BMP2 Requires TGF-beta To Induce Osteophytes During Experimental Osteoarthritis

Esmeralda N. Blaney Davidson, Elly L. Vitters, Arjen B. Blom, Arjan PM van Caam, MSc, Miranda B. Bennink, BSc, Wim B. van den Berg, PhD, Fons AJ van de Loo, PhD, Peter M. van der Kraan, PhD.
Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.

Disclosures:

Introduction: Osteophyte formation is one of the hallmarks of osteoarthritis (OA). We have shown that either overexpression of TGF-beta or BMP2 can induce osteophytes in murine knee joints. However, comparing osteophytes induced by experimental OA, TGF-beta or BMP2 showed us that TGF-beta-induced osteophytes rather than BMP2-induced osteophytes more closely resemble those during observed in experimental OA. TGF-beta-induced osteophytes develop mainly from periosteum whereas BMP2-induced osteophytes originated from cells with a more advanced chondrocyte-like phenotype as can found in the growth plate. We additionally demonstrated that in mesenchymal stem cells TGF-beta could induce chondrogenesis when BMPs were inhibited but not vice versa. This suggested that BMP2 might require an alternative trigger like TGF-beta to induce the initial stages of chondrogenesis. Therefore we wanted to know whether this could be extrapolated to osteophyte formation during experimental OA: can BMP2 induce chondrogenesis in experimental OA in an TGF-beta independent manner? Therefore we tested hypothesize if BMP2 requires TGF-beta for induction of osteophytes.

Methods: We made a unique transgenic mouse which expresses BMP2 under control of the Col2a1 promoter but only when exposed to doxycycline (Col2a1-rtTA-BMP2). As a result chondrocytes start to produce BMP2 only when this unique transgenic mouse is exposed to doxycycline. We exposed these mice to doxycycline in food up to 8 weeks to investigate osteophyte formation in knee joints histologically. In addition we induced osteoarthritis by destabilization of the medial meniscus (DMM-model), which amongst others results in osteophyte formation, and investigated whether BMP2 augmented osteophyte formation. Moreover, to investigate whether TGF-beta was required for this osteophyte formation we combined the DMM-model with intra-articular injection of an adenovirus overexpressing the specific TGF-beta inhibitor LAP with our without doxycycline to overexpress BMP2. Murine knee joints were isolated 4 weeks after DMM exposure for histology to investigate effects on osteophyte formation.

Results: exposed to doxycycline for 8 weeks, only 4 out of 10 dox-treated Col2a1-rtTA-BMP2 mice had a osteophyte score higher than controls, but dox versus non-dox treated groups were not significantly different. When OA was induced in these mice clearly osteophytes developed with an average of 4.25 osteophytes per knee joint. However, when these mice were treated with doxycycline, thus inducing chondrocyte-specific BMP2 expression in addition to OA, we found a significant increase in the number of osteophytes (8.0) compared to DMM non-dox (Figure A, B). This score did not include a measure for the size of the osteophytes. These were much larger in the group with elevated levels of chondrocyte-specific hBMP2 (Figure A,C). The lack of osteophytes when treated with dox alone compared to DMM with Dox implied that the DMM treatment provided a trigger crucial for BMP2 to be able to aggravate osteophyte formation. To investigate whether that trigger was TGF-beta we combined the experiment with TGF-beta inhibition by i.a. injection of Ad-LAP. This showed that without TGF-beta, BMP2 was no longer capable of augmenting the DMM-induced osteophyte formation as there were no significant differences in osteophyte number comparing DMM-Ad-LAP treated animals with or without doxycycline (Figure B,C).
Discussion: Our data show that BMP2 is capable of inducing osteophyte formation, but is dependent on an additional prior trigger to achieve this, as present in OA. In OA conditions, BMP2 can severely aggravate osteophyte formation, both in number and size. However, when TGF-beta is blocked BMP2 is no longer capable of aggravating osteophyte formation. Therefore our data show for the first time that BMP2-induced osteophyte formation requires TGF-beta.

Significance: Our data show for the first time that BMP2 is dependent on TGF-beta to induce osteophyte formation. This provides novel insight into the mechanism behind osteophyte formation and provides clues for future therapeutic application for osteophyte formation in OA.

Acknowledgments: -

References: -

ORS 2014 Annual Meeting
Poster No: 1459