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Review Article

SHOX And *SHOX2* Share a Tissue-Specific Functional Redundancy in Temporomandibular Joint Formation

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Abstract

SHOX is a human *pseudoautosomal* gene that was first identified as a potential gene for the short stature phenotype of Turner Syndrome and Leri-Weill syndrome. Patients with Langer syndrome exhibit extremely short and bowed arm and leg zeugopod elements. That is, they have short radius/ulna and short tibia/fibula. This makes it important to investigate whether *SHOX* contributes to short stature phenotype and to assess the function of *SHOX* and *SHOX2* in long bone development and in the formation of TMJ. Since there is no *SHOX* ortholog in the mouse genome, and the mouse Shox2 shares 99% identity at the amino acid level and exhibit a similar expression pattern to that of human *SHOX2*, replacing murine *shox2* with human SHOX will be an effective model for studying the functional link between human *SHOX* and *SHOX2* during embryogenesis, especially in the formation of the temporomandibular joint. This article gives a review of the role *Shox2* plays in the formation of TMJ and the functional redundancy that exists between human *SHOX* and *SHOX2* in TMJ formation. Overall, functional redundancy that exist between human SHOX and SHOX2 during temporomandibular joint formation is only in a tissue-specific manner.

Keyword: Temporomandibular joint; *SHOX; SHOX2; Shox2*; Indian hedgehog

Abbreviations: TMJ: Temporomandibular joint; SAN: Sinoatrial Node; Ihh: Indian hedgehog

Introduction

SHOX is a human pseudoautosomal gene that was first identified as a potential gene for the short stature phenotype of Turner Syndrome [1]. It has been made known that some idiopathic short stature patients tend to have mutations in the SHOX gene [2]. In addition, mutations in *SHOX* have been identified as causative for a mesomelic short stature syndrome called Leri–Weill syndrome [1,3,4]. The contribution of *SHOX* to the abnormal phenotype in patients with Tuner Syndrome is due to haploinsufficiency, however, the role of *SHOX* is more obvious in Langer syndrome because the Langer Syndrome is caused by a complete lack of *SHOX* function [5]. Patients with Langer syndrome have extremely short and bowed arm and leg zeugopod elements. That is, they have short radius/ulna and short tibia/fibula. These different clinical findings, as far as bone deformities and growth is concerned, have prompted various researchers to investigate whether *SHOX* causes or contributes to short stature phenotype [6], and to assess the function of *SHOX* and *SHOX2* in long bone development and in the formation of TMJ. Due to the paucity of data from *SHOX* - mutant human embryos, to understand the developmental basis of these Short limbs and the overall role *SHOX* plays in bone and TMJ formation, a mouse model is used [5].

Although mice have lost their *SHOX* gene over time, they still have an autosomal *Shox2* paralog, which is found in humans. Murine *SHOX2* share 99 percent amino acid identities with human *SHOX2*. It is also similar to the human *SHOX* (79 percent, with an identical DNA -binding homeodomain). In addition, murine Shox2 and human *SHOX2* and *SHOX* are highly expressed in proximal domains of developing limbs [6]. Clement-Jones M, et al. [6], have shown that the *SHOX2* orthologue, Og12x (*Shox2*), represents the closest mouse *SHOX* homologue. *SHOX* and *SHOX2* are closely related members of the SHOX (short stature homeobox) gene family in humans, however there is no *SHOX* ortholog in the mouse genome. These

two genes in humans exhibit overlapping and distinct expression patterns in many developing organs and therefore it is important to understand the possible functional redundancy that exist between them [7]. Since there is no *SHOX* ortholog in the mouse genome, and the mouse *Shox2* shares 99% identity at the amino acid level and exhibit a similar expression pattern to that of human *SHOX2*, replacing murine *shox2* with human *SHOX* will be an effective model for studying the functional link between human *SHOX* and *SHOX2* during embryogenesis especially in the formation of the temporomandibular jaw (TMJ). This review therefore seeks to summarize the role *Shox2* plays in the formation of TMJ and consequently assess the functional redundancy that exists between human *SHOX* and *SHOX2* in TMJ formation.

Mechanism of Action

The temporomandibular joint (TMJ) is a complex structure made up of the condyle, fibrocartilaginous disc, and glenoid fossa. It is exclusively present in mammals and is necessary for jaw movement [8,9].

Even though *SHOX2* has not been associated to any known syndrome in humans, *Shox2* gene is required for the development of all long bones that go through endochondral ossification [5,10]. Studies have shown that null mutation in *Shox2* leads to a large array of developmental defects, which includes formation of the cleft palate, TMJ ankylosis, virtual deletion of the stylopod in limbs, as well as embryonic lethality at the mid-gestation stage resulting from failed differentiation of SAN cells and dysplasia of the sinus valves [11,12]. In their quest to study the functional redundancy between *SHOX* and *SHOX2*, Liu H, et al. [7], developed a knock-in mouse strain (referred to as *Shox2* KI/KI) by replacing murine *Shox2* with human *SHOX* and demonstrated that murine *Shox2* and human *SHOX* possess similar transcriptional activity and hence Human *SHOX* is able to substitute for *Shox2* in regulating the development of many organs. They discovered that *SHOX* expression at the *Shox2* locus appears to execute many of the same functions as *Shox2*, as evidenced by the absence of embryonic lethality and the restoration of developmental abnormalities in several organs when *Shox2* was absent. As a result, *Shox2* KI/KI mice develop a normal palate and live to adulthood and thus, they did not have TMJ dysplasia or ankylosis when they were born.

Notwithstanding, even though the TMJ ankylosis was completely rescued, *Shox2* KI/KI mice exhibited premature wear of the articulating disc, a new TMJ defect, and this seemed to lead to a wasting syndrome. This is clinically referred to as TMJ disc disorders [7,13]. This indicates that a functional redundancy exists between these two genes. However, given that *Shox2* KI/KI mice suffer a premature wear out defect in the TMJ's articulating disc and differential recovery of the forelimb deficit versus the hind limb, it can be inferred that functional redundancy exists between *SHOX* and *SHOX2* only in a tissue specific manner [7].

To understand the cause of this premature wear out articular disc in the *Shox2 SHOX*-KI/KI mice, the molecular and cellular bases for early articular disc wear out in the TMJ of mice bearing the human *SHOX* replacement allele in the *Shox2* locus (*Shox2 SHOX*-KI/KI) were examined by Li X, et al. [8]. While the developmental process and expression of numerous important genes in the TMJ of *Shox2 SHOX*-KI/KI mice looked to be identical to controls, they discovered that the disc of the *Shox2 SHOX*-KI/KI TMJ had a lower level of Col I and Aggrecan, as well as higher MMP activity and Ihh expression. Interestingly, pre-hypertrophic chondrocytes produce Indian hedgehog (Ihh) in the growth plate to regulate chondrocyte proliferation and parathyroid-hormone-related protein (PTHrP), leading to the induction of intramembranous bone collar formation around the diaphysis during bone formation, [14-16] and Ihh is expressed in the mandibular condyle growth plate in mouse embryos, and as such, condylar fibrous and polymorphic cell layers express its receptors and related signaling molecules preferentially [17,18]. Ihh signaling is therefore necessary for chondroprogenitor cell proliferation, PTHrP expression, and condylar growth, according to Shibukawa Y, et al. [17]. Therefore, the low level of Col I and Aggrecan, increased activities of matrix metalloproteinases (MMPs) and most especially, the downregulation of Ihh expression observed in the TMJ of *Shox2 SHOX*-KI/KI mice by Li et al. [8] led to the rapid increased cell apoptosis in the disc and consequently contributed to the observed disc phenotype.

Conclusion

Shox2 and human *SHOX* possess similar transcriptional activity and therefore *SHOX* can be substituted for *Shox2* in regulating the development of many organs. This is evidenced by the absence of embryonic lethality and the restoration of developmental abnormalities in several organs when *Shox2* was absent. However, since *Shox2* KI/KI mice exhibited premature wear of the articulating disc, which led to a new TMJ defect even though the TMJ ankylosis was completely rescued, functional redundancy that exist between human *SHOX* and *SHOX2* during temporomandibular joint formation is only in a tissue specific manner and that the observed low level of Col I and Aggrecan, increased activities of matrix metalloproteinases (MMPs) and the down-regulation of Ihh expression observed in the TMJ of *Shox2 SHOX*-KI/KI was the possible cause of the new TMJ defect. Hence, while the human *SHOX* can regulate early TMJ development in the same way as the mouse *Shox2* does, it is obvious that it has a unique role in the regulation of tissue homeostasis molecules.

Acknowledgement

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Conflict of Interest

The author declares no conflict of interest.

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