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REVIEW (English version)

Noggin's role in obesity: Biomarker potential?

Papel de la Nogina en obesidad: potencial biomarcador?

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Abstract

Obesity is a multifactorial disease resulting from the interaction between genetic, behavioral and environmental factors that can influence the individual response to eating and exercise habits. Its prevalence has increased drastically in the last decade, becoming a public health problem because is associated with diseases such as type II diabetes, cardiovascular damage, hyperlipidemias and cancer, which affect both sexes, all ages and all ethnic groups. Currently, it is the most prevalent metabolic disease in developed countries.

There are many *loci* and several genes that have been associated with the predisposition for obesity and thinness, obesity development and classified according to their expression in different stages of this condition, such as in early onset, predisposition to obesity, late onset, severe obesity (morbid).

In this article I review the potential role of the Noggin gene in adipogenesis and the possible mechanisms or signaling pathways in which this gene intervenes to lead to obesity.

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Keywords

Noggin; obesity; overweight; adipogenesis

Resumen

La obesidad es una enfermedad multifactorial resultado de la interacción entre factores genéticos, conductuales y ambientales que pueden influir en la respuesta individual a los hábitos alimenticios y de ejercicio físico. Su prevalencia ha aumentado dramáticamente durante la última década convirtiéndose en un problema de salud pública porque se asocia a patologías como diabetes tipo II, daño cardiovascular, hiperlipidemias y cáncer, que afectan a ambos sexos, todas las edades y todos los grupos étnicos. Actualmente, es la enfermedad metabólica más prevalente en los países desarrollados.

Hay muchos *loci* y varios genes que se han asociado con la predisposición a la obesidad, a la delgadez, y al desarrollo de la obesidad y se clasifican según su expresión en diferentes etapas de esta condición, como inicio temprano, predisposición a la obesidad, inicio tardío, obesidad severa (mórbida).

En este artículo se revisa el papel potencial del gen Nogina en la adipogénesis y los posibles mecanismos o vías de señalización en los que este gen interviene para conducir a la obesidad.

Palabras clave

Nogina; obesidad; sobrepeso; adipogénesis

Abbreviations

The following abbreviations are used in this manuscript

BMI	Body mass index
NOG	Noggin gene
BMP	Bone morphogenic protein
SIM1	Symphalangism
PI3K	Fosfatidilinositol 3 kinasa
mTOR	Mammalian Target of Rapamycin
cAMP	Adenosine-3`,5`-monophosphate
AKT	Serine-threonine protein kinase
PPAR-γ	Peroxisome proliferator-activated receptor gamma
IGF-1	insulin-like growth factor-1
MSC	Mesenchymal stem cell
TGF-b	Transforming growth factor-b
C/EBPs	Enhancer binding proteins
Pax-1	Paired box gene-1

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Introduction

Overweight and obesity prevalence has dramatically increased during the last decade and reached epidemic dimensions. By 2030 it is expected that there will be 2.16 billion overweight individuals with 1.12 billion adults predicted to be clinically obese. With current trends, by the same year, some researchers project that 86.3% of American adults will be overweight (25 < body mass index (BMI) ≤ 30) or obese (BMI > 30) and that overall 51.1% will be obese[1-7].

In the early 2000s, the World Health Organization (WHO) emphasized, through the term “globesity”, the pandemic nature of obesity that affects most countries and at all socioeconomic levels, therefore, is considered an important public health problem since the chronic diseases with which is associated imply a considerable increase in the use of health resources and a significant economic burden for health systems[5].

Obesity is a multifactorial disease that occurs from the interaction between a genetic predisposition and the presence of certain external factors (caused by both genetic and non-genetic factors)[1,8,9]. It is characterized by an increase in body weight beyond the needs of the skeletal physical structure, as a result of the excessive accumulation of body fat[1,9-12]. Usually is defined in adults as a BMI greater than 30 kg/m2. This pathology has become one of the main public health concerns since it occurs in both sexes, all ages and all ethnic groups[1,2].

In obesity, there is an increase in body fat as a result of a chronic energy imbalance, almost always related to modifiable environmental factors such as physical activity and diet, together with endogenous hormonal factors, in genetically predisposed individuals. The genetic factor justifies a small percentage of obesity: 1.8% of obese adults and up to 6% of children with severe obesity are obese monogenic dominant caused by mutations in different genes[13].

Obesity increases the risk of cardiovascular diseases, diabetes and dyslipidemia, although it has also been associated with gastrointestinal diseases such as gastroesophageal reflux, cholelithiasis, colon, esophageal and pancreatic cancers, among others[13-15].

Among the genes involved in the etiology of obesity are they find metabolic genes, genes that code for peptides that control the signals of hunger and satiety, regulatory genes of energy expenditure and genes that regulate the growth and differentiation of adipocytes[1].

Regarding the etiology of the genetic type, it has been proposed that it may be of monogenic, syndromic origin, as well as polygenic or multifactorial, in which hereditary factors participate between 40 and 70% in the development of the disease. Have been described approximately 200 cases of obesity in humans related to simple mutations in 11 genes. In

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syndromes with Mendelian inheritance patterns where obesity is constant, around 50 *loci* have been found to be involved in approximately 210 cases. 430 chromosomal sites with genes and regions linked to obesity traits have also been identified and 244 genetic mutations that affect weight and adiposity have been determined in mice, many of which are present in the human and related to metabolic processes such as generation and consumption of energy (homeostatic regulation)[16-19].

It has been proposed that one of these genes involved in adipogenesis and obesity is the Noggin gene.

Noggin gene (NOG)

Noggin (NOG, of the English language noggin: head) was discovered by Richard M. Harland and William C. Smith at the University of California and was first isolated from *Xenopus*. This finding was based on the body's ability to restore the normal dorsal-ventral axis of the body in embryos that had been artificially ventilated from UV treatment[20].

Noggin is a glycosylated-secreted protein known for its inhibitory effects on bone morphogenetic protein (BMP) signaling by sequestering the BMP ligand. The NOG gene is mapped to chromosome 17q22[21] and consists of a single coding exon of 696 bp, encoding a 232 amino acid protein that is secreted as a homodimer. Noggin binds and inactivates BMP proteins[22], (signaling proteins specific to the transforming growth factor b (TGF-b) superfamily) and is associated with the development of bones, tissues muscular and nervous system[23-25].

In humans, the NOG gene encodes the noggin protein and at the amino acid sequence level, high homology has been observed between human NOG, rat, mouse, and *Xenopus*[24-25]. Its functions are associated with the development of the embryonic head, so that when it is expressed in high concentrations it produces a head of great proportions in the embryo.

NOG modulates the bioactivity of "morphogenesis", through signals that function as growth factors and cell differentiation involved in the establishment of specific patterns in the architecture of organs and tissues. On the other hand, its signals promote the development of axial orientation patterns in the somites of the embryo[24-25].

NOG is produced in the embryo notochord, where it regulates the actions of BMPs during animal development. Specifically, the absence of BMP4 under the action of NOG causes aligned patterns of orientation of the neural tube and somites of the developing embryo, therefore, it has been described that the noggin is necessary for the proper development of the nervous system central and skeletal, as well as for the development of the forebrain[24-26].

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In view of the close association of BMP proteins and their regulation by the noggin, it has been suggested that in addition to their contribution in the development of the bone and in the fusion of the nerve tube, the noggin in mice is involved, especially at the level of hippocampus, in the development of learning and cognition[27].

In embryonic developing mice where the NOG and another protein called chordin are absent, the animal practically lacks a head. It is of interest that when these mice are only absent from the noggin, only slight errors are seen in the development of the animal's head suggesting an additive contribution between the two proteins[28].

The trademark of NOG-related syndromes is proximal symphalangism (SIM1), defined by abnormal fusion of the proximal interphalangeal joints of the hands and feet. Several additional features secondary to NOG mutations are usually but inconsistently observed, including characteristic facies with a hemicylindrical nose, congenital conductive hearing loss due to stapes fixation, and hyperopia. The variable clinical presentations led to the designation of five different autosomal dominant syndromes, all subsequently found to have resulted from NOG mutations. These include proximal symphalangism; multiple synostoses syndrome 1; stapes ankylosis with broad thumbs and toes; tarsal-carpal coalition syndrome; and brachydactyly type B2. The embryo can also grow with short limbs, absence of bone components or even with the total absence of some joints[23,24].

The Noggin protein participates in the specific derivation of the germ layer of specialized cells. The formation of the notochord, hair follicles, neural tissues and ocular structures arise from the germ layer of the ectoderm. The activity of Noggin in the mesoderm prepares the pathway for the formation of cartilage, bone and muscle growth, on the other hand, in the endoderm; the noggin is involved in lung development[20,26].

In the early stages of craniofacial development, the presence of noggin influences the formation and growth of the palate, jaw and skull, a process that occurs through its interaction with the cells of the neural crest. Studies in mice that lack NOG show that these animals have a cleft jaw and palate growth. Additionally, the absence of noggin also causes conductive hearing loss due to uncontrolled growth of the cochlear duct[20].

Since noggin is a secreted protein, it has been proposed that it has a paracrine function (although the mechanism is still unknown) promoting obesity. It is possible that noggin acts through BMP receptors that lead to adipocyte differentiation, while signaling through the BMP-Ib receptor leads to osteoblast differentiation[29,30].

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Noggin and obesity

Specific NOG levels in obese individuals indicate that it may be a potential biomarker for obesity. Sawant *et al* in 2012[30], demonstrate a novel role for noggin as an inducer of adipogenesis and show that noggin acts as a key regulator balancing bone formation and adipogenesis[30-32]. Obese people have an increase in bone fat along with a reduction in trabecular bone mass, and in older women with osteoporosis there are also high levels of bone fat and greater susceptibility to fractures. That authors suggest that increasing NOG levels could increase bone fat and reduce bone density (BMD), so NOG could act as a molecular switch that controls the fate of mesenchymal stem cell (MSC) differentiation[30,33,34].

These authors also determined that noggin-mediated adipogenesis of MSC is independent of adipogenesis pathways, where activation of PI3K, mTOR/AKT and cAMP occurs. It is well described that the signals of these activators induce the expression of C/EBPδ,C/EBPα and PPAR-γ, which are transcription factors that regulate adipogenesis. In this context Noggin can induce the expression of these three transcription factors during adipocytic differentiation of MSC. On the other hand, PPARγ and C / EBPα regulate each other to maintain gene expression, so the two transcription factors, alone or in cooperation with each other, induce the transcription of many adipocyte genes that encode proteins involved in the formation and maintenance of the adipocyte phenotype[30,35].

Although the mechanisms are unknown, NOG overexpression has been reported to induce adipogenesis. In this sense, insulin-like growth factor-1 (IGF-1), an important differentiation factor for osteoblasts, suppresses the expression of NOG[30,36], in addition, it is important for the maintenance of bone homeostasis and during obesity. IGF -1 decreases the expression of NOG, therefore, the interaction between IGF-1 and NOG could be one of the pathways involved in the NOG-mediated adipogenesis process[30,34].

The incidence of obesity has increased to pandemic levels and more studies are required to understand the mechanisms of adipogenesis regulation and the signaling pathways involved to address new treatment strategies. Although bone morphogenetic proteins (BMP) influence adipogenesis, the effect of BMP antagonists such as Noggin is still unknow[26].

On the other hand, adipocyte differentiation (and the process of adipogenesis) is characterized by changes in the expression of several genes that lead to the establishment of the adipocyte phenotype and the appearance of early, intermediate and late mRNA/protein markers and triglyceride accumulation, among others[37,38].

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In this context, it has been described that Pax-1 (which codes for a DNA binding protein with transcriptional activation properties and plays a role during embryonic design[30,39,40] can participate in adipogenesis. Mutation in the Pax gene -1 in mice produces a substantial decrease in adiposity index[30,41] and the promoter analysis of the PPAR-γ, C / EBP-α and C / EBP-δ genes also suggests an additional role of Pax-1 in the adipogenesis.

On the other hand, mice with noggin haploinsufficiency exhibit reduced levels of Pax-1. The gene promoter regions encoding the transcription factors mentioned above show supposed Pax-1 binding sites, indicating a possible role of Pax-1 in noggin-mediated adipogenesis, however, more studies are needed to elucidate the mechanism molecular of the positive regulation of Pax-1 induced by noggin in this process, since at the level of embryonic development it is already known that Noggin induces the expression of Pax-1 during the development of the sclera in the early stage of somite[30,42] and that the noggin mutation completely cancels Pax-1 expression and results in a lower survival of the sclera[30,43].

Conclusions

Obesity is a complex disease, in which the expression of many genes or proteins, could be decisive in the identification of pathways and processes altered and involved within their biological context, therefore, the precise study of specific genes, encoded proteins , metabolic or biochemical pathways, the effects affected and their exact impact on the functions that lead to obesity, is the challenge for future studies and for the identification of potential biomarkers such as Noggin, which could be involved in the molecular mechanisms that induce adipogenesis and obesity.

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Conflicting Interest (If present, give more details)

The author declares no conflict of interest.

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