

On the Horizon From the ORS

Annexins: Novel Therapeutic Targets for the Treatment of Osteoarthritis?

Takeshi Minashima, PhD
Kirk Campbell, MD
Thorsten Kirsch, PhD

Osteoarthritis (OA) is the most common form of arthritis, affecting an estimated 27 million Americans.¹ The lack of current treatments to slow OA progression is due to the lack of both early detection methods and therapeutic targets for OA. Thus, there is an urgent need for the discovery of potential new therapeutic targets for the treatment of OA.

Annexins are cytoplasmic proteins that, in the presence of Ca^{2+} , translocate and bind to membranes. The role of annexins in disease pathology is an emerging field of investigation, with many studies highlighting the role of annexins not only as prognostic and diagnostic markers but also as being actively involved in causing diseases such as Alzheimer's disease, autoimmunity, cancer, diabetes, and cardiovascular diseases. Specifically, their modulatory action on major signaling pathways involved in disease pathologies has made the annexins novel and exciting therapeutic targets.²

We have shown that annexin A6 (AnxA6) is highly expressed in OA cartilage but not in normal healthy articular cartilage.³ Because annexins have been shown to stimulate nuclear factor kappa B (NF- κ B) signaling, a major catabolic signaling pathway in OA,^{4,6} we tested the possibility that AnxA6 stimulates NF- κ B signaling in OA cartilage, thereby leading to accelerated cartilage destruction. Loss of AnxA6 resulted in decreased activation of NF- κ B and mRNA levels of catabolic markers, including a disintegrin and metalloproteinase with thrombospondin motif

(ADAMTS)-5, inducible nitric oxide synthase (iNOS), interleukin (IL)-6, and matrix metalloproteinase (MMP)-13, in IL-1-treated mouse articular chondrocytes, whereas overexpression of AnxA6 resulted in increased NF- κ B activity and mRNA levels of these catabolic markers in articular chondrocytes. Cartilage destruction in IL-1-treated knee joints of AnxA6 knockout mice was markedly reduced compared with cartilage destruction in wild-type mouse joints. AnxA6 interaction with p65 resulted in increased nuclear translocation and retention of the active p50/p65 NF- κ B complex.

Based on the detrimental effects of NF- κ B signaling on cartilage destruction during OA pathogenesis, NF- κ B signaling has become a major therapeutic target in OA disease.⁴ Because NF- κ B, however, plays a pivotal role in many physiologic processes, selective targeting of this signaling pathway in OA joints has become a major challenge. Annexins appear to specifically stimulate NF- κ B signaling only during disease pathology but not under physiologic conditions. For example, only the high expression of AnxA1 in breast cancer cells results in constitutive activation of NF- κ B and ultimately high metastasis of these cancer cells, whereas low expression of AnxA1 does not lead to constitutive NF- κ B activation and, as a consequence, low metastasis.⁵ Similarly, our findings suggest that only high expression of AnxA6 in OA cartilage results in NF- κ B activation, whereas low AnxA6 expression in healthy articular cartilage does not. Therefore,

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From the Musculoskeletal Research Center, Department of Orthopaedic Surgery, New York University School of Medicine, Hospital for Joint Diseases, New York, NY.

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targeting the modulatory actions of annexins on NF- κ B signaling may provide a novel and selective way to inhibit NF- κ B signaling in diseases, such as cancer and OA.

Future research needs to determine strategies of how to interfere with the modulatory role of annexins on NF- κ B signaling. Recent findings showing that AnxA4 modulates NF- κ B signaling by directly interacting with the p50 unit of the heterodimeric p50/p65 NF- κ B complex in a Ca²⁺-dependent manner⁶ suggest that the interactions of annexins with NF- κ B signaling components and, ultimately, the stimulation of

NF- κ B activity by annexins require their ability to bind Ca²⁺. Therefore, interfering with the Ca²⁺-binding ability of these annexins may emerge as a potential novel strategy to specifically inhibit NF- κ B activity in OA and other diseases.

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