BMP-2 Carrier and Interbody Spinal Fusion Outcome: Rabbit Spinal Fusion Chamber Study Using BMP Antagonist

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Objective

Recombinant human bone morphogenetic protein (rhBMP-2) has been widely used in clinical practice to enhance spinal fusion surgery. Supraphysiological doses of rhBMP-2 are required to achieve the consistent fusion rate which in turn has led to side effects such as heterotrophic bone formation and seroma formation. To address these problems, various carriers have been developed to optimize rhBMP-2 delivery. From our previous study, PEC can control the release of rhBMP-2 by optimizing the pharmacokinetics of the carrier, thereby lowering the dose of rhBMP-2 required to achieve fusion, and mitigating side effects. However, the molecular events underlying the two releasing systems, pertaining to the different healing outcomes remain unknown. In this study, a rabbit interbody spinal fusion chamber was designed to provide a sealed and stable environment in the repair tissues, to compare the expression level of osteogenic markers and molecular antagonists of BMP signaling, between controlled release carrier PEC and burst release carrier ACS.

Materials and Method

Seventy-six rabbits were allocated to following groups: Group 1, PEC + 100µg rhBMP-2 (n=16); Group2, ACS + 100µg rhBMP-2 (n=16); Group 3 ACS + 300µg rhBMP-2 (n=12) Group 4 autologous bone graft (n=16) and Group 5 empty chamber (n=16). A retroperitoneal approach was used to expose the L5/6 intervertebral disc and the intervertebral disc defect was created using a trephine saw. Poly-ether-ketone-ketone spinal fusion chambers with the relevant carriers were implanted into the disc defect and secured with screws and sutures. The rabbits were sacrificed at the 1, 4 and 8 weeks. Fusion was assessed by manual palpation and µCT scan. Tissues within the chamber channel were harvested for the evaluation of the target genes and proteins. BMP antagonists and osteogenic markers were analyzed by real-time PCR and ELISA.

Results

Manual palpation showed that all the samples in Groups 1 and 3 and 50% of the samples from Group 2 achieved interbody spinal fusion while the rest of groups were not fused. Quantitative µCT parameters and resin histology confirmed the manual palpation results. PCR Array profiling indicated that at the 1-week time point, the BMP antagonist (Chordin and Noggin) was highly upregulated in Groups 2 and 3, and was down-regulated at Weeks 4 and 8. The osteogenic marker alkaline phosphatase was in the order of Group 3 > Group 1 > Group 2 > Group 4. Expression of the late osteogenic marker, COL1, correlated well with ALP expression pattern.

Conclusion

Using the rabbit interbody spinal fusion chamber, analysis of the expression of osteogenic markers and BMP-2 antagonists showed that high BMP-2 antagonist expression was coupled with low expression of osteogenic markers in the burst release delivery of BMP2 which resulted in non-fusion. Conversely, the low antagonist expression coupled with strong expression of osteogenic markers in controlled release of BMP-2 achieved fusion. These results are consistent with the high antagonist expressions in fracture non-union[1]. We speculate that the manner of BMP2 release at the interbody spinal defect site could re-balance the in-situ osteogenic and anti-osteogenic activities and affect the fusion outcomes.