Clin Orthop Relat Res (2016) 474:1827–1829 / DOI 10.1007/s11999-016-4912-2

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

Published online: 31 May 2016

CORR Insights

CORR Insights®: The NLRP3/Caspase-1/Interleukin-1β Axis Is Active in Human Lumbar Cartilaginous Endplate Degeneration

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Where Are We Now?

Discogenic back pain is a common cause of low-back pain. Modic changes in the vertebra adjacent to the hyaline cartilage endplate, which serves as the third component of the intervertebral disc and separates the disc from the bony vertebra, is highly correlated with back pain [9]. Modic changes are signal-intensity changes visible on MRIs originating from bone-marrow lesions. There are three types of Modic changes: Modic change Type 1 is characterized by hypointensity on T1-weighted images and hyperintensity on T2-weighted images. Modic change Type 2 is characterized by hyperintensity on T1-weighted images and hyperintensity or isointensity on T2-weighed images. Modic change Type 3 is characterized by hypointensity on T1- and T2-weighted images. More importantly, each type is dependent on changes to the bone marrow: Edema and hypervascularity, fatty replacement, and bone sclerosing, respectively. Patients with Modic changes experience a greater frequency and duration of low back pain than those without Modic changes [4].

In the current study, Tang and colleagues compared the expression of inflammatory cytokine IL-1β and its activators caspase-1 and NLRP3 in cartilage endplates to patients with Modic changes or burst fractures as controls. The comparison to young adults with burst fractures is a thoughtfully chosen control group by the authors. Patients with acute-onset low back pain following a vertebral fracture and an endplate defect clinically present with Modic change Type 1 intensity in the bone marrow, but the pain and Modic type 1-like changes eventually resolve [12].

Where Do We Need To Go?

Since the etiology of the pain in patients with Modic changes is unclear, there is no consensus on treatments (steroid injections, disc replacement, fusion, or physical therapy), as all of them are associated with mixed results [3]. There is growing evidence that the presentation of nerve fibers and inflammatory factors in the endplate contribute to pain in patients

This CORR Insights® *is a commentary on the article* "The NLRP3/Caspase-1/Interleukin-1β Axis Is Active in Human Lumbar Cartilaginous Endplate Degeneration" *by Tang and colleagues available at:* DOI: 10.1007/s11999-016-4866-4.

The author certifies that he, or a member of his immediate family, has no funding or commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

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This *CORR* Insights® comment refers to the article available at DOI: 10.1007/s11999-016-4866-4.

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with Modic changes [5]. However, few studies have explored the pathobiological influence of cytokines from the cartilage endplate.

Tang and colleagues demonstrated that the gene expression of markers indicative of degenerative-like changes increased in the cartilaginous endplate of the Modic change group. Secondly, and more importantly, gene and protein expression by Western blotting and immunohistochemistry of NLRP3, Caspase-1, and Interleukin-1β showed greater expression in the cartilage endplate of the Modic change group. These data offer a potential mechanism of treatment if the increased inflammatory signals coming through or originating from the cartilage endplate are contributing to Modic changes of the vertebra.

The data here point to a couple of unresolved issues. A greater sample size of endplates from patients with Modic changes may offer insight into whether these and other cytokines are differentially regulated. Next, the interaction of the remainder of the intervertebral disc in spines from patients with Modic changes must be considered to contribute to the induction of pain, since herniated discs release proinflammatory mediators and osteoclastic factors [2, 10]. Overall, an animal model is needed to elucidate the cascade of changes to the spinal unit with Modic change.

How Do We Get There?

An animal model would help us map out whether each of the three Modic changes are individual occurrences or part of a unified cascade of changes, as well as determine what the molecular mechanisms are to attempt to stave back the induction of debilitating pain. Rodent models may offer some insight. Tail-disc puncture is a common methodology to induce disc degeneration, and it also induces an inflammatory response within the disc. Over time, tail-disc puncture presents with epiphyseal sclerotic bone and fibrovascular marrow spaces [8, 11]. Secondly, axial compression of mouse tail discs shows promise in modeling Modic changes because it demonstrates bone marrow edema and increased vascularity [7]. Work by the same group demonstrated that TNF-alpha was required for the induction of the bone marrow edema, but not for its maintenance [6]. Studies of this nature may better inform the clinical community as to the potential therapeutic limitations involved. Some followup studies may tackle the benefit of genetic ablation of receptors for cytokines or the cytokines affects induction of edema, vascularization, and/or sclerosis in these rodent models. Additionally, these models may help determine the potential reasons current therapeutic approaches (mentioned above) are limitedly effective. Lastly, dogs have been reported to present with Modic changes [1]. Chondrodystrophic dogs have an age-related propensity for disc degeneration and may offer an opportunity to study how their disc degeneration may influence endplate changes and develop Modic changes.

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