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Possible Role of Noggin Gene in Mandibular Development

Posible papel del gen noggin en el desarrollo mandibular
Possível papel do gene noggin no desenvolvimento mandibular

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ABSTRACT
Background: Noggin (Nog) gene is one of the antagonists of bone morphogenic proteins (BMPs) and its function is to modulate the signs. When Nog's action is ineffective, an excessive activity of BMPs occur causing serious developmental abnormalities. Studies have shown that Nog is critical for chondrogenesis, osteogenesis, and joint training and appears to be involved in the growth of craniofacial structures, including the jaw. There are in the literature a few studies about the relationship between Nog and its role in mandibular development. *Purpose:* To reviews the molecular factors involved in the jaw development. *Method:* Focusing primarily on BMPs, their function, and signaling pathway as Nog regulates this path. It leads to hypothesize the Nog's possible role on the mandibular development and how its alteration can cause mandibular micrognatism.

KEYWORDS
Bone morphogenetic proteins; craniofacial structures; mandibular development; noggin gene

THEMATIC FIELDS
Craniofacial anomalies; genetics

RESUMEN
Antecedentes: El gen noggin (*nog*) es uno de los antagonistas de las proteínas morfogénicas óseas (BMP) y tiene como función modular la señal de estas. Cuando su acción no es efectiva, ocurre una actividad excesiva de las BMP que causa serias anormalidades en el desarrollo. Algunos estudios han demostrado que nog es crítico para la condrogénesis, la osteogénesis y la formación de las articulaciones y parece estar involucrado con el crecimiento de estructuras craneofaciales, entre ellas la mandíbula. Existen en la literatura pocos estudios acerca de la relación entre *nog* y su papel en el desarrollo mandibular. *Objetivo:* Describir los factores moleculares que intervienen en la formación de la mandíbula. *Método:* Se hace hincapié en las BMP, su función y vía de señalización, y cómo *nog* regula esta vía para conducir a formular una hipótesis del posible papel de este gen en el desarrollo mandibular y cómo su alteración podría llegar a causar micrognatismo mandibular.

PALABRAS CLAVE
Desarrollo mandibular; estructuras craneofaciales; gen Noggin; proteínas morfogenéticas óseas

ÁREAS TEMÁTICAS
Anomalías craneofaciales; genética

RESUMO
Antecedente: O gene Noggin (Nog) é um dos antagonistas das proteínas morfogênicas ósseas (BMPs) e tem como função modular o sinal das mesmas. Quando sua ação não é efetiva, ocorre uma atividade excessiva das BMPs causando sérias anormalidades no desenvolvimento. Estudos veem demonstrando que nog é essencial para a condrogênesis, osteogênesis, formação das articulações e parece estar envolvido com o crescimento de estruturas craniofaciais, incluindo a mandíbula. Na literatura há poucos estudos sobre a relação entre Nog e seu papel no desenvolvimento mandibular. *Objetivo:* Descrever o desenvolvimento da mandíbula e os fatores moleculares envolvidos na sua formação. *Método:* Principalmente se trabalha com as BMPs, sua função, via de sinalização e como Nog regula esta via, levando-nos a formular uma hipóteses do possível papel de Nog no desenvolvimento mandibular e como sua alteração poderia causar micrognatismo mandibular.

PALAVRAS CHAVE
Desenvolvimento mandibular; estruturas craniofaciais; gene Noggin, proteínas morfogenéticas ósseas.

ÁREAS TEMÁTICAS
Anomalias craniofaciais, genética

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INTRODUCTION

The lower jaw, teeth, and Meckel's cartilage develop when cells of the cranial neural crest (CNC), which give rise to the dorsal neural tube, migrate into the gill arches (1-3). As the jaw develops, the ectoderm guides patterning into the mesenchyme (3) involving an antagonistic action between a signal of bone morphogenic proteins (BMP-4) and fibroblast growth factor-8 (FGF8) (3,4). BMPs, which belong to the superfamily of transforming growth factor β (TGF-β), operate in a variety of tissues in space and time, requiring adjustment to different levels that ensure their specific responses (5,6). These regulations are given by modulators containing extracellular cysteine-rich domains that are folded in the form of rings of different sizes. Based on the number of ring cysteine domains, they are classified as: (a) 8-ring cysteine proteins, members of DAN (7,8); (b) 9-ring cysteine proteins, twisted gastrulation (tgs) (9,10); and (c) 10-ring cysteine proteins, Chordin (Chd) and Noggin (Nog) (11-14). The latter proteins are encoded by Chd and Nog genes respectively, which are expressed in the pharynx and during early and late formation of the lower jaw (15). Specifically, the Nog gene encodes for the homodimeric Nog protein, which has a molecular weight of 64 KDa, regulates BMPs (14,15), bonds with some BMPs, and prevents its activation by blocking the smad-dependent route (13-16). The Nog gene is a pleiotropic factor that is expressed in both early and late stages of development of various structures derived from ectoderm, such as neural tube, teeth, hair follicle, dermal papilla, and eye (17). Nog is also expressed in tissues derived from the mesoderm and is required for skeletal patterning where it plays a critical role in embryonic chondrogenesis and osteogenesis during the formation of joints. The expression is promoted by Wnt-1 and Shh genes (18). Its role in skeletal physiology has been documented by studies in mice and humans that show that mutations in this gene cause abnormalities in skeletal development (19-21). Computational analyses predicted that the alteration of the Nog heparin-binding site might have caused proximal symphalangism and conductive hearing loss (22). Another study by Matsui and Klingensmith (23) employed the extraction of genes in relevant tissue domains for the formation of upper and lower jaw, in order to determine the role of Nog. They found that the expression of the Nog middle-axial domain is relevant to the development of the first pharyngeal arch in the early stages of development, which in turn promotes the growth of the mandibular right bud, and suggests an indirect mechanism for secondary cleft palate. Based on that evidence, this review aimed at briefly describing the current knowledge regarding the Nog mechanisms that could be involved in mandibular disorders.

DEVELOPMENT OF THE JAW

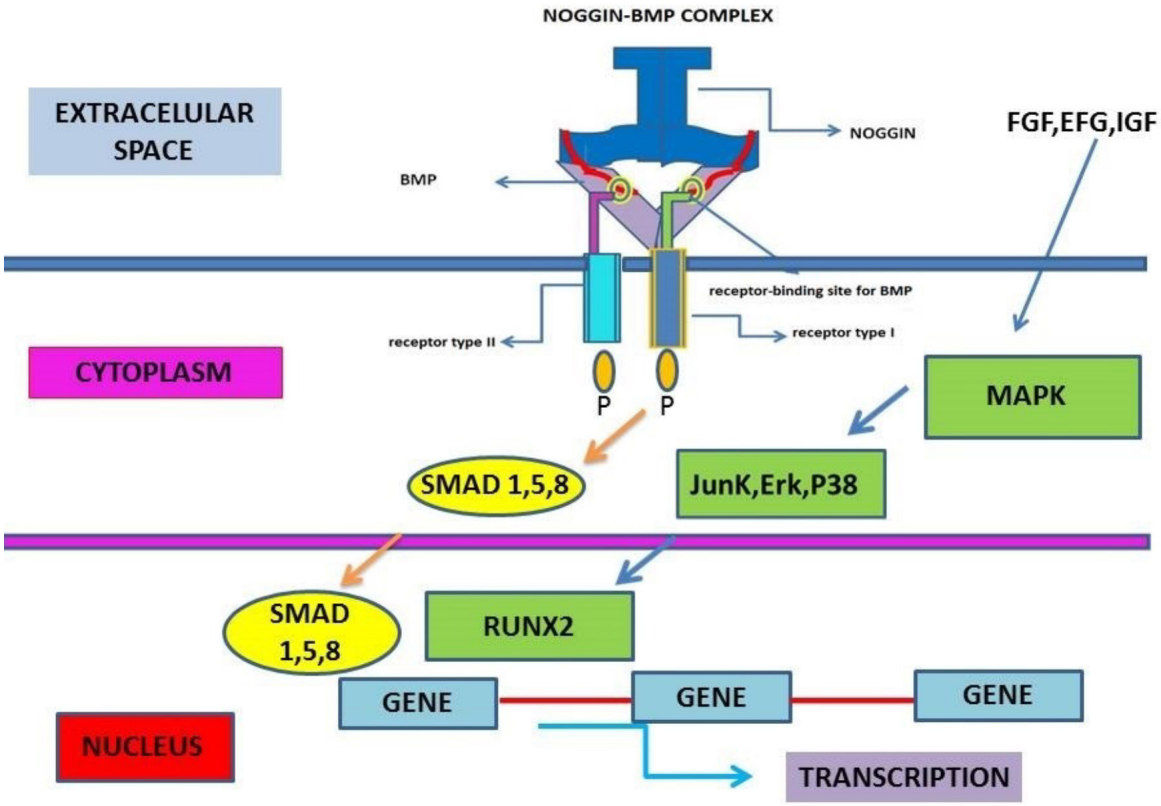
The development of the jaw is carried out by multiple processes which include the formation of its skeletal elements, which are derived from cells of the CNC of the first gill arch. In this formation, the condylar development plays an important role, in a form that any alteration level specifically contributes to causing mandibular condyle asymmetries. When the condyle is affected bilaterally, jaw rotation in a posterior-inferior direction is produced causing anterior open bite (24,25). However, if it is affected unilaterally (24), lateral cross bite type occurs. Only the condylar cartilage jaw endures through life and contributes to growth and joint function, becoming a tissue that serves several functions at once (26,27). Studies in human fetuses of 8 weeks of intrauterine life show that the growth of the ramus of both its width and its height is faster than the body of the mandible (28), and this seems to be due to the presence of this cartilage. Previous research which focused on the study of development of the symphysis and condyle (29) found that the cartilage of the mandibular condyle allows the endochondral bone to grow, thus exerting an adaptive role in the growing site, being this growth determined by genetic and epigenetic factors (30); but it can also be influenced by cytokines, hormones, vitamins and mechanical stimuli (31,32). Thus cytokines and the growth factors are molecules that rapidly degrade. Specifically, this latter are involved in the proliferation and differentiation of the cells forming the mandibular condyle. Among them are: The vascular endothelial growth factor (VEGF), insulin growth factor (IGF), FGF, TGF, the related protein parathyroid hormone (PTHrP), Indian hedgehog (Ihh) and BMPs, this of special interest in their specific role in mandibular growth and development (32-35). These growth factors have the role of nuclear transcription factors present in chondrocytes and these latter are found in the Sox and Runx2 family members, which are substantial in the initiation of embryonic growth of the condyle. In Table 1, growth factors and transcription involved in mandibular growth and development and specific action in this region is summarized.

Given the fact that the BMPs act by modulating the growth and development of the 3 mandibular components. The focus will be on understanding how these work. BMPs are synthesized by cells such as osteo-

Table 1
Factors involved in the mandibular growth

Name	Action at mandible
VEFG	Express at chondrocytes for the induction of bone formation in development and adaptation to mechanical charges (33,34).
IGF	Involves in the growth and development of tooth, mandible, maxillary and tongue (36,37).
FGF	Express in chondrocytes. FGF-2 is highly expressed in the absence of mechanical charge, reduces MEC production that directs to bone formation. FGFR-3 induces chondrocytes proliferation. Mutations of FGFR-3 cause skeletal dysplasia such achondroplasia (38). FGF-8 expression is critical for jaw development (39), as well as for facial mesenchymal neural crest derived and growth regulation of facial primordium (40).
TGF	TGFβ-1 is strongly expressed at mature layers and hypertrophic condyle of mandible (39,40). Also increases proliferation and synthesis of glycosaminoglycans, and decreases chondrocytes hypertrophy and bone mineralization (41).
PTHrP and Ihh	Regulates proliferation and growth of chondrocyte. Prevents chondrocyte hypertrophy (PTHrP). Blocks ossification (Ihh) and is involved at the early formation of TMJ (42-46)
BMPs	Modulates growth and development of the 3 mandible components (47). Wnt inhibits part of chondrogenesis activity by BMP-2.
Sox 9	Regulates chondrocytes for collagen type II production at the cartilage (48,49).
RunX-2 (cbfa1)	Express in osteoblasts and mesenchymal condensation prechondrogenic. Regulates hypertrophy chondrocytes, calcification of bone matrix and differentiation of osteoblasts and osteoclasts (50,51).

Figure 1
Signaling route of BMPs



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blasts, chondrocytes and platelets (52,53) and belong to the family of TGFß, except the BMP1. Not only do they act on the bone level but they also have different functions in the formation of organs like the teeth, in embryonic development, repair, apoptosis and chemotaxis of various tissues (54,55). They additionally regulate iron homeostasis and induce intramembranous ossification and chondrogenesis (56). To this day there are 20 types of BMPs that have been grouped according to the similarity of its sequence and its functions. BMPs are dimeric molecules made up of 120 amino acids including cysteine residues highly conserved (57,58), a signal peptide at its N-terminal region composed of 50 to 100 hydrophobic amino acids which guides the protein and its secretory pathway C-terminal prodomain that allows proper folding (59), also contains N- and O-glycosylated sites that give stability and specificity with which the receivers to be coupled (60,61). Signaling pathway of BMPs, is regulated by extra- and intra cellular mediators which may be attached directly to them or any component blocking the transduction signal leading to a decrease in the bone formation (Figure 1). Nog expression blocks the effects of BMPs in osteoblasts, whether they are differentiated or undifferentiated (62). Also it inhibits intramembranous ossification and prevents chondrogenesis. BMPs may act in an autocrine and paracrine form (63).

The BMPs (Color Purple) begin their signaling by uniting to two different receptor types I and II in the extracellular region causing phosphorylation of proteins. This attachment may activate Smad cytoplasmic proteins, including three classes: the Smad 1, 5 and 8 which bind transcription factors in the nucleus (gene promoter region) important genes for transcription. Another signaling pathway of BMPs is independent Smad, which is initiated by growth factors such as FGF, epidermal growth factor (EGF) and the growth factor (IGF), which in turn activate the MAP kinase (MAPK) pathway that also includes 3 proteins Kinases: Erk, JNK and p38 MAPK. When the BMP (violet) joins the antagonist Nog (Blue), they form the Nog / BMP complex, which results in inhibition and modulation of its signal causing decrease in bone formation.

Noggin gene

The human NOGGIN gene (NOG), with a length of 1.9 kb is located on chromosome 17q22 (NOG; MIM # 602991). Consists of a single exon and encodes a protein of 232 amino acids (NP 005441) with a molecular weight of 25,7 KDa (UniProt NOGG_HUMAN, # Q13253). The protein on the other part is characterized by a carboxy-terminal cysteine-rich, which is used to classify antagonists of BMPs in the different subfamilies: chordin and noggin, DAN and twisted gastrulation (7). The form of this protein is the two axes; one is butterfly-shaped and another called snake-shaped clip, which is rolled around the ligand and occludes BMPs and these binding sites to their type I and II receptors. Nog dimers forming the shaft 1, consisting of two pairs of chains extending β preceded by an N-terminal 20 amino acids that form the axis 2 (CLIP segment) (13) (Figure 2A).

Nog acts as a modulator of BMPs, a regulator of BMP signaling complex: 2, 4, 6, and 7 in particular. Nog has a very important role in embryogenesis, as it influences the differentiation and development of cartilage, skeletal muscle, and neural tissues and craniofacial structures (64). Nog is critical to chondrogenesis and osteogenesis embryonic joint formation (19-21). It is regulated by the FGF-2 and FGF-9 which in recent studies showed that when combined with Nog prolong human embryonic stem cells *in vitro* (65) they could be used to normalize or balance somehow bone remodeling activity (66).

Noggin/BMP complex

As mentioned earlier, BMPs are important for both embryonic and postnatal skeletal and bone development (67,68). The activity of BMPs is regulated by several soluble antagonists among them Nog are very important because it prevents the binding of BMPs to the surface of its receptors avoiding signal transduction BMPs start on target cells (13,67) (Figure 2B).

Nog antagonistic action occurs in undifferentiated mesenchymal cells that are to be differentiated into osteoblasts (69). However, sometimes antagonists are promiscuous, that is, their role is not limited to BMPs. They can join other members of the superfamily of TGF β (17). For example Nog and sclerotin interact with each other to cancel their respective antagonism (70). This indicates that the function of the antagonists is dependent on its affinity for BMPs with which they interact (62,70). BMP2 interacts or has high affinity for heparin sulfate proteoglycans. Nog and chd also interact with these proteoglycans, however it is not clear whether these associations which are covalent unions, are irreversible at some point (71). What is clear is that the potential for interaction between receptors and ligands may also depend on the concentrations of ligand. For example, at low concentrations it appears that BMPs can join dimeric receptors Type I. Specific receptor affinities have not been determined for all

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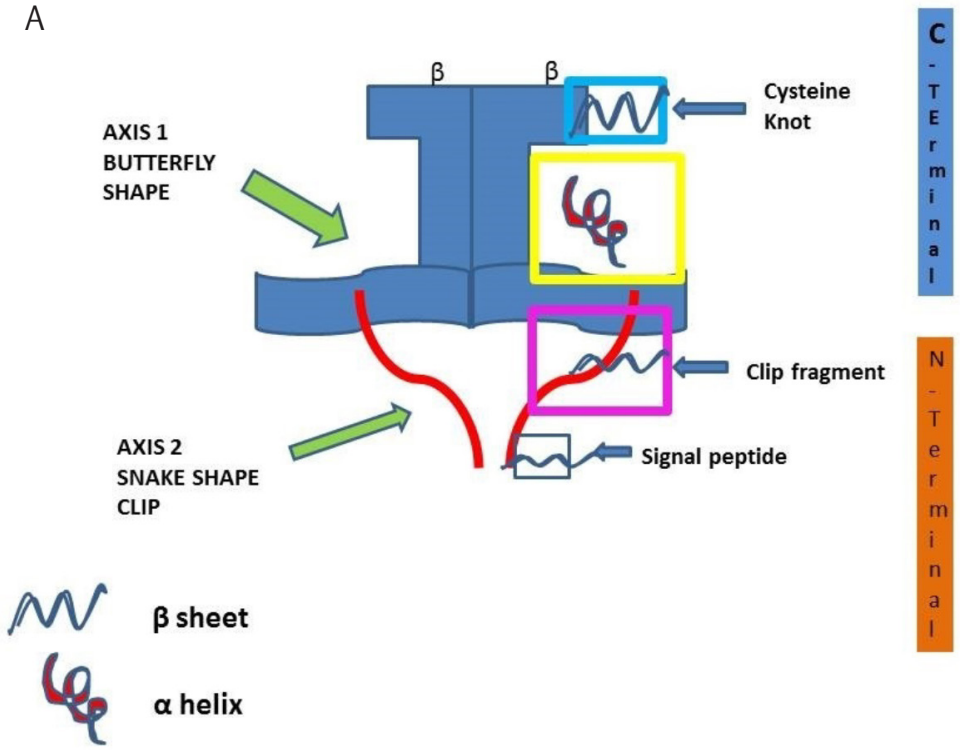
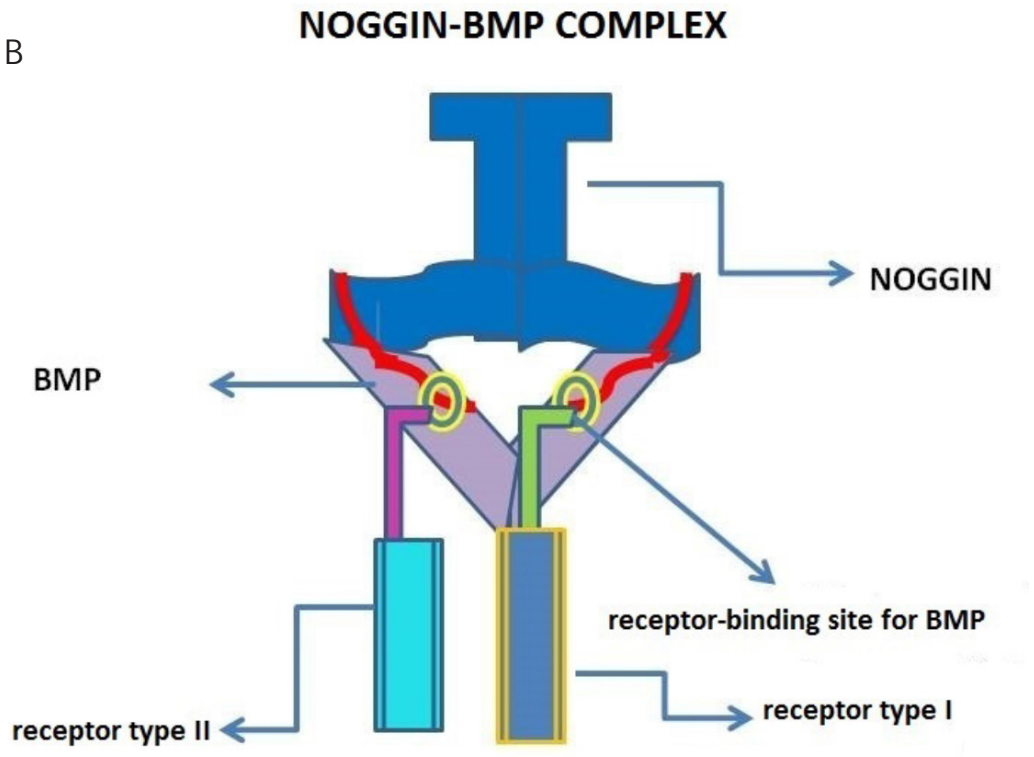
Figure 2
Nog protein structure



A) The N-terminal domain of the noggin protein involves the peptide signal and the clip fragment, which are formed by approximately by 20 amino acids This region is constituted in totality by β-sheet, while the C- terminal region is formed by α helix and β sheet. And contains the cysteine Knot which allows this protein classification.



B) The union of Nog to some BMPs inhibits activation of these receptors by the CLIP segment (red). The type I receptor (ALK1, Alk2, Alk3, and ALK6) and type II (BMPR-II, ActR-II and ActR-IIB) are the ones that primarily occlude by its high specificity with some BMPs. This receptor blockage by Nog prevents signaling through Smad-dependent pathway and nondependent Smad. As for the dimerization of BMPs, this is similar to Nog; it extends in the form of butterfly (violet) but from a central body allowing it to be assembled with Nog.

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BMPs (60,72-73). It has been found that the BMPs are expressed in a specific time and place in order to regulate the growth of craniofacial elements derived from the neural crest, and that Nog union alters this growth through via binding to type I receptor Alk2 using the Wnt pathway, which results in cleft lip and palate and mandibular hypoplasia (74). Similarly, the loss of these inhibitors of BMPs (Nog-Chd) may affect mandibular growth and positioning of the temporomandibular joint, which definitely seems to suggest that, the dose of BMPs is very important (41,75-78). Mutations in the Nog/Bmp complex are manifested in rare skeletal disorders such as the multiple synostosis syndrome 1 (78). Also it has been observed in mouse model that Nog overexpression causes a severe form of osteoporosis, while its haploinsufficiency can act in the protection from arthritis (79). Moreover, Nog transgene expression under the control of skin keratin 14 promoter, cause tumorgenesis, suggesting that this gene may inhibit tumor suppressing properties of the BMPs (80). It has also been reported that Nog, could act as a molecule that maintains pluripotency by short periods from stem cells that are supported on hydrogel matrices, which could be used in case of bone regeneration (81). BMPs can be integrated with other signaling proteins according to cell needs and are regulated from the nucleus epigenetic shape. They also influence growth factors such as FGF, Wnt, Sonic hedgehog (Shh) and Notch in order to develop different tissues. It is unclear what role the BMP antagonist Nog plays in the formation of the craniofacial skeleton, due to its multiple domains of expression during formative stages.

Noggin and jaw development

The mandibular development takes place in three components: The first component comprises the prominence of the jaw which grows distally from the embryo. The second component is the formation of teeth (Odontogenesis) and the third component is the development of the supporting structures of the jaw (82,83). The three components require specific modulation of the activity of the BMPs, this has been demonstrated by the ectopic application over the jawbones (22,84-85). It has also been shown that the lack of function of its antagonist Nog results in skeletal defects and neural tube. Nog has a unique role in the early development mandibular (17,86) but acts with Chd for mandibular growth. Apparently both antagonists are also expressed in the three major phases of development of the gill arches and are both expressed around the pharynx and mandibular buttons (22). Winnier et al. in 1995 (87) analyzed the pharyngeal endoderm and ectoderm mandibular BMP-4 mutant mice, finding absence of the development of the early phases of the jaw, with implications in the almost complete loss of the jaw.

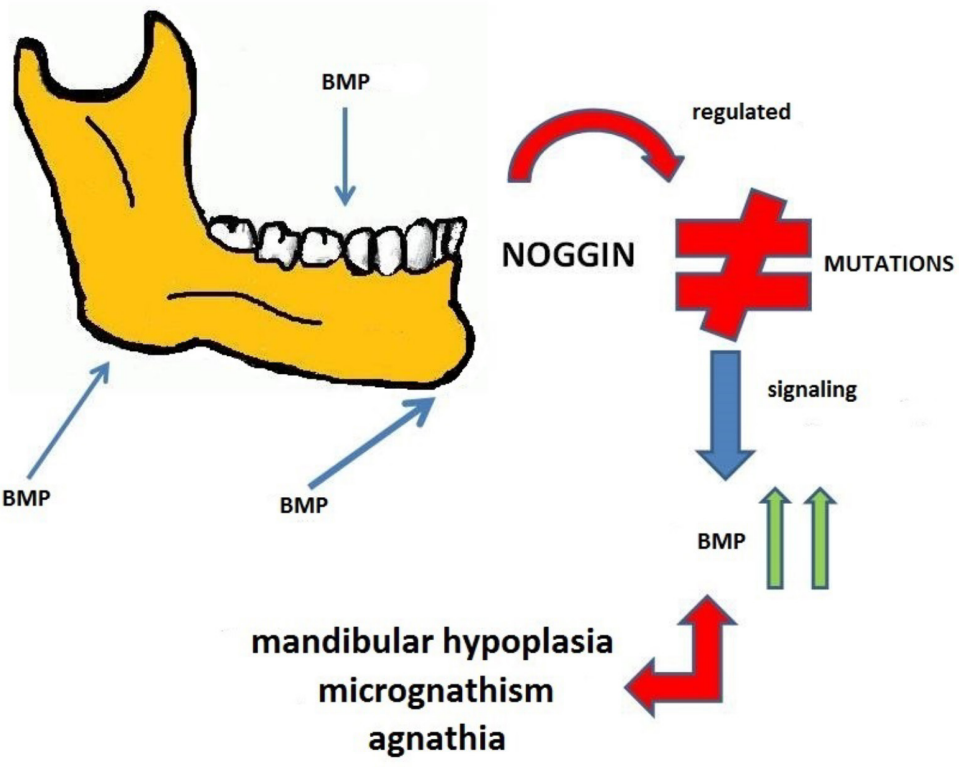
Studies in knockout of Nog shows abnormalities in the neural tube and the somites and mandibular defects ranging over a range of phenotypes from the mandibular hypoplasia, passing through an intermediate phenotype micrognathia (poor formation of the jaw) to agnathia (absence of mandibular formation) (88,89). It has also been suggested that gene coding Nog variants can act as a holoprosencephaly aetiological factor for human, in which the presence of the mandibular micrognathism is evident (90). Nog seems to play an important role in the early mandibular development (89) and functions redundantly with Chd for mandibular growth (88,89). Analysis of the NOG gene polymorphisms in Colombian individuals with mandibular micrognathia suggests that this gene is involved in the genesis of this anomaly (91). Studies in mice with mutations in the Nog gene (Nog +/-) have shown micrognathia with incomplete penetrance, a thin jaw and bilateral asymmetries. In general, the most severe defects were found in double mutants than in heterozygotes (40,89).

Similarly, it has been observed that the direct application of Nog regulates the BMPs in chondrogenesis, deducing that the activity of these proteins is increased when the antagonists decrease, and this increase reduces the expression of FGF-8 leading to improper migration of neural crest cells of the first gill arch, causing stunt growth of the bones of the upper and lower jaws. This shows that the coordination of the expression of FGF-8 and BMP-4 in time and adequate space is also critical to the jaw development (92).

Mandibular development therefore appears to be influenced by the modulation occurring in the BMPs by their antagonists, (Nog and Chd). Given that BMP signaling is key to the formation and migration of neural crest cells and jaw formation depends on this migration, alteration of this signal produces, among other craniofacial bone defects, a severe hypertrophic jaw. This is shown in studies conducted in mouse embryos, where expression of BMP-4 and their antagonists was blocked presenting cell death of mesenchymal cells of the mandibular base causing agnathia (9,40).

Considering the above, the hypothesis proposes how mutations in the gene Nog can alter the formation of its protein, which in turn would prevent a proper fitting

Figure 3
Structural changes in jaw development



of the BMPs receivers causing a lack of regulation of their signaling. This leads to overexpression of BMPs generating apoptosis of mesenchymal cells involved in mandibular growth. This lack of growth is based on the dose, going from a range of hypoplasia, micrognathia through agnathia (Figure 3).

The BMPs play an important role in the migration of neural crest cells for the formation of the 3 components of the jaw (thin blue arrows). Mentonian symphysis, teeth and supporting structures such as ascending branches and Meckel's cartilage. Nog modulates of BMPs signal through binding to their receptors in the extracellular space. When the gene which encodes Nog protein suffer impaired function primarily by mutations, the dose of the BMP signaling is increased which leads to lack of migration and death of mesenchymal cells of the neural crest which form the jaw. Therefore this could explain the presence of the different phenotypes according to the dose of signaling and these can range from hypertrophy and / or mandibular hypoplasia, through the micrognathism, up to the total lack of formation of the jaw called agnathia.

CONCLUSIONS

In conclusion, in the development of the mandible there are numerous genes involved in each stage of the formation of this structure. By altering these genes, defects occur that affect its growth, leading to abnormalities. Among these defects, the most often is mandibular micrognathia. It is known that the mandibular tissue derived from the neural crest, which in turn interacts with tissue as the endoderm and ectoderm result in the formation of this structure and the BMPs in turn play a key role as a regulator of development of neural crest cells and their derivatives.

It is also known that these BMPs have main antagonists (Nog and Chd) and modulating the signal act in regulating the development of craniofacial structures. The Nog antagonist specifically, plays an essential role and acts as both in the early pleiotropic development in the late development of the jaw and in the presence of BMP 2, 4, 5, 6 and 7 increases its expression in osteoblast cells and chondrocytes.

RECOMMENDATIONS

The mechanisms by which this gene could cause this malformation are not well understood. Therefore is necessary to undergo more molecular studies of the NOG gene and other regulator genes of the BMPs signaling in patients with mandibular micrognathism and mandibular growth alterations, which can give light to the etiology of this anomaly. Epigenetic studies are

suggested in order to determine not only the aspects which influence the ethiology of these anomalies from the classic genetics standpoint, but also the environmental factors involved.

PROSPECTS AND CHALLENGES

For several decades, studies have been conducted on craniofacial development and morphogenesis and have identified alterations in the gene sequences involved in the formation of these tissues. Animal models have also been used in which specific mutations and embryological techniques have been performed, allowing us to determine the importance of different signaling pathways. The Nog gene has recently attracted attention due to its involvement in the development of the mandible and several other craniofacial elements derived from neural crest cells (NCCs). Moreover, a lack of proper Nog function appears to be related to another craniofacial malformation that has one of the highest rates of morbidity in the world, one of them being cleft palate. Several studies using a topical treatment of the noggin recombinant human protein (rh Noggin) in mice with craniosynostosis (premature closure of cranial sutures) have shown that rhNoggin prevents this premature closure and may be a potential medical alternative for treating craniofacial syndromes. Furthermore, rhNoggin may also be used to treat mandibular growth alterations, such as prognathism and micrognathia as well as cleft palate. Viral and non-viral methods have been designed for transgene introduction and are potential strategies for craniofacial regeneration and treatment because more studies are focusing on designing safe gene therapy protocols for a single gene with the long-term goal of using similar protocols to treat complex diseases that involve several genes in their etiology. The use of these *ex vivo* strategies, such as cell transduction with retroviruses, is promising and may lead to successful treatment. However, it is essential to perform each step carefully, taking into consideration genotoxicity, and to begin integrating gene therapy with craniofacial engineering.

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