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BMP-7: Therapeutic target for ocular fibrotic disorders

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Abstract Scarring of cornea, glaucoma, after-cataract and also proliferative vitreoretinopathy(PVR) related tractional retina detachment, age related macular degeneration and diabetic retinopathy etc., which are the major and seriously impair vision diseases in eyes, with various appearance and different therapy method, but maybe they have the similar pathogenesis—fibrosis, and all the above ocular diseases can be regarded as fibrotic disorders. Thus inhibition of the fibrotic process may provide a potentially novel therapeutic approach to the treatment of these ocular diseases mentioned above. Now numerous studies have proved that BMP-7 significantly reversed renal, hepatic, pulmonary fibrosis, including inhibition of Transforming growth factor-β (TGF-β) production, suppression of epithelial-to-mesenchymal transition (EMT), and repair of severely damaged epithelial cells. So it is reasonable to refer that BMP-7 may have the same preventive effect in these ocular fibrotic disorders. A potential clinical therapy can be developed by using the anti-fibrosis effect of BMP-7.

Introduction

What's the fibrotic disorder?

Fibrotic disorders are a group of diseases that can affect many tissues of the human body, relating to hepatic diseases, renal diseases, pulmonary diseases, etc., and characterized by persistence of inflammation, appearance of myofibroblasts, and excess accumulation of extracellular matrix (ECM) with resultant tissue contraction and impaired function [1—3]. Following primary tissue repair post-injury, on one hand, tissues are continuously remodeling normal structure and function, and on the other hand, inflammation induced by the injury provides inflammatory/fibrogenic growth factors/cytokines, which often lead to fibrotic lesion causing failure of tissue remodeling and dysfunction of tissues due to excess accumulation and contraction of ECM [4—6]. TGF-β signals play an important role in the process [7]. Modulated by TGF-β signals, a number of myofibroblast derived from both actived fibroblasts and epithelial cell types, which plays a central role in the process of tissue fibrosis/scarring [8,9]. Meanwhile, the epithelial cells lose their epithelial phenotype and acquire mesenchymal, fibroblast-like properties and show reduced intercellular adhesion and increase motility, which is called epithelial-to-mesenchymal transition (EMT) [10,11]. Instead of interacting with the ECM at the basal cell surface, the transdifferentiated

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cells acquire the ability to invade the ECM [10,12]. TGF-β signals also induce the expression of the majority of the ECM components and enzymes involved in matrix reorganization/maturation [13].

BMP-7 and its anti-fibrotic role in fibrotic diseases

BMPs are secreted proteins that constitute the largest subfamily within the TGF-β superfamily of growth factors. It was originally identified that BMPs play essential roles in bone and cartilage formation. However, BMPs are expressed in many tissues other than bone, and have been implicated in the pathophysiology of several diseases, including cancer, kidney diseases, pulmonary hypertension, arthritis, and cerebrovascular disease [14]. BMP-7 is a member of BMPs, interacting with TGF-β, and participates in the process of tissue fibrotic degeneration. The antagonistic role of BMP-7 in fibrosis has been demonstrated by many studies. It was reported that BMP-7 can inhibit the EMT and its expression significantly decreased in experimental and human renal fibrosis [15—17]. Myllärniemi et al. [18,19] considered that there is a balance between TGF-β and BMP signaling, which is important for lung regenerative events and is significantly perturbed in pulmonary fibrosis. Rescue of BMP signaling activity may represent a potential beneficial strategy for treating human pulmonary fibrosis. Similar protective role of BMP-7 has also been proved in hepatic and cardiac fibrosis [20,21].

Are they similar in eyes?

In the field of ophthalmology, are ocular tissues also susceptible to the fibrotic disease and also have the similar pathomechanism? Scarring in cornea, glaucoma, after-cataract, and also proliferative vitreoretinopathy (PVR) related tractional retina detachment, age related macular degeneration and diabetic retinopathy are most common but seriously impairing vision and visual function diseases. Recently there is no effective therapy for these diseases except operation. However, operation can't solve the problems fundamentally, and the further fibrosis would make the operation end in failure. But can we consider these diseases in another point of view? Can we hypothesize that a balance consists in the ocular tissues, in which all sorts of cytokines interact with each other and form a network? Under physiological conditions, the cytokines restrict with each other and form a balance. However, when tissues suffer from endogenous or exogenous injury, i.e., trauma, operation, inflammation, external force, elevated IOP, high glucose, even minimal changes of internal environment, the over-expression of inflammatory/fibrogenic growth factors/cytokines were elevated which breaks the previous balance to make a fibrotic lesion. In this process, partial of the normal ocular tissues undergoing fibrous degeneration, lose their prior morphous and biological function, thus the subsequent symptoms and signs appear. BMP-7 would probably rebuild the broken balance by inhibiting the inflammatory/fibrogenic growth factors/cytokines, which represents a potential beneficial strategy for treating fibrotic disorders in eyes.

The hypothesis

In view of this, we hypothesize that all the above ocular diseases are all have a common, fibrotic component to their mechanism, and in these ocular tissues there would be a balance between the cytokines, which is broken in some cases and lead fibrotic lesion. BMP-7 is able to rebuild the broken balance, and reverse the fibrotic disorders in eyes, which may give us a new prospect on the ocular disorders.

Evaluation of the hypothesis

Though they are characterized with different pathological changes and clinical features respectively, ocular diseases including scarring in cornea, glaucoma, after-cataract, PVR and diabetic retinopathy may have a common property that fibrosis plays an important role in all of them. The former studies related to BMP-7 have also given us some inspirations.

Cornea

The cornea is an avasucular tissue of the eyeball shell and must remain transparent and of a regular curvature to refract light properly. When the cornea is injured, the components of the diseases process include inflammation, fibroblast activation and ECM accumulation. So the transparency of the cornea is reduced by stromal fibrosis/scarring, leading to the impairment of the patients' vision [22].

Wall et al. [23] were the first to report the existence of a BMP in the cornea. Saika et al. [24] demonstrated the therapeutic effect of BMP-7 on a corneal alkali injury model in the mouse. The exogenous BMP-7 resulted in the activation of the receptor of Smad-1, 5, 8 and suppressed the generation of myofibroblasts and appearance of inflammatory cells, which suggested the effective treatment of BMP-7 to alkali burns of cornea.

Trabecular meshwork(TM) and optic nerve head

There would be some morphological and biochemical changes in the TM of patients with primary open-angle glaucoma(POAG), which increases resistance of aqueous humor outflow and elevates the IOP [25]. The expression of TGF-β in glaucomatous aquous humor are elevated obviously, which shift the balance between ECM deposition and degradation, resulting in the accumulation of ECM in TM, increased outflow resistance and also elevated IOP [26]. Meanwhile, the elevated IOP is a continuous injury for optic nerve head, which would be a reason for optic nerve lesion in glaucoma.

Wordinger et al. [27] were the first to report the expression of BMP mRNA and proteins in the adult human TM and optic nerve head. Fuchshofer et al. [28] have demonstrated the BMP-7 could inhibit TGF-β2 induced proteins associated with ECM. An antagonist of BMP gremlin was found expressed significantly increased in glaucomatous TM cells, which interrupts the binding of BMP, and reduces their ant-TGF-β effect [29].