Synovial Fluid Biomarkers Are Indicative of Synovial Inflammation Following Articular Fracture

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Purpose: Joint injuries, such articular fracture of any joint, can progress to posttraumatic arthritis (PTA). Acute local inflammation is reported and likely drives degradative joint changes. Levels of some cytokines, chemokines, and matrix-degrading proteases (MMPs) are reported to be increased acutely (1-7 days) post-fracture (fx) and may serve as biomarkers of joint inflammation. We proposed to determine if biomarkers previously identified in patient fracture samples reflect the severity of acute synovial inflammation following articular fracture in a mouse model of closed articular fracture.

Methods: All procedures were performed under an IACUC-approved protocol. Adult C57BL/6 mice (4.5-month age, male, JAX # 005304) were subjected to a moderate closed articular fracture of the left knee. Mice were sacrificed on day 3 (n = 4) and day 7 (n = 4) post-fx and compared to uninjured pre-fx mice (n = 4). Fracture energy was calculated from the area under the load-displacement curve (Acumen 3, MTS). At the time of sacrifice, serum and synovial fluid were collected from all mice. Hindlimbs were harvested for formalin-fixed paraffin histologic assessment of synovitis from hematoxylin and eosin (H&E) stained sections. Synovial fluid and serum concentrations of analytes were quantified using a biomarker multiplex panel. Statistical tests and references will be reported in the presentation.

Results: 7 of 10 synovial fluid biomarkers were significantly increased in the fractured knee at day 3: interleukin (IL)-1β, IL-6, keratinocyte chemoattractant/human growth-related oncogene (KC/GRO), serum interferon-γ-induced protein (IP)-10, monocyte chemoattractant protein (MCP)-1, vascular endothelial growth factor (VEGF), and matrix metalloproteinase (MMP)-9. The following synovial fluid biomarkers were significantly correlated (Spearman) with the total joint synovitis scores: IL-1β ($r = 0.64$; $P = 0.03$), IL-6 ($r = 0.74$; $P = 0.009$), KC/GRO ($r = 0.62$; $P = 0.03$), VEGF ($r = 0.65$; $P = 0.03$), and MMP-9 ($r = 0.62$; $P = 0.03$). For serum biomarkers, only IL-1β and IP-10 were significantly increased at day 3 post-fx compared to pre-fx. No significant correlations were found between serum biomarkers and synovitis scores.

Conclusion: We found several candidate biomarkers that may reflect of the degree of synovial inflammation following an articular fracture. Concentrations of these inflammatory factors in synovial fluid peaked at day 3, whereas tissue inflammation, in synovitis scores, was greatest at day 7 post-fracture. Defining the acute response to articular fracture and development of PTA is important for translating potential therapies.