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_{2}H_{2} type in their C-terminal 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

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. 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 GGGCGGG motifs or related GC-rich sequence. This family comprises of nine members (Sp1-Sp9) in mammals. Each members are located adjacent to a HOX gene cluster.

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. 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.

The SP-Family
The first identified member of this family is termed SP1, for Specificity Protein, in the 21-bp 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](image)

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

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 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
responsible for 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

<table>
<thead>
<tr>
<th>Factors</th>
<th>Expression</th>
<th>Chromosomal Location</th>
<th>Major phenotypes in knockout mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sp1</td>
<td>Ubiquitous, Dental epithelium</td>
<td>Human: 12q13.1</td>
<td>Growth retardation, prenatal lethality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mouse: 15</td>
<td></td>
</tr>
<tr>
<td>Sp2</td>
<td>Ubiquitous</td>
<td>Human: 17q21.32</td>
<td>Growth retardation, prenatal lethality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mouse: 11</td>
<td></td>
</tr>
<tr>
<td>Sp3</td>
<td>Ubiquitous, Dental epithelium</td>
<td>Human: 2q31</td>
<td>Growth retardation, Defect in tooth, lung, bone and hematopoetic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mouse: 2</td>
<td></td>
</tr>
<tr>
<td>Sp4</td>
<td>CNS, liver, lung, kidney, heart, gonads, intestine, Dental papilla, and dental sac</td>
<td>Human: 7q15.3</td>
<td>Postnatal mortality, smaller body size</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mouse: 12</td>
<td></td>
</tr>
<tr>
<td>Sp5</td>
<td>Mesoderm precursors, derivates posterior neuroectoderm.</td>
<td>Human: 2q31</td>
<td>No morphological changes enhanced frequency of taillessness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mouse: 2</td>
<td></td>
</tr>
<tr>
<td>Sp6/Epiprofin</td>
<td>Developing teeth, caudal neuropore, limb bud, hair follicles, skin and dental epithelium</td>
<td>Human: 17q21.32</td>
<td>Enamel defect, supernumerary teeth, defective cups and root formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mouse: 11</td>
<td></td>
</tr>
<tr>
<td>Sp7/Osterix</td>
<td>Developing bone and teeth Odontoblast and dental follicle cells</td>
<td>Human: 12q13.13</td>
<td>Death at birth, Failure in ossification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mouse: 15</td>
<td></td>
</tr>
<tr>
<td>Sp8</td>
<td>CNS, limb buds</td>
<td>Human: 7q15.3</td>
<td>Neural tube closure failure, shorter limbs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mouse: 12</td>
<td></td>
</tr>
</tbody>
</table>
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. Sp4 and Sp7 are expressed in dental mesenchyme. Since I was working with Sp6 gene that we believed might play role in tooth development.

<table>
<thead>
<tr>
<th>Sp9</th>
<th>In specific domain of CNS, limb</th>
<th>Human: 2q31 Mouse: 2</th>
<th>unknown</th>
</tr>
</thead>
</table>

**Sp6 in tooth development**

Sp6 mRNA is expressed tooth germ. 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 ameloblast. Figure 2 is describing the expression of Sp6 in each stage of tooth development.

<table>
<thead>
<tr>
<th>Initial stage</th>
<th>Bud stage</th>
<th>Cap stage</th>
<th>Bell stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>E11.5</td>
<td>E13.5</td>
<td>E14.5</td>
<td>E17.5</td>
</tr>
</tbody>
</table>

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.

WT

Mutant

3 weeks old

12 months old
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Figure 3. Amazing teeth phenotype in Sp6 deficient mice

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

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


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