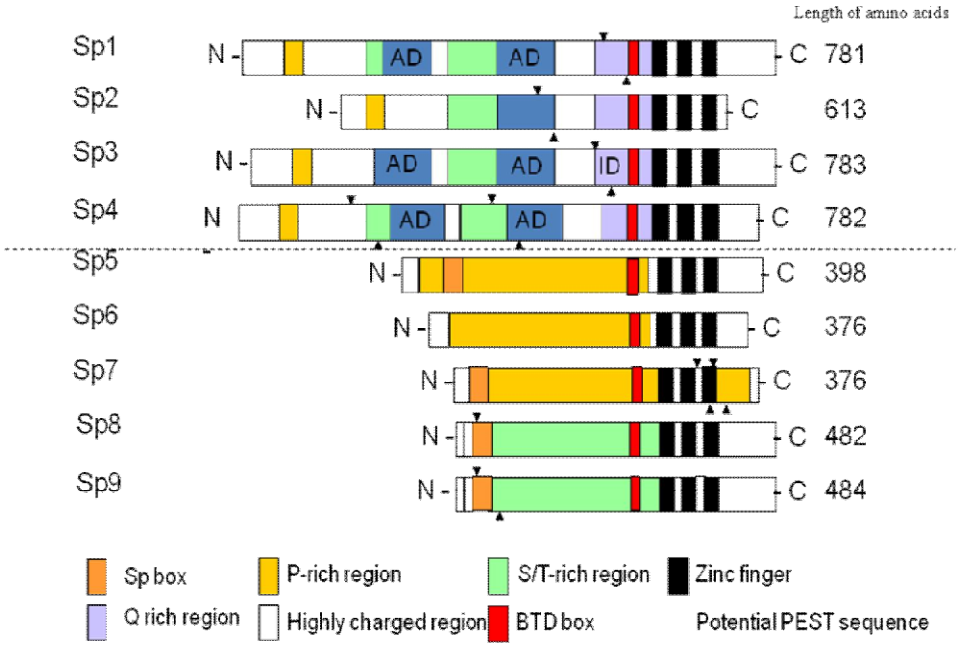

Figure 1. The domain structure of Sp-family transcription factors (*Modified from Bowman P. and Philipsen S., 2002)*[8]

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 transactivation [3]

Regulation of Sp transcription factors in tooth development

Both of *Sp1* and *Sp3* have been reported to exhibit ubiquitous expression and dental epthelium. *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 stages [9]. *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 epithelium [11]. I also worked using this *Sp6* gene, our laboratory has found that *Sp6* promotes amelogenesis through inhibition of follistatin gene expression while follistatin is responsiblefor the formation of an enamel-free area in the mouse incisor and molar by inhibiting ameloblast differentiation [12]. For overview of the expression pattern of Sp transcription factors,

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

Table 1. Expression pattern of Sp transcription factors in vertebrate embryos [9]

Factors	**Expression**	**Chromosomal Location**	**Major phenotypes in knockout mice**
Sp1	Ubiquitous, Dental epthelium	Human: 12q13.1 Mouse : 15	Growth retardation, prenatal lethality
Sp2	Ubiquitous	Human: 17q21.32 Mouse : 11	Growth retardation, prenatal lethality
Sp3	Ubiquitous, Dental epthelium	Human: 2q31 Mouse : 2	Growth retardation, Defect in tooth, lung, bone and hematopoetic
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, derivates 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/Osterix	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

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.

Sp6in tooth development

*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,

IDJ, Volume 1,No. 1, Tahun 2012

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 ameloblast [9]. Figure 2 is describing the expression of *Sp6* in each stage of tooth development.

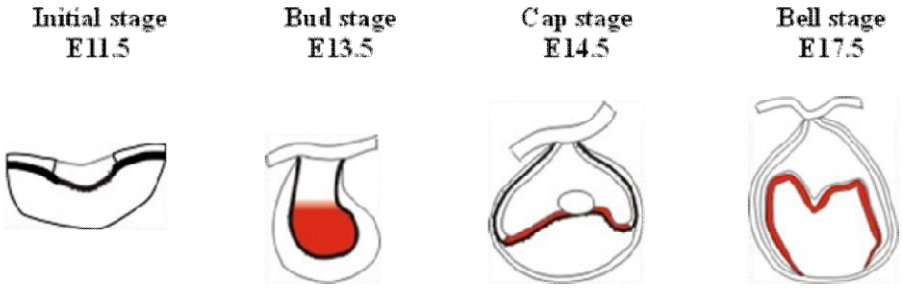

Figure 2.the expression of Sp6 during tooth development. The meaning of the red symbol ( ) expression *Sp6* in epithelium (http:bite- it.helsinki.fi/)[14]

As reported Nakamura et.al., 2011, in Table 1. *Sp6* knockout mice showed enamel defect, supernumerary teeth, defective cups and root formation. This result is consistence with their previous report in 2008, are showed in Figure 3, *Sp6* deficient mice.

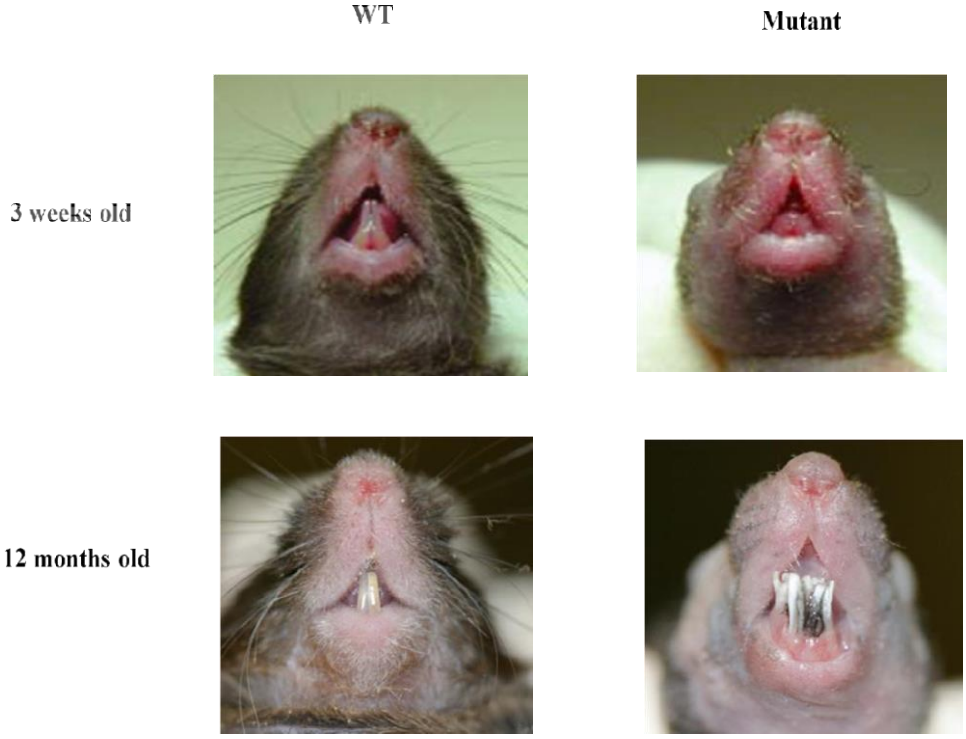

Figure 3. Amazing teeth phenotype in Sp6 deficient mice[11]

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 contras 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.

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