

Differential roles of TGF- β signalling in joint tissues during osteoarthritis development

Osteoarthritis (OA) is the most common degenerative joint disease. The aetiology of OA is multifactorial, including joint injury, obesity, ageing and heredity. Inactivation of transforming growth factor beta (TGF- β) or its downstream molecules may be an important signalling event contributing to OA pathogenesis because mutations of *Smad3*, a central molecule in TGF- β signalling, have been found in patients with early-onset OA.^{1–3} It has been known for many years that TGF- β promotes matrix protein synthesis, inhibits chondrocyte hypertrophy and stimulates expression of *Prg4*, which encodes for lubricin, a critical molecule for lessening joint friction.⁴ Lubricin, which is present in synovial fluid and on the surface (superficial layer) of articular cartilage, plays an important role in joint lubrication and synovial homeostasis.

The disease of OA affects the entire joint.⁵ TGF- β signalling may play differential roles in joint tissues during OA development. For example, *Smad3* global knockout (KO) mice showed inhibition of chondrocyte hypertrophy and OA-like articular cartilage damage.⁶ The deletion of *Tgfb2*, encoding for type II TGF- β receptor,⁷ or *Smad3*⁸ in articular chondrocytes consistently led to an OA-like phenotype. In contrast, the activation of TGF- β signalling in mesenchymal progenitor cells of subchondral bone also caused OA-like lesions.⁹ These findings suggest that TGF- β signalling may play differential roles in the various joint tissues.

A recent report in the *Annals of the Rheumatic Diseases* demonstrated that the disruption of decorin-restricted TGF- β signalling led to increased articular cartilage matrix stiffness, rendering joints more resistant to OA.¹⁰ This suggests that the loss of *Dcn* could decelerate OA development because of the release of endogenous TGF- β into the joint. To further understand the functional significance of decorin in regulation of TGF- β signalling and in OA development, it will be important to generate *Dcn* conditional KO mice targeting different tissues in the joint. It will also be interesting to determine whether mutation(s) of *Dcn* can be detected in patients with an aneurysms–OA syndrome in which *Smad3* has been proposed as a disease-causing gene for some patients.

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