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Targeting mechanobiological pathways to attenuate dysfunctional remodeling in TMJ-OA

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Temporomandibular joint (TMJ) osteoarthritis (OA) is a clinical syndrome associated with arthralgia, limited joint mobility, and decreased quality of life. Although systemic illness, aging processes, hormonal factors, and behavioral factors have been implicated in TMJ OA etiology, growing evidence suggests that mechanical overload is a key initiating factor for a series of degenerative changes in the TMJ that culminate in condylar resorption and deformity (Arnett et al. 1996a; 1996b, Tanaka et al. 2008). Therefore, an evaluation of the molecular basis of cellular load transmission would lead to a better understanding of the mechanism of TMJ OA pain and disability that would aid in the early diagnosis and lead to the development of new therapeutic agents for the management of TMJ OA. The long-term goal of this proposal is to further the understanding of the clinical problems associated with TMJ function and cartilage pathophysiology, including defining precise methods of TMJ OA classification, prevention, and treatment. This proposal focuses on the role an established mechanically activated pathway, the integrin-focal adhesion kinase (FAK) signaling axis, as a therapeutic target for TMJ OA. FAK signaling controls cell attachment, survival, proliferation, and motility. In dermal fibroblasts, FAK is mechanically activated (Yanoshita et al. 2018; Zhou et al. 2015), and promotes both the chemoattraction of inflammatory cells and pro-fibrogenic matrix synthesis (Wong et al. 2012; Yanoshita et al. 2018). FAK signaling in the tissues of the TMJ is less well understood. A recent study has illustrated that mechanical activation of FAK enhances the viability of mandibular chondrocyte (Ma et al. 2016). The role of mechanically activated FAK on fibrogenic signaling and the chemoattraction of inflammatory cells has never been studied in the context of TMJ OA. This represents a potentially critical knowledge gap in the etiopathogenesis of TMJ OA, contextually linking a mechanically activated molecular mechanism with parallel fibrogenic and inflammatory pathways contributing to dysfunctional remodeling. The central hypothesis of this application is that mechanical overloading of the TMJ activates the FAK signaling axis through a phosphorylation event, and that this molecular mechanism is a critical regulator for the progression of TMJ OA. This proposal tests the central hypothesis with two specific aims. In Aim 1, we will define downstream signaling pathways of mechanically activated FAK in mandibular chondrocytes using an in vitro culture system that can be exposed to mechanical loading using a custom compression bioreactor. In Aim 2, we will implicate FAK activation as a critical regulator of TMJ OA pathophysiology by quantifying the amount of activated FAK in tissues removed during TMJ replacement surgery and blocking FAK activation in a preclinical animal model of TMJ OA using small molecule inhibitors. If the specific aims of this proposal prove successful, these data will justify further evaluation of FAK inhibition as an achievable clinical goal for the management of TMJ OA. The overall objective and long-term goals of this application strongly align with the investigators backgrounds, research interests, and clinical practice, demonstrating a commitment to addressing a critical need facing oral and maxillofacial surgeons and their TMJ OA patients. In doing so, this project fosters inter-professional research collaboration between two junior faculty at the UIC College of Dentistry. We anticipate that this collaboration will yield valuable data and have a high chance of facilitating research independence for all investigators because the long-term goal and specific aims ideally interface with the current needs facing translational TMJ-related research, the mission of the National Center for Advancing Clinical and Translational Science, and the objectives and mission of the Oral and Maxillofacial Surgery Foundation.