

Discovery of Circulating Blood Biomarkers in Patients with and without Lumbar Modic Changes

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INTRODUCTION: Low back pain (LBP) is the world's most disabling condition.¹ Such pain can result in decreased daily activity and function, time off from work, psychological stress, lost wages and increased health-care costs. For patients that fail conservative treatment, surgical intervention is an option, which may result in complications and unsatisfactory outcomes. As a result, health-care costs for such treatment are substantial and more "cost-effective" measures must be sought to treat and understand the etiology of specific subsets of chronic LBP (cLBP) between patients. In fact, the modest results of interventions are thought to be due to heterogeneity of the LBP phenotype. Intervertebral disc degeneration (DD) is an age-related phenomenon and a major risk factor for LBP. However, it is believed that not all LBP is discogenic in origin and that "vertebrogenic" causation of pain may be present and have unique signatures.² Modic changes (MC) are pathological vertebral endplate and bone marrow changes visible on magnetic resonance imaging (MRI) that are highly associated with cLBP and increase with age.³ Type 1 MC (MC1), characterized as inflammation, have been found to be highly relevant imaging phenotypes related to pain and pain severity, however, Type II MC, traditionally thought to represent fatty infiltration, may also be symptomatic.³ In one of the first studies, our team had identified circulating blood proinflammatory cytokines that were related to DD and severity of DD⁴ as well as a specific blood biomarkers that were significantly elevated between MC and asymptomatic patients.⁵ The following study aimed to determine the existence and expression of specific proinflammatory cytokines, chemokines and growth factors in circulating blood between symptomatic patients who presented to clinic with or without MC of the lumbar spine on MRI.

METHODS: Following Ethics Committee approval and based on the prospective Rush Omics Spine Study (ROSS), 47 patients that underwent surgery were recruited. No patient had any deformity, tumor, infection of inflammatory condition related to the spine. All patients had saliva, disc tissue, skin samples, and blood collected on the day of surgery and stored. Peripheral fasting blood was collected in tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. Tubes were centrifuged for 15 min at 2000 ×g within 30 min of collection. Resulting blood plasma samples were aliquoted and stored at -80 °C until biochemical analyses. Samples were analyzed in duplicates after appropriate dilution using commercially available ELISA systems. An 80-plex panel was utilized with the addition of CCL5/RANTES. Cytokines known to be related and not-related in LBP subjects were assessed, including GM-CSF; IFN gamma; IL-1 beta; IL-2; IL-4; IL-5; IL-6; IL-12 p70; IL-13; IL-18; TNF alpha; Eotaxin; GRO-alpha; IL-8; IP-10; MCP-1; MIP-1 alpha; MIP-1 beta; SDF-1 alpha etc. Lower and upper limits of detection were computed for each assay. Preoperative T2/T1-weighted axial and sagittal MRI of L1-S1 was obtained of all subjects to determine the presence of MC. The threshold for statistical significance was established at p<0.05.

RESULTS: At time of analyses, 33 consecutive subjects were included in this study. Based on preoperative MRI assessment, there were 13 subjects with MC (42%) and 18 with no MC (58%). There was no significant difference between groups with respect to age, sex-type, and BMI (p>0.05). Blood biomarker assessment could not be performed in 51 of the 81 cytokines due to the levels of detection being low. The following markers were found to be significant and elevated in the MC patients: Macrophage Migration Inhibitory Factor (MIF, p<0.01), C-X-C Motif Chemokine Ligand 5 (CXCL5, p<0.05), C-C Motif Chemokine Ligand 5 (CCL5, p<0.01); or trending toward significance: Pentraxin 3 (PTX3, p<0.06), Galectin-3 (Gal-3, p<0.07).

DISCUSSION: This is the first study, to our knowledge, that has identified specific and significant circulating blood biomarkers to be related to symptomatic patients with MC of the lumbar spine. Specifically, MIF, CXCL5 and CCL5 protein levels were found to be significantly different in MC patients as compared to non-MC subjects. This study further "replicated" CCL5 as a viable biomarker of MC that was previously noted by the authors representing another cohort.⁵ Although our recent findings are preliminary and require larger-studies and validation, our work provides evidence that symptomatic MC patients may exhibit unique inflammatory signatures easily identifiable in the blood. Such knowledge can lend credence to more refined classification and subphenotyping of MC patients that could also have direct impact on future precision-based spine care models of management and predictive modeling.

SIGNIFICANCE/CLINICAL RELEVANCE: Although these are preliminary findings at this stage, our study serves as direction setting for larger-scale initiatives and sheds light on a deeper understanding of pathomechanisms and potential targets that can ultimately lead to the development of novel, personalized therapeutics. These findings will be further coupled with the ongoing ROSS Microbiome/Metabolomic initiative of these patients to further elaborate upon an integrative, poly-omic and multi-modal perspective of profiling spine surgery patients for potential patient stratification and refined patient management.

REFERENCES: [1] GBD, Lancet Rheum, 2023; [2] Lotz et al, Gopal Spine J, 2013; [3] Maatta et al, Medicine, 2016; [4] Grad et al, Eur Cell Mater, 2016; [5] Karppinen et al, Euro Spine J, 2021