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REGULAR ARTICLE

Fibroblast growth factor-21 may be a potential novel drug for preventing the development of traumatic TMJ bony ankylosis

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Prevention

Abstract Trauma is the leading cause of temporomandibular joint (TMJ) bony ankylosis. The treatment of the condition poses a significant challenge because of the high incidence of recurrence. We previously proposed a new view that the development of traumatic TMJ bony ankylosis may be a course similar to hypertrophic nonunion, and the ensuing animal experiments preliminarily verified this view through histological analysis and molecular biology examination. In view of the similarity between bone healing and bony ankylosis, and the importance of recruitment and differentiation of mesenchymal stem cells (MSCs) during the course of bone healing, it is reasonable to select MSCs as the breakthrough point for prevention of bony ankylosis. Recent studies reveal that fibroblast growth factor 21 (FGF21), a key mediator of peroxisome proliferator-activated receptor-γ (PPARγ), can promote adipocyte differentiation, inhibit osteoblast differentiation of MSCs and stimulate osteoclast activity by activation of PPARγ. Therefore, we hypothesize that local FGF21 injection may prohibit the onset of traumatic TMJ bony ankylosis through formation of a fat pad separating the condyle from the glenoid fossa, inhibition of new bone formation and promotion of bone resorption in the joint space, which thus may be a potential novel treatment for TMJ bony ankylosis.

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Introduction

Post-traumatic temporomandibular joint (TMJ) bony ankylosis is regarded as bony fusion between the two injured articular surfaces [1]. It is a severe disability that results in restricted mouth opening and masticatory difficulty. So far, surgery is the only method to treat this condition. Due to the difficulty of operation and the recurrence rate of 9–20% [2–4], surgical treatment of bony ankylosis is still a considerable challenge for craniomaxillofacial surgeons. Prevention of the development of traumatic TMJ bony ankylosis may be the most effective treatment modality. However, no effective method of prevention has been reported. Finding a novel, effective, non-surgical treatment for bony ankylosis seems quite important.

The development of traumatic TMJ bony ankylosis: a course similar to hypertrophic nonunion?

The precise pathogenic process and molecular mechanism of the traumatic TMJ bony ankylosis remain ill-defined [5]. Our understanding of the pathogenesis of the disease derives mainly from several popular hypotheses, including organisation and ossification of the haematoma [1,6], distraction osteogenesis of the lateral pterygoid muscle [7,8] and genetic predisposition [9]. Recently, through reviewing the literature, we found that the occurrence condition for traumatic TMJ bony ankylosis was in fact to establish the microenvironment for the bone healing of the two articular surfaces [10–12] and that bone graft in the joint or restricted jaw movement can accelerate the process of ankylosis [13–15]. Taking into account the inhibitory role of the opening movement in bone formation in the joint space [16], we proposed a new view that the development of traumatic TMJ bony ankylosis was a compromised bone healing course, especially a course similar to hypertrophic nonunion [17], which was a supporter to the hypothesis of ossification of the haematoma.

To test this new opinion, a sheep model of TMJ bony ankylosis was established by mimicking the traumatic microenvironment of sagittal condylar fracture [18]. The histological analysis of the animal model demonstrated that endochondral ossification was the main type of bone formation during the formation of bony ankylosis and a prolonged chondral phase was revealed compared to condylar fracture healing, which indicates a similarity between bony ankylosis and compromised bone healing [18].

Based on the established animal model, the endogenous messenger RNA (mRNA) expression of a series of genes regulating cartilage formation, bone formation and endochondral ossification was examined. We found a continuous up-regulation trend in the gene expression of Wnt1, Wnt2b, Wnt3a, β-catenin, Sfrp1, Lrp6, Lef1, CyclinD1 and Runx2 at 3 and 6 months compared with 1 month, which indicated that the Wnt signalling that played important roles in fracture healing was also activated during the formation of TMJ bony ankylosis [19]. Through examining the differential expression among fibrous ankylosis, bony ankylosis and condylar fracture by real-time polymerase chain reaction (PCR), we found that the mRNA expression levels of Wnt5a, β-catenin, Lef1, Runx2, Osterix, Sox9, Col10a1, Alp, Ocn, Bmp2 and Bmp7 in bony ankylosed callus were inclined to be higher than those in fibrous ankylosed callus, but lower than those in fracture callus at several time points [20]. These results demonstrated that the development of bony ankylosis was a compromised bone healing, especially a course that was similar to the hypertrophic nonunion, with low activity of osteogenesis in the joint space in the molecular level [20]. Another study by Xiao et al. [21] has isolated and identified mesenchymal stem cells (MSCs) from the radiolucent zone of human bony ankylosed specimens, and showed that MSCs in the radiolucent zone possessed a lower proliferation and osteogenic differentiation capacity compared with those from normal mandibular bone marrow.

In summary, so far, a series of clinical and experimental studies have preliminarily verified our view regarding the pathogenesis of traumatic TMJ bony ankylosis and also provided important information for exploring suitable methods to prevent the development of the disease.

PPARγ and MSCs

In view of the similarity between bone healing and bony ankylosis, and the importance of recruitment and differentiation of MSCs during the course of bone healing, it is reasonable to select MSCs as the breakthrough point for prevention of bony ankylosis. It is well known that MSCs can differentiate into different cell lineages under specific transcription factors, such as differentiation into osteoblasts determined by Runx2/Osterix and differentiation into chondrocytes determined by Sox5/6/9 [22]. Peroxisome proliferator-activated receptor-γ (PPARγ) is the key transcription factor for the differentiation of MSCs into adipocytes [23]. PPARγ is also the molecular switch between the osteogenic and adipogenic pathways [24]. Overexpression of PPARγ in MSCs can not only suppress the expression of Runx2 and the osteoblast differentiation but also promote their terminal differentiation into adipocytes [25]. Recent studies reveal that PPARγ can inhibit osteoblastogenesis from bone-marrow MSCs and promote osteoclast differentiation from haematopoietic stem cells [26,27], suggesting that PPARγ plays important roles in skeletal homeostasis.

FGF21, a key mediator of PPARγ

Fibroblast growth factor-21 (FGF21) is an atypical member of the FGF family. It activates cell signalling through binding with the classic FGF receptors complexed with b-Klotho in the cell surface [28]. FGF21 has broad metabolic actions, mainly in regulation of glucose and lipid metabolism. It can increase energy expenditure, enhance insulin sensitivity and reduce body weight when administered to diabetic rodents and monkeys [29,30].

Recent studies on the FGF21-knockout mice reveal that FGF21 can activate PPARγ by inhibition of its sumoylation, promoting the differentiation of MSCs of the adipose tissue into adipocytes while inhibiting osteoblast differentiation [31]. FGF21 can also promote the differentiation of MSCs of the bone marrow into adipocytes through the same mechanism [32]. In addition, FGF21 can stimulate osteoclastogenesis and bone resorption by activation of PPARγ and change of the ratio of receptor activator of NF-kappaB ligand/osteoprotegerin (RANKL/OPG) [32]. These findings demonstrate that FGF21 is a key factor regulating the physiological and pharmacological functions of PPARγ.

Hypothesis

Our hypothesis is that FGF21 may be a potential drug for preventing the development of traumatic TMJ bony ankylosis. On the one hand, FGF21 can stimulate the differentiation of the MSCs in the joint space to adipocytes while suppressing its osteoblast differentiation, thus resulting in the formation of a fat pad separating the condyle from the glenoid fossa and inhibiting new bone formation meanwhile. On the other hand, FGF21 can activate PPARγ and change the RANKL/OPG ratio, thus promoting osteoclastogenesis and bone resorption in the joint space.

Evaluation of the hypothesis

Traumatic TMJ bony ankylosis remains an enigma, partly due to the ambiguous recognition of the nature of the condition and the lack of understanding of molecular mechanisms underlying the disease onset and progression. We believed that the nature of the disease was a compromised bone healing under the interference of the opening movement, and the ensuing experiments preliminarily verified this notion [18–21]. Therefore, theoretically all methods of inhibiting bone formation or fracture healing, such as non-steroidal anti-inflammatory drugs [33], low-dose irradiation [34,35], antagonists of BMP and Wnt signalling pathways [36,37] and so on, may be beneficial to the prevention of TMJ bony ankylosis. However, it can be anticipated that the outcomes of the above-mentioned strategies may only convert bony ankylosis into fibrous ankylosis rather than prevent the onset of bony ankylosis because abundant fibrous tissue will grow into the joint space while bone formation is inhibited.

However, if we take an alternative approach, namely inhibition of bone formation and simultaneous stimulation of the adipocyte differentiation of the MSCs, the outcome may be different. The fat pad will form in the joint space and separate the condyle from the glenoid fossa, serving as a physical barrier and a mechanical buffer like a normal disc, ultimately prohibiting the onset of bony ankylosis. Experimental studies have observed 'adipogenic healing' at the nonunion site, indicating that the adipose tissue can be present during fracture healing [38,39]. In addition, clinical studies have demonstrated that autologous fat grafts placed around the TMJ can prevent the postoperative recurrence of ankylosis [40,41]. Therefore, FGF21, the key mediator of PPARγ, may be a promising drug specific for prevention of the TMJ bony ankylosis.

Testing the hypothesis

Use of recombinant adenoviruses (Ad) to express secreted growth factors represents a powerful method in studies with experimental animals [42]. This strategy can produce a large amount of recombinant protein with a single injection. Hence, we can construct an adenoviral expression of FGF21 (Ad-FGF21) and inject it into the joint space of the sheep which are induced into TMJ bony ankylosis as previously described [18], then observe whether adipose tissue forms and whether this handling can prevent the progress of bony ankylosis or not. If this hypothesis proves to be true, local FGF21 injection will be a novel treatment for bony ankylosis without surgical resection in the future.

Conflict of interest statement

None declared.

Overview box

First Question: What do we already know about the subject?

1. Traumatic TMJ bony ankylosis may be a course similar to hypertrophic nonunion.
2. FGF21 can promote adipocyte differentiation, inhibit osteoblast differentiation of MSCs and stimulate osteoclast activity by activation of PPARγ.

Second Question: What does your proposed theory add to the current knowledge available, and what benefits does it have?

FGF21 may prohibit the onset of traumatic TMJ bony ankylosis and thus may be a potential novel treatment for bony ankylosis.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?

An interference experiment using adenoviral expression of FGF21 (Ad-FGF21) can be performed in the established animal model.

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