A MECHANOBIOLOGICAL MODEL TO SIMULATE ANTIOXIDATIVE TREATMENT IN IMPACTED CARTILAGE

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Introduction

Joint injuries can trigger cell-driven cartilage degeneration which may ultimately culminate into post-traumatic osteoarthritis (PTOA) [1]. When applied acutely after injury, antioxidants such as N-acetylcysteine (NAC) mitigate cell-driven proteoglycan (PG) degeneration [1,2]. Here, we aim to develop a computational mechanobiological model to assess how protection with NAC alters cell damage (oxidative stress) and subsequent PG loss in impacted cartilage over a two-week period after injury and acute treatment.

Methods

Our mechanobiological model relied on information from previous explant experiments involving drop-tower impacts (Fig. 1) [2]. We incorporated healthy, necrotic, apoptotic, and damaged cell states ($C_{\mathrm{d,c}}$), post-impact damaged cell concentration as an initial condition [2], and enzymatic degeneration of PGs as in our previous 2-D mechanobiological model [3]. Apoptosis rate ($k_{\mathrm{apoptosis}}$) and damaged cell-related enzymatic PG degeneration were estimated by matching simulated and experimental data post-impact [2]. An earlier report was used to estimate NAC transport properties in cartilage [4] and experimental 4-day NAC culture data [2] was used to calibrate the rate coefficient describing the extent to which NAC treatment reduces oxidative stress, interpreted as rate of cells switching their state from damaged to healthy ($k_{\mathrm{d\rightarrow h,c}}$). Finally, we simulated PG content during 1-day NAC treatment followed by a 13-day period without NAC. The simulated relative PG content (bulk PG content in the 4-mm-wide impact vs. intact area) was evaluated from the model and compared to the experiments [2].

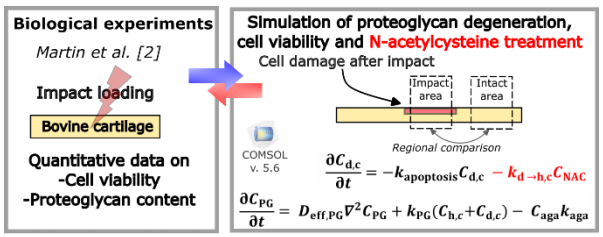

Figure 1: The NAC treatment model was constructed based on previous in vitro *data of impacted cartilage.*

Results

Without NAC treatment, we observed lower PG content at the superficial cartilage (Fig. 2A) and a relative PG content of 83% in the full-depth impact region when compared to the unloaded intact region at day 14 (Fig. 2B, red line). Simulated NAC treatment mitigated PG loss showing a similar temporal trend as observed in the experiments (93% relative PG content in the impact area at day 14, Fig. 2B, blue line).

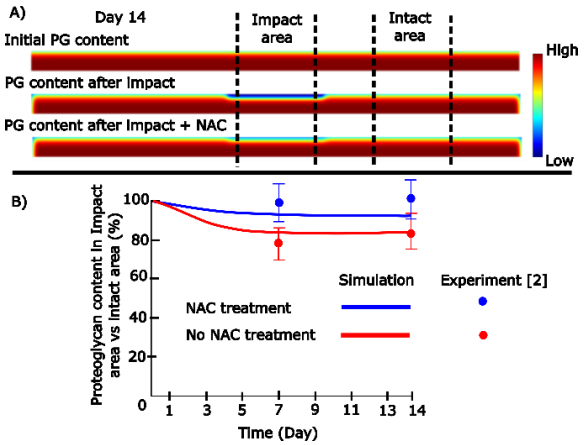

Figure 2: A) Proteoglycan distribution in the cartilage explant and B) comparison of the relative proteoglycan contents against earlier experimental data.

Discussion

Our model successfully predicted mitigation of PG loss after NAC treatment due to reduction in the damaged cell concentration and oxidative stress. Interestingly, our simulation seemed to slightly overestimate the PG loss compared to the experimental NAC-treated group (Fig. 2B), suggesting that sublethal cell responses mitigated by NAC are not yet fully captured by the model. Next, we aim to expand our approach to consider possible biomechanical loading- and NAC-regulated alterations in PG biosynthesis. In the future, this model could be used to assess severity of an injury and to optimize treatment timing/dosage to mitigate oxidative stress and development of PTOA.

References

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