Synovial Fluid Analysis Reveals a Novel Panel of Biomarkers Altered Following Articular Fracture

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Purpose: There are currently no effective screening methods to determine who is at risk for developing posttraumatic arthritis (PTA). This is a prospective observational cohort study with an overall objective to identify changes in synovial biomarkers following articular fracture that are associated with joint injury that may be predictive of the development of PTA.

Methods: Patients with unilateral articular fracture of the knee were enrolled in an IRB- and USAMRMC HRPO-approved study. 8 patients (50% female; 25-83 years of age; average body mass index 32.4 kg/m^2) had synovial fluid (SF) collected by direct aspiration from both the fractured (Fx) and contralateral non-fractured (Non-Fx) knee. SF was stored at -80° until analyses. Enzyme-linked immunosorbent assays were used to quantify SF levels of 40 acute markers of joint metabolism (8 analytes). Joint biomarkers included matrix metalloproteinase (MMP)-1, -2, -3, -9, and -10, COMP (cartilage oligomeric matrix protein), sulfated glycosaminoglycans (sGAG), and C-telopeptide of type II collagen (CTXII). Paired t tests were used to test the differences of biomarkers in SF between the injured limb (Fx) and the contralateral control limb (Non-Fx). The Benjamini-Hochberg (BH) method was used to control for false discovery rate (FDR) due to multiple testing. Biomarkers meeting BH-adjusted $P < 0.05$ were identified. Ingenuity Pathway Analysis (IPA) was used to identify pathways of relevance.

Results: Comparisons of biomarker concentrations in SF from Fx and Non-Fx knees identified 16 analytes of the 48 measured having significantly higher concentrations in SF from the fractured knee. These biomarkers were associated with inflammatory response (14 of 16) and injury (15 of 16) and are illustrated as they are associated with molecular events following fracture. Upon injury, vascular disruption occurs resulting in the release of biomarkers of angiogenesis (vascular endothelial growth factor [VEGF], VEGF-C, VEGF-D, PIGF), which upregulate the expression of MMPs. This is followed by an inflammatory stage in which macrophages and other immune cells are recruited to the fracture sites and secrete proinflammatory cytokines (interleukin [IL]-4, IL-8, IL17a, tumor necrosis factor [TNF]-α), resulting in synovitis and eventual cartilage degradation.

Conclusion: Identification of the inflammatory mediators involved in acute injury may provide key insights into potential adjunctive therapies that could improve outcomes following surgery. In addition, the patterns of biomarkers following acute injury may aid in risk stratification and identification of those at highest risk for developing PTA.