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Cartilage-protective effects of C-type natriuretic peptide over expression in K/BxN TCR arthritis model

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Purpose

The c-type natriuretic peptide (CNP) signaling pathway is known as a major contributor to skeletal growth in children. CNP is produced and secreted by both growth plate and joint chondrocytes, and has a paracrine regulatory effect on cartilage tissue. CNP increases matrix production by chondrocytes and promotes their proliferation. In this study, we investigated whether over-expression of CNP in chondrocytes would be protective of joint cartilage degradation during chronic inflammatory arthritis in vivo.

Methods

We first developed transgenic mice that over-express CNP ($CNP^{col2a1TG}$) in chondrocytes under the control of the collagen 2a1 promoter and enhancer. Then, we obtained K/BxN TCR transgenic mice from a collaborator and analyzed both transgenic mice for their joint cartilage clinical and histologic findings over time. We crossed $CNP^{col2a1TG}$ mouse with K/BxN TCR transgenic mouse to produce mice with both K/BxN TCR and $CNP^{col2a1TG}$ backgrounds. The degree of arthritis and cartilage damage in the offspring was analyzed using a clinical scoring system and two histological scoring systems. Differences between the scores were analyzed using the Student's t-test.

Results

Mice that carried the transgene for both $CNP^{col2a1TG}$ and K/BxN TCR showed less severe clinical and histologic arthritis findings in the joint cartilage compared to wild type littermates. Between the ages of 6-14 weeks, the average arthritis score of K/BxN TCR transgenic mice that over-expressed CNP was 4.37 ±1.38 (n=8), while the average arthritis score of K/BxN TCR arthritic mice of the same age was 8.66 ±3.26 (n=14), ($p<0.05$). Histological staining and morphometry did not show any evidence of cartilage degradation in the joint cartilage of $CNP^{col2a1TG}$ mice. The knee and ankle cartilage of $CNP^{col2a1TG}$ mice was thick and showed increased proteoglycan content by Safranin-O staining. However, the double-transgenic offspring mice (K/BxN/$CNP^{col2a1TG}$) developed less cartilage damage and less chondrocyte disorganization while still developing inflammatory changes (pannus) in the synovium, similar to the K/BxN TCR mice. We adapted the ICRS histological scoring system and gave scores to the knee joint cartilage of the 8-week-old male mice. K/BxN mice (n=7) scored significantly lower for both chondrocytic cell distribution (III) and chondrocyte matrix content (II) ($p<0.001$ and $p<0.05$, respectively) than the (K/BxN/$CNP^{col2a1TG}$ mice (n=12).

Conclusion

K/BxN TCR arthritic mice over-expressing CNP did not have joint cartilage damage due to chronic inflammation. We conclude that excess paracrine production of CNP in the joint cartilage of double-transgenic K/BxN/$CNP^{col2a1TG}$ arthritic mice was able to overcome the effects of pro-inflammatory cytokines on joint cartilage *in vivo*. CNP and the effector molecules of CNP signaling pathway may have therapeutic potential in protecting cartilage homeostasis during chronic inflammatory arthritis.

Disclosure

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