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Mini-Review

Role of extracellular matrix and minor fibrillar collagens in Sox induced chondrogenesis during craniofacial development - A mini-review

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ABSTRACT

An essential aspect of craniofacial development is chondrogenesis, the process of chondrocyte differentiation from multipotent neural crest cells. These multipotent cells delaminate from the neural tube during neurulation, travel along specific routes and differentiate into various cell types forming different tissues. The formation of this wide range of neural crest cell derivatives is dependent on multiple factors, including transcription factors, extracellular matrix proteins, and growth factors. Sox proteins are transcription factors that play a role during development of various tissues. L-Sox5, Sox6 and Sox9 play a role in the differentiation of neural crest cells into chondrocytes by binding to regulatory elements, enhancing the expression of chondrocyte-specific collagens. Minor fibrillar collagens V and XI contribute to chondrogenesis of the craniofacial skeleton by mechanisms that include the regulation of collagen fibrillogenesis and a bridging function between major fibrillar collagens and other cell or matrix molecules. However, the mechanism of regulation is not fully understood. Disruption of craniofacial development during chondrogenesis can lead to Stickler Syndrome or Campomelic Dysplasia as a result of collagen XI and Sox9 mutations, respectively. Here, we focus on potential additional mechanisms by which the extracellular matrix plays a role in Sox-mediated chondrogenesis during craniofacial development. PTHrP may be the link between the expression of extracellular matrix and Sox transcription factor family-mediated regulation of chondrogenesis, creating a regulatory cycle that supports growth and development of cartilage-derived structures.

KEYWORDS: Sox9, craniofacial, chondrogenesis, neural crest cells, collagen, PTHrP

ABBREVIATIONS

Sox (Sry (Sex determining Region Y)- HMG box), ECM (Extracellular Matrix), EMT (Epithelial-Mesenchymal Transition), FGF (Fibroblast Growth Factor), Hox (Homeobox), NCC (Neural Crest Cell), CD (campomelic dysplasia), cyclic-AMP (cAMP) response element-binding (CREB), BMP (Bone Morphogenetic Protein), MAP (Mitogen-Activated Protein), PGC1-α (Proliferation activated receptor gamma co-activator 1- alpha), TRAP (thyroid hormone receptor associated protein), PKA (Protein Kinase A), PNS (Peripheral Nervous System), PTHrP (Parathyroid hormone-related protein)

INTRODUCTION

Congenital craniofacial abnormalities span a spectrum of deformities including cleft palate, deformed jaw, severe defects of the eye and mental retardation. Due to the nature of these

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disorders, treatment is limited and can lead to lifelong physiological and psychological suffering of the concerned individuals.

The craniofacial skeleton is formed via intramembranous and endochondral ossification in which cartilage formation precedes that of bone. Multipotent mesenchymal cells condense and differentiate into chondroblasts, which then proliferate rapidly and differentiate into chondrocytes. Chondrocytes deposit the cartilage-specific extracellular matrix (ECM) proteins, proliferate and become hypertrophic. Upon hypertrophy, the cells grow in size, alter their collagen expression and eventually undergo apoptosis. Simultaneously, mesenchymal cells surrounding the hypertrophic cartilage differentiate into osteoblasts and secrete bone matrix, while osteoclasts degrade the hypertrophic cartilage as the cartilage model is replaced with newly formed bone tissue [1].

Collagen is the most prevalent protein found in the ECM, with 29 different types discovered to date [2, 3]. Based upon abundance, collagens are divided into major fibrillar collagens, including collagen types I and II, and minor fibrillar collagens, including types V and XI. Collagens V and XI can form hybrid molecules, therefore they are considered to belong to the same collagen type which can be referred to as collagen type V/XI. *In vivo* studies of collagen V/XI morphants have demonstrated their role as regulatory proteins that contribute to fibrillogenesis [4, 5]. However, while major fibrillar collagens have been studied extensively, additional roles for minor fibrillar collagens in cellular differentiation and signaling require further study and are still being defined.

The cartilaginous framework of the craniofacial skeleton is formed by differentiation of multipotent neural crest cells (NCCs) into mature chondrocytes. Disruption of chondrogenesis causes severe facial skeletal structure abnormalities and has detrimental effects on the embryo. Deformities of the craniofacial features can be induced by genetic factors. For instance, mutations in minor fibrillar collagens V/XI can cause Marshall, Stickler, or Ehlers-Danlos syndromes which all present complex phenotypes of flattened face, hearing loss, eye abnormalities and joint problems. Likewise a mutation of the *Sox9* gene in humans can result in campomelic dysplasia (CD) [6], a genetic condition characterized by craniofacial defects, severe damage of the endochondral bone, and sex reversal [7]. Similar anomalies are observed *in vivo* when *Sox9* ortholog genes are knocked out in other species including zebrafish (*Danio rerio*), mouse (*Mus musculus*) and frog (*Xenopus laevis*). Interestingly, Parathyroid Hormone- related Protein (PTHrP) homozygous mutant mice also exhibit a chondrodysplastic phenotype characterized by a deformed skull, short snout and mandible, protruding tongue, and disproportionately short limbs which are all similar to characteristics in human osteochondrodysplasias [8]. In all the above mentioned disorders, chondrogenesis and bone formation are interrupted in the development of the craniofacial structures.

NCCs represent a population of multipotent stem cells that arise from the rhombomeres of the hindbrain in vertebrates. These cells undergo an epithelial-mesenchymal transition (EMT) during the first few weeks of embryogenesis and migrate to different sites in the body, where they differentiate into neuronal cells, cardiac crest cells, pigment cells, chondrocytes, and osteocytes [9, 10, 11]. Differentiation into this wide array of derivative cells is tightly regulated by transcription and growth factors. The different transcription and growth factors work together within a complex system and achieve proper formation of the craniofacial skeleton and other developmental structures during embryogenesis. Growth factors such as fibroblast growth factor (FGF), Wnt, bone morphogenetic protein (BMP), PTHrP and transcription factors including Hox and Sox proteins influence chondrogenesis and thus the development of the craniofacial skeleton [12]. Within the Sox (SRY- HMG box) transcription family, L-Sox5, Sox6 and Sox9 regulate chondrogenesis [13] shown by *L-Sox5*s*ox6* double mutants, which lack endochondral bones and exhibit severe skeletal abnormalities [14]. Similarly, PTHrP plays a role in proper endochondral ossification as indicated by PTHrP deficient mice exhibiting abnormalities of the craniofacial cartilages and skeletal deformities [15].

Due to similar anomalies observed in PTHrP, Sox9, and minor fibrillar collagen mutant model organisms, investigation into the potential link between the three factors may provide fundamental

knowledge regarding the mechanisms at play during chondrogenesis of neural crest derivatives, a possibility that has not been characterized.

Craniofacial development and neural crest cells

Craniofacial cartilage structures can be divided into seven prominences including the frontonasal, and one pair each of the mandibular, maxillary and lateral nasal (Figure 1) [16]. The frontonasal features arise from NCCs to comprise the forehead, nose, upper lip, and primary palate. Structures of the mandibular and maxillary prominences include the lower jaw, sides of the face and lips [16, 17].

Upon gastrulation, the ectoderm forms the non-neural ectoderm, the neural plate and the NCCs [18]. Cells of the non-neural ectoderm form the epidermis, while the neural plate folds to give rise to the central nervous system including the brain and the spinal cord [19]. During the initial stages, the brain is divided into three primary vesicles: the forebrain, midbrain and hindbrain. The hindbrain, or rhombencephalon, consists of rhombomeres where NCCs originate. These mesenchymal cells migrate to the frontonasal region and to one or more of the 6 pharyngeal arches (Figure 1). Each pharyngeal arch gives rise

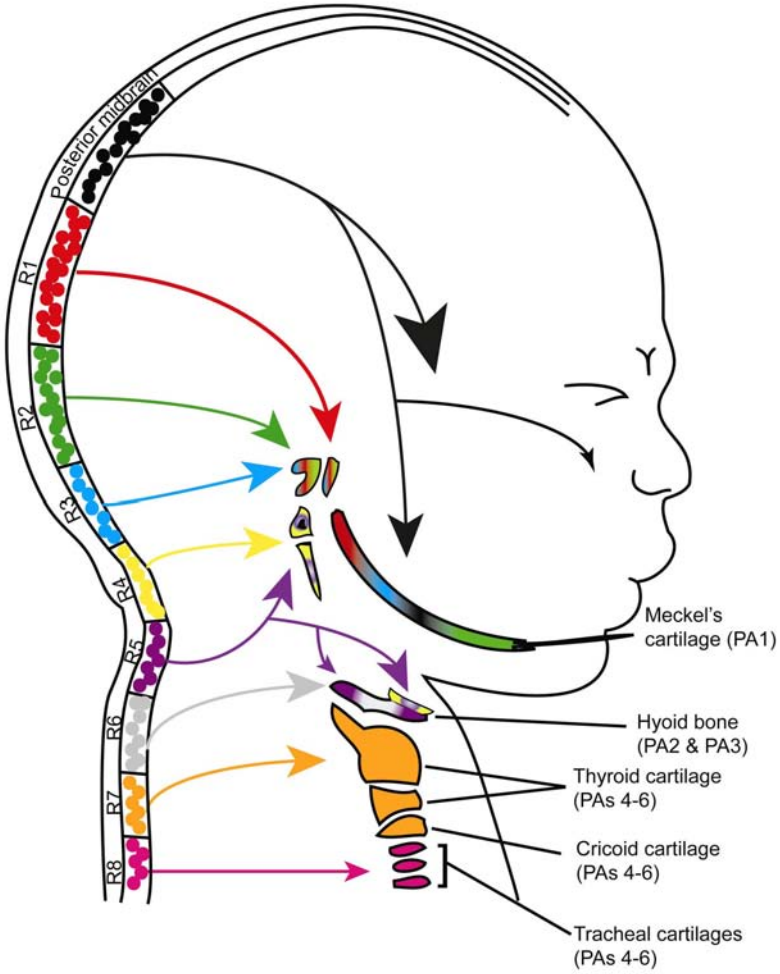

Figure 1. Neural crest cell migration from the posterior midbrain and rhombomeres of the hindbrain to various sites of differentiation. NCCs from the posterior midbrain migrate to the frontonasal region and contribute to nasal structures as well as to the first pharyngeal arch forming Meckel's cartilage. NCCs migrate from rhombomeres 1, 2 and 3 form Meckel's cartilage, whereas rhombomeres 4 and 5 make up ear structures and part of the hyoid bone. NCCs from rhombomeres 5 and 6 form the greater horn of the hyoid bone. Similarly, rhombomere 7 NCCs migrate to form thyroid and cricoids cartilages. NCCs from rhombomere 8 give rise to tracheal cartilages.

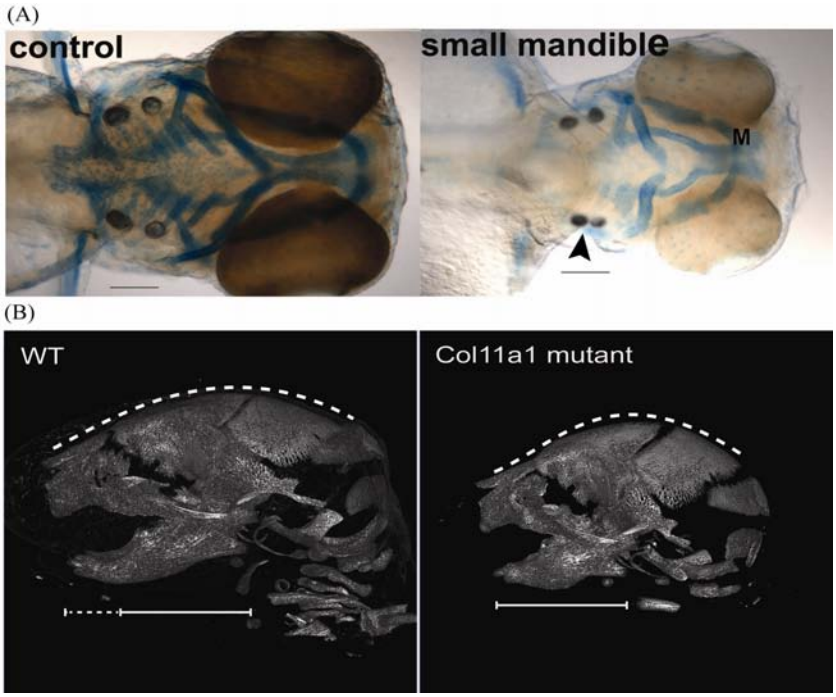

Figure 2

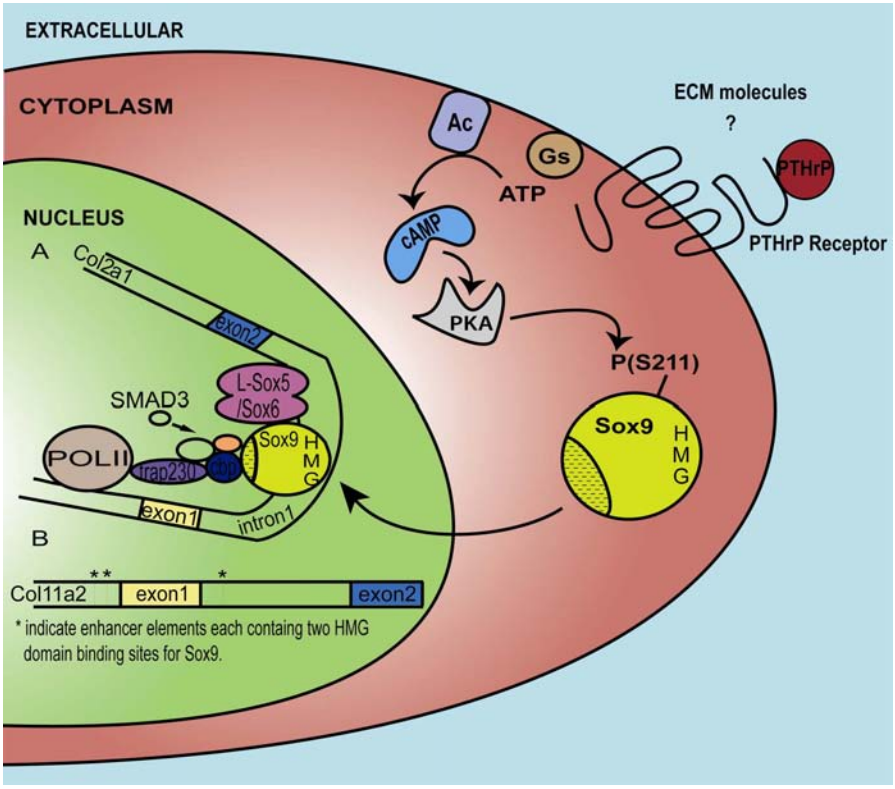

Figure 3

to specific structures of the craniofacial and neck skeleton. Pharyngeal arch 1 forms the mandibular and maxillary structures including the maxilla, zygomatic bone, temporal bone, incus, malleus and Meckel's cartilage. Pharyngeal arch 2 shapes the stapes, styloid process and hyoid bone. Pharyngeal arch 3 makes up the greater horn of the hyoid bone, and pharyngeal arches 4-6 form the arytenoid cartilage, thyroid cartilage and other laryngeal cartilages [20].

Collagens V/XI are expressed in pre-migratory NCCs as well as in developed craniofacial cartilages in zebrafish [21, 22]. Interestingly, the expression patterns of the minor fibrillar collagens are highly comparable to that of Sox9 in the craniofacial structures, although there is no direct evidence showing an interaction between Sox9 protein and minor fibrillar collagen genes. Similarly, accelerated endochondral bone formation and chondrocyte maturation in the craniofacial cartilaginous structures in PTHrP deficient mice indicate expression of PTHrP in the craniofacial structures [23].

Minor fibrillar collagens and SOX proteins

During endochondral ossification, chondrocytes deposit major collagen type II and minor fibrillar collagen type V/XI [24]. As cartilage is mineralized and converted to bone, chondrocytes change their overall expression pattern to collagen type I and more predominantly minor fibrillar collagen V. Collagens consist of three peptide alpha chains forming either heterotrimers or homotrimers [25, 26, 27]. Three different collagen XI alpha chains have been described; *Col11a1*, *Col11a2* and *Col11a3* [28, 29]; where *Col11a3* is actually a modified form of *Col2a1*. Similarly, three collagen V alpha chains have been described in humans; *Col5a1*, *Col5a2* and *Col5a3* [21]. Minor fibrillar collagens V and XI play a role in the organization of major fibrillar collagens I and II respectively by forming heterotrimers with them. Collagens V/XI share strong homology among their respective protein domains and are interchangeable, forming collagen V/XI isoforms [30, 31, 32].

What can we learn from animal models?

The role of collagen V/XI in chondrogenesis of craniofacial skeletal structures has been studied in mouse and in zebrafish [4, 5]. Expression of *Col5a1* in developing cranial cartilages, *Col11a2* expression in cephalic mesoderm and a unique *Col11a1* expression in the hindbrain has been identified in zebrafish [21], suggesting a potential role in the induction and differentiation of NCCs into craniofacial cartilages. This potential is supported by vertebral and craniofacial abnormalities in zebrafish *Col11a1* morphants. The abnormalities include a smaller lower jaw and abnormal otolith genesis (Figure 2A). Analogous defects have been observed in chondrodysplasia (*cho/cho*) mice lacking a functional Col11a1 protein (Figure 2B). The *cho/cho* mouse demonstrates a morphology characteristic of Marshall's and Stickler syndromes and fibrochondrogenesis in humans [33]. Likewise, mutations in *Col11a2* have been linked to osteochondrodysplasias in humans [34].

Multiple families of transcription factors are responsible for the expression of genes necessary for chondrogenesis. One essential family of transcription factors is represented by the highly conserved Sox family. All Sox proteins share the same high mobility (HMG) domain that is extraordinarily conserved among vertebrates (Figure 3) and bind to a similar minor groove

Legend to Figure 2. Effects of Col11a1 knockdown in mouse and zebrafish. Col11a1 morphant zebrafish show a smaller mandible (M) and smaller otoliths (arrowhead). Similarly, microcomputed tomography representation of wildtype (WT) and Col11a1 mutant chondrodysplastic (cho) mice at embryonic day 17.5 show an overall smaller, deformed cranium (dashed lines), and decreased jaw length (bar) illustrating the role for Col11a1 in craniofacial development.

Legend to Figure 3. Schematic of a potential mechanism by which extracellular matrix proteins can act upstream or downstream of PTHrP in the cell. Collagens V/XI may act upstream and interact with PTHrP or PTHrP receptor in the extracellular matrix; activate the PKA pathway and regulate chondrogenesis via Sox9. Alternatively, PTHrP may regulate the expression of minor fibrillar collagens V/XI by activating the PKA pathway and phosphorylating Sox9 in the cytoplasm which can then move to the nucleus and regulate the expression of the minor fibrillar collagens in a similar manner that it regulates *Col2a1*. Both *Col11a1* and *Col11a2* have transcription sites for Sox9.

DNA motif of (A/T)(A/T)CAA(A/T)G resulting in bending of the DNA helix [7, 35, 36]. Bending of the DNA facilitates the unwinding of the DNA double helix, which in turn causes the gene promoters to be in a more open conformation and enhance transcriptional activity. Sox transcription factors are divided into 8 subgroups of A-H [37]. Sox9 is a transcription factor that belongs to subgroup E and has a characteristic transcription domain at its C-terminus [38]. *Sox9* is expressed in a variety of cell types including mesenchymal NCCs, Sertoli cells of the testes, cardiac neural crest cells, the kidney, and all chondroprogenitor cells [4]. Along with Sox9, other SoxE members such as Sox8 and Sox10 play a role in the development of the NCCs prior to their migration. Once the NCCs start migrating, *Sox9* expression is downregulated and expression of *Sox8* and *Sox10* are lost. However, upon arrival at the site of chondrogenesis, the NCCs up-regulate *Sox9* [16]. Sox9 does not play a role in NCC migration as evidenced by normal cell migration patterns in *Sox9* mutant cells [1]. Nonetheless, at the site of chondrogenesis, *Sox9* plays a crucial role in not only mesenchymal cell condensation, but also proliferation and differentiation into chondrocytes [39, 7].

Additionally, L-Sox5 and Sox6 are required for the development of chondroblasts [40]. Both Sox factors *L-Sox5* and *Sox6* are co-expressed with *Sox9* during chondrogenesis except for the period prior to mesenchymal condensation verified by experiments with *Sox5sox6* double mutants demonstrating normal mesenchymal condensations but no chondrogenesis [10, 40]. All three Sox proteins are required for the differentiation of chondroblasts to chondrocytes [14]. L-Sox5 and Sox6 belong to subgroup D and share a similar sequence in their coiled-coil region forming homo- or hetero-dimers [4]. Dimerization of L-Sox5 and Sox6 facilitates their binding to the first intron of *Col2a1*. They share the common HMG domain with Sox9 [41]. As neither L-Sox5 nor Sox6 have a transcription activation domain, they act as architectural factors that do not influence the transcriptional activity but can indirectly modulate gene activity [42].

L-Sox5, Sox6, and Sox9 recognize HMG binding sites on *Col2a1* and *Aggrecan*, the major structural proteoglycan found in the ECM of cartilage. Collagen type II, the major protein of the cartilage, contains a 48 bp sequence in its first intron, which contains 4 binding sites for Sox proteins [12]. Sox proteins can bind to *Col2a1* and *Aggrecan* enhancing their expression [12]. Similarly, HMG binding sites have been identified on *Col11a2* that can be recognized by Sox9 [39, 43, 44]. Computational analyses have also identified seven conserved pairs of HMG binding domains in the promoter region of *Col11a1* in both humans and mouse, which could further show a relationship between Sox9 activity and collagen type XI [45]. Recent EMSA studies have determined true Sox9 binding sites on Col11a1 [46]. However, to date, regulation of *Col11a1* expression by Sox9 has not been demonstrated. One possibility is that the growth factors mediating expression of cartilage-specific extracellular matrix proteins may do so through the activity of Sox family transcription factors.

Regulation of chondrogenesis

Binding of L-Sox5, Sox6 and Sox9 to *Col2a1* promotes the assembly of a multiprotein enhancer complex and activates the basal transcriptional machinery required for chondrogenesis (11). L-Sox5, Sox6 and Sox9 regulate transcription in chondrogenesis using a cyclic-AMP (cAMP) response element-binding (CREB) protein mediated by DNA acetylation [37]. Sox9 activity can be regulated by multiple factors. For instance, Smad3 increases the interaction between Sox9 and CREB-Binding Protein (CBP/p300), which in turn increases Sox9 transcriptional activity [47]. Similarly, proliferation activated receptor gamma co-activator 1-alpha (PGC1-α) co-activates Sox9 during chondrogenesis [48]. The interaction between Sox9 and thyroid hormone receptor-associated protein 230/Med12 (TRAP) also significantly increases Sox9 transcriptional activity [49]. Since *Col11a1* and *Col11a2* both contain multiple Sox9 binding sites, it is possible that the same transcriptional machinery may be used to regulate their expression in cartilage (Figure 4). Further studies are required to verify the role for Sox9 in *Col11a1* and *Col11a2* expression.

Sox9 expression is regulated by many growth factor signaling pathways. For instance, FGFs use the Mitogen Activated Protein (MAP) pathway to

increase *Sox9* expression in chondrocytes and mesenchymal cells. Both chondrocytes and mesenchymal cells express FGF receptors [50]. Likewise, PTHrP increases cAMP levels and phosphorylates Sox9 by activating the Protein Kinase A (PKA) pathway *in vivo* [51]. Phosphorylation of Sox9 enhances its activity and leads to increased *Col2a1* expression in the prehypertrophic zone of the growth plate [51] (Figure 4). Both Sox9 and PTHrP prevent proliferating chondrocytes from becoming hypertrophic [45]. As a result, cartilage is conserved and bone formation is inhibited. Inhibited differentiation of proliferating chondrocytes into hypertrophic chondrocytes could alternatively be due to the lack of ECM components as suggested by Akiyama. Indeed, mice lacking *Col11a1* show premature ossification [5] (Figure 2B). Col11a1 binds to heparin sulfate proteoglycans and through this interaction may facilitate FGF signaling that is dependent on heparan sulfate [52, 53]. FGF can subsequently stimulate chondrogenesis via Sox9 activation. Similarly, Sox9, PTHrP and Col11a1 all show similar or overlapping effects in preventing chondrocytes from becoming hypertrophic and thus mineralizing. It is notable to mention that pre-hypertrophic chondrocytes express Sox9 and the PTHrP receptor [46]. Extracellular matrix may modulate PTHrP-mediation of chondrogenesis and the transition from proliferative chondrocyte to hypertrophic chondrocyte. Alternatively, PTHrP may induce changes in the expression of extracellular matrix molecules that are critical for the formation of cartilage. To date, the analysis of PTHrP-mediated changes during skeletal development has not included an analysis

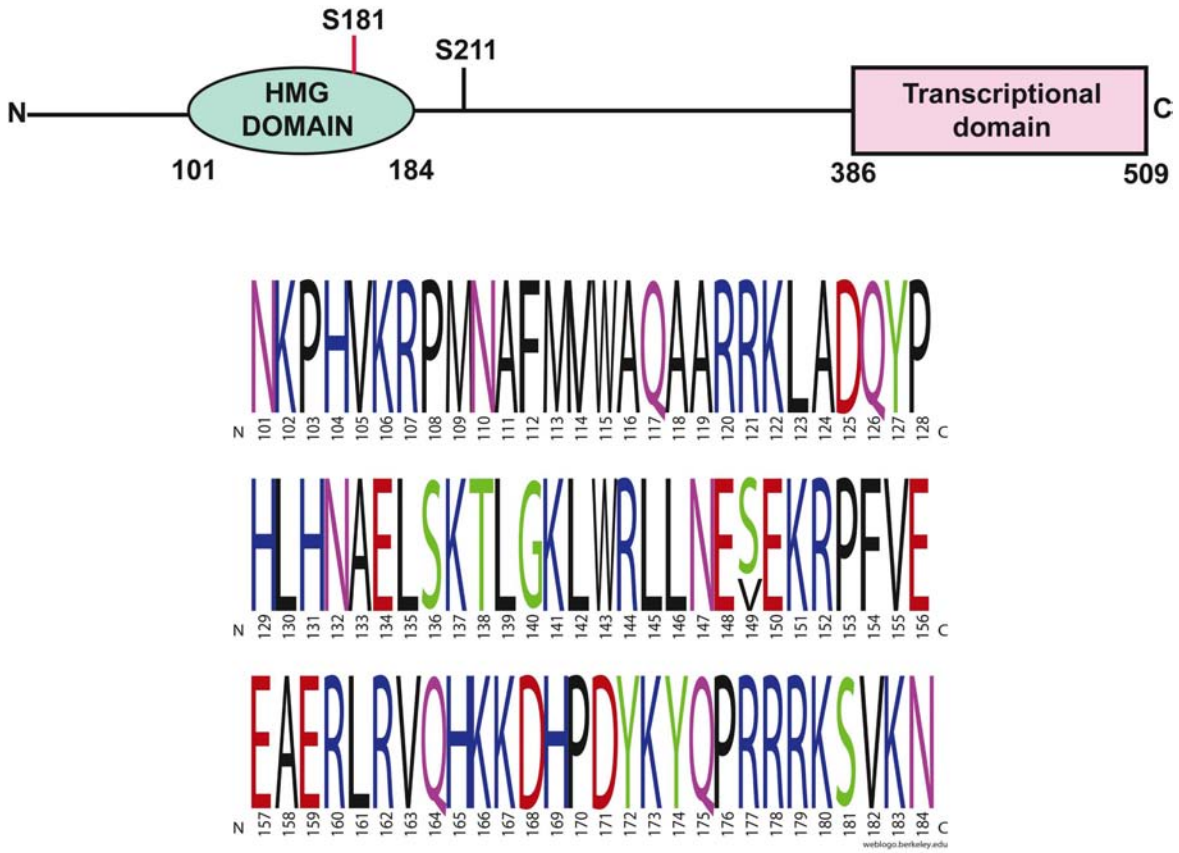

Figure 4. Sox9 protein has highly conserved high mobility group (HMG) domain and sites of phosphorylation. The HMG domain is a conserved domain (amino acids 101-184) within human (*H. sapiens*), mouse (*M. musculus*), rabbit (*O. cuniculus*) and zebrafish (*D. rerio*). Serine 181 (S181) and serine 184 (S211) are PTHrP dependent sites of phosphorylation on Sox9. Sequence logo was generated using WebLogo 3.0 [54, 55].

of the minor fibrillar collagens. It is possible that minor fibrillar collagens in the ECM bind to PTHrP or alternatively to its receptor and regulate the PTHrP pathway, acting upstream of the cellular signaling pathway during chondrogenesis. Studies on the regulation of PTHrP-Sox mediated chondrogenesis may provide us with a better understanding of the molecular mechanism of craniofacial development.

CONCLUSION

The role of minor fibrillar collagens V/XI in L-Sox5, Sox6 and Sox9 mediated chondrogenesis and the interaction with growth factors that provide external cues during craniofacial development is a relatively new area of investigation. Since the cartilage abnormalities in Col11a1 *cho/cho* mice, and *Col11a1* zebrafish mutants are similar to those induced in *Sox9* mutant mice and zebrafish, and PTHrP-deficient mice, an investigation of the interaction between these molecular constituents may provide fundamental information. Studies are needed to look at the role of PTHrP in Sox-mediated chondrogenesis and the relationship to minor fibrillar collagens. The multipotency of NCCs is of great interest to basic science as well as to the development of regenerative medicine approaches for the treatment of skeletal injuries. Understanding the interplay between minor fibrillar collagens, Sox proteins and PTHrP in NCC-derived structures could explain the multiple levels of regulation of chondrogenesis and thus proper cartilage formation during craniofacial development of the embryo. The results could help us understand the mechanism by which minor fibrillar collagens regulate chondrogenesis as well as how minor fibrillar collagens are regulated during this process. Having a better understanding of the mechanisms by which chondrogenesis and cartilage formation occur may provide us with new tools to diagnose and prevent disorders of the craniofacial skeleton including cleft palate and osteochondrodysplasias *in utero*.

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