Roles of M1 polarized macrophage and Fyn tyrosine kinase in osteoarthritis development

With the support by the National Natural Science Foundation of China, the research team led by Prof. Bai XiaoChun (白晓春) and Cai DaoZhang (蔡道章) at the Southern Medical University, uncovered the roles of M1 macrophage and Fyn tyrosine kinase in the development of osteoarthritis (OA), which were published in *Ann Rheum Dis* (2018 Jul 10, annrheumdis-2018-213450) and *Ann Rheum Dis* (2018, 77(6): 935—943), respectively.

OA is a highly-prevalent and degenerative joint disorder, causing pain and functional disability, the typical feature of which is the progressive degradation of articular cartilage. Despite the identified risk factors, which include ageing, joint injury, obesity, genetics, sex and anatomical factors related to joint shape and alignment, the exact pathogenesis of OA remains undefined. There is still no effective disease-modifying treatment for OA and a novel approach for its treatment is urgently required.

In one study, Prof. Bai and Cai's group used proteome-wide screening to identify the proteins involved in cartilage degeneration and noticed the tyrosine kinase Fyn accumulated in degenerated and damaged articular cartilage in aged mice and patients with OA. They demonstrated that loss of Fyn efficiently prevents the development of post-traumatic and age-dependent OA in mice. Moreover, they established links between Fyn, β-catenin and OA. During OA development, Fyn phosphorylates (Tyr142) and stabilizes β-catenin, leading to the activation of the β-catenin pathway independent of Wnt signalling in articular cartilage chondrocytes. Importantly, PP1, an inhibitor of Fyn, delays the development of OA and is therefore a potential drug for the treatment of OA.

In another study, they found that M1-type polarized macrophages were clustered in the synovial tissues of OA patients and OA model mice. Constitutive activation of the mechanistic targets of rapamycin complex 1 (mTORC1) in the myeloid lineage increased M1 polarization in synovial macrophages and exacerbated OA in mice. Inhibition of mTORC1 enhanced M2 polarization and alleviated OA in mice. M1 polarized macrophages produced high levels of inflammatory cytokines/enzymes and promoted chondrocyte differentiation *in vitro*. M1 macrophage promoted cartilage degeneration and osteophyte formation partially through secretion of Rspo2 and activation of β-catenin signaling in chondrocytes. Further management of the behavior of polarized synovial macrophages may be a suitable approach to prevent OA.

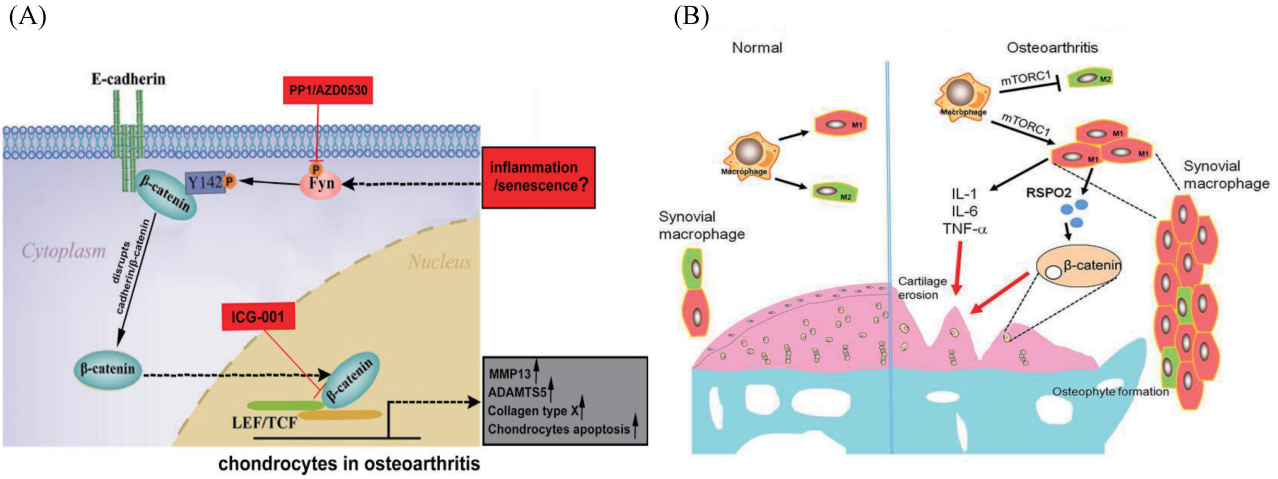

Figure Proposed model for the role of Fyn (A) and M1 polarized macrophages (B) in OA development.