Orthopaedic Surgery
School of Medicine
University of Missouri Health

Thompson Laboratory for Regenerative Orthopaedics

Defining Osteoarthritic Patient Phenotype Clusters Based on Infrapatellar Fat Pad Metabolic Profiles

Lee AB, Stoker AM, Salisbury SY, Keeney JA, Cook JL

Thompson Laboratory for Regenerative Orthopaedics, University of Missouri, Columbia, MO

www.thompsonlab.missouri.edu

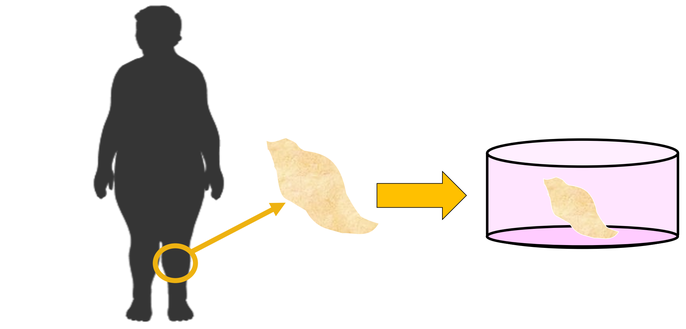
Introduction and Purpose

- Osteoarthritis (OA) is an irreversible musculoskeletal disease often progressing from an initial insult or injury to whole-joint inflammation and degeneration.
- The infrapatellar fat pad (IPFP) is thought to contribute to the pro-inflammatory metabolic responses of OA, however patient-to-patient variability is seen in these responses.
- This study was designed to further elucidate metabolic profiles for IPFPs obtained from patients undergoing total knee arthroplasty (TKA) to develop relevant phenotype cohorts using cluster analysis.

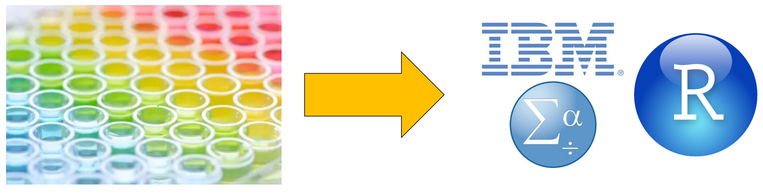
Hypothesis

- A K-Means cluster analysis can be used to separate patients into cohorts based on the variability in their IPFP metabolism thought to be representative of unique metabolic profiles for respective patient types.

Methods



1) With IRB approval and informed patient consent, IPFP (n=47) tissues were collected from patients undergoing total knee arthroplasty.
2) IPFP explants (n=3/tissue/patient) were created and cultured for three days in 7 ml of supplemented DMEM at 37° C and 5% CO_2.
3) On day 3 of explant culture, media were collected for biomarker analyses and tissues were weighed to determine the dry weight.



4) Media were tested for IL-2, IL-4, IL-6, IL-8, IL-10, MCP-1, GRO-α, MIP-1α, MIP-1β, RANTES, TNF-α, NO, VEGF, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-13, TIMP-1, TIMP-2, TIMP-3, TIMP-4, MMP Activity, and PGE2 using commercially available assays according to the manufacturer's protocol.
5) Media biomarker concentrations were standardized to tissue weight and the mean production level of each biomarker was utilized as the value for that patient. Patients were clustered into 5 cohorts using a K-Means cluster analysis. Significant differences in patient demographic data and media biomarker concentrations were determined with a Kruskal-Wallace test with post-hoc analysis and Bonferroni correction ($p<0.05$).

Results and Discussion

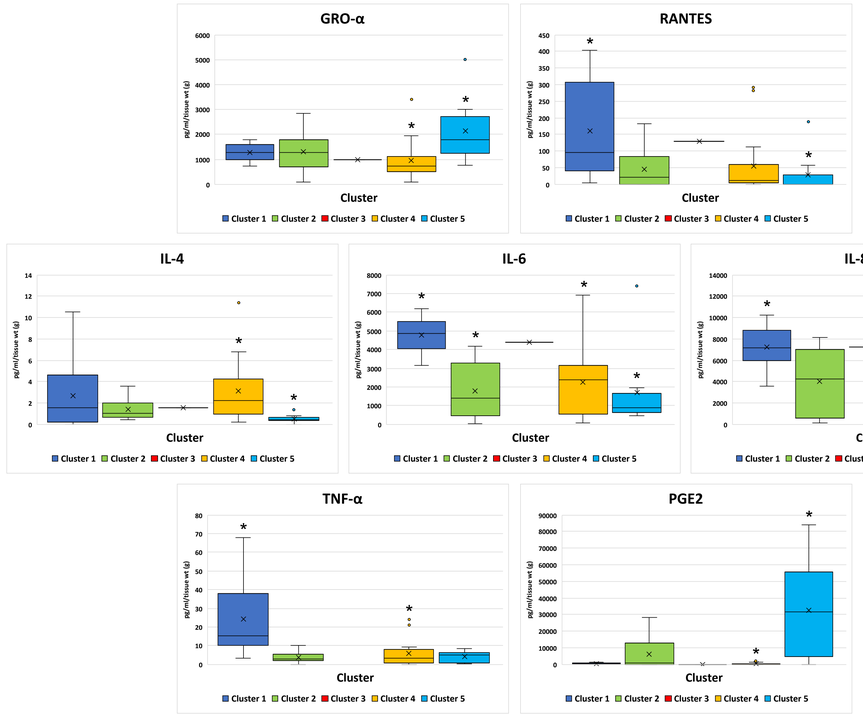


Figure 1: Relative production of inflammation-related biomarkers by IPFPs in each cluster at the time of total knee arthroplasty. * indicates a significant difference in biomarker production between clusters.

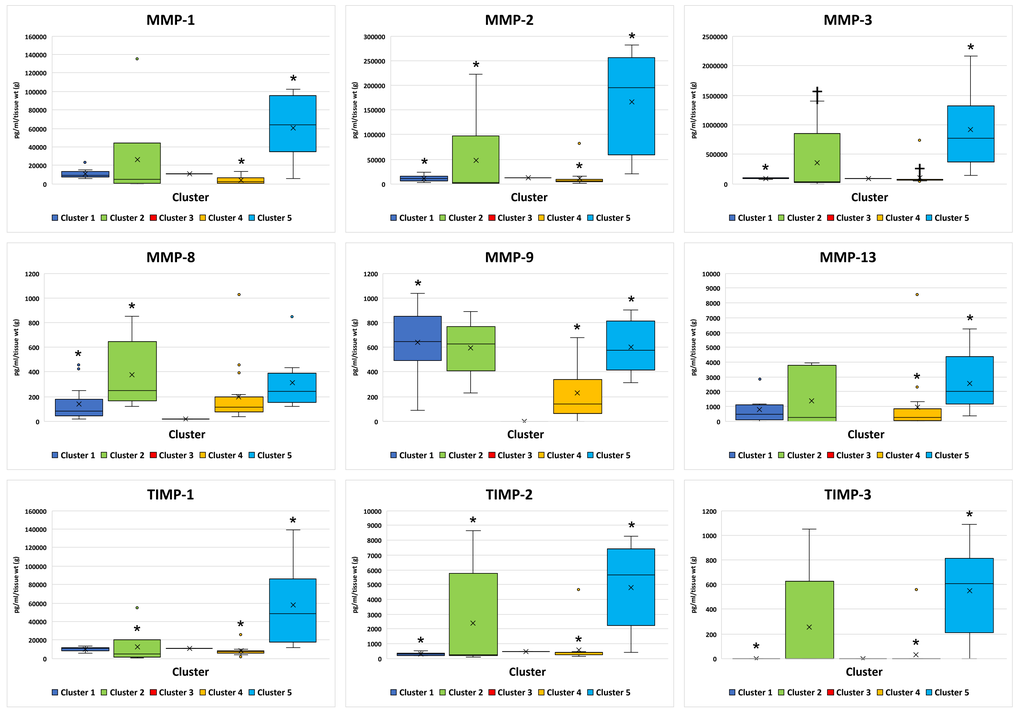


Figure 2: Relative production of degradation-related biomarkers by IPFPs in each cluster at the time of total knee arthroplasty. * indicates a significant difference in biomarker production between clusters.

Cluster	Number	Sex	Mean Age (Range)	BMI (Range)	VAS Pain (Range)
Cluster 1	14	10F 4M	59.15 (28-76)	34.36 (26-48)	3.71 (0-8)
Cluster 2	6	4F 2M	65.63 (53-74)	35.50 (26-43)	3.67 (0-8)
Cluster 3	1	1M	57	30	0
Cluster 4	17	8F 9M	64.22 (52-76)	38.59 (27-48)	2.35 (0-8)
Cluster 5	9	6F 3M	65.23 (53-83)	38.89 (30-48)	1.88 (0-8)

Table 1: Patient demographics at the time of TKA for each of the five clusters created based on biomarker production by the IPFP.

- **Of the 26 biomarkers tested, significant differences in IPFP production levels between patient cohorts were observed for 16 of them.**
- **Clusters 1, 2, 4, and 5 contained enough patients for statistical analysis.**
- **Cluster 1 produced significantly higher levels of pro-inflammatory biomarkers and reported the highest mean VAS pain score and the lowest mean age and BMI.**
- **Cluster 2 produced moderate levels of inflammatory and degradative biomarkers and had the highest mean age.**
- **Cluster 5 produced significantly higher levels of pro-degradative biomarkers and reported the lowest mean VAS pain score and the highest mean BMI.**
- **Cluster 4 produced significantly lower levels of both inflammatory and degradative biomarkers, yet had similar mean age, BMI, and VAS pain scores as cluster 5.**
- **Cluster 4 was the only cohort containing more male than female patients.**

Conclusions

- **Significant differences between patient cohorts were noted among relevant biomarkers produced by osteoarthritic infrapatellar fat pad explants in culture.**
- **Potential relationships were indicated between IPFP inflammation and pain perception, IPFP inflammation and age, IPFP degradation and pain perception, and patient sex and IPFP biomarker production.**
- **Metabolic response profiles for IPFPS from patients with knee OA can be utilized to characterize patient phenotypic cohorts that potentially indicate clinically relevant mechanisms of disease.**
- **Further characterization of these metabolic response profiles has the potential to lead to the development of clinical biomarker panels for improved assessment of symptomatic OA in order to guide patient-specific diagnostic, staging, and treatment strategies.**