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Targeting JAK-STAT Signalling Alters Proinflammatory and Metabolic function of PsA Synovial Fibroblasts

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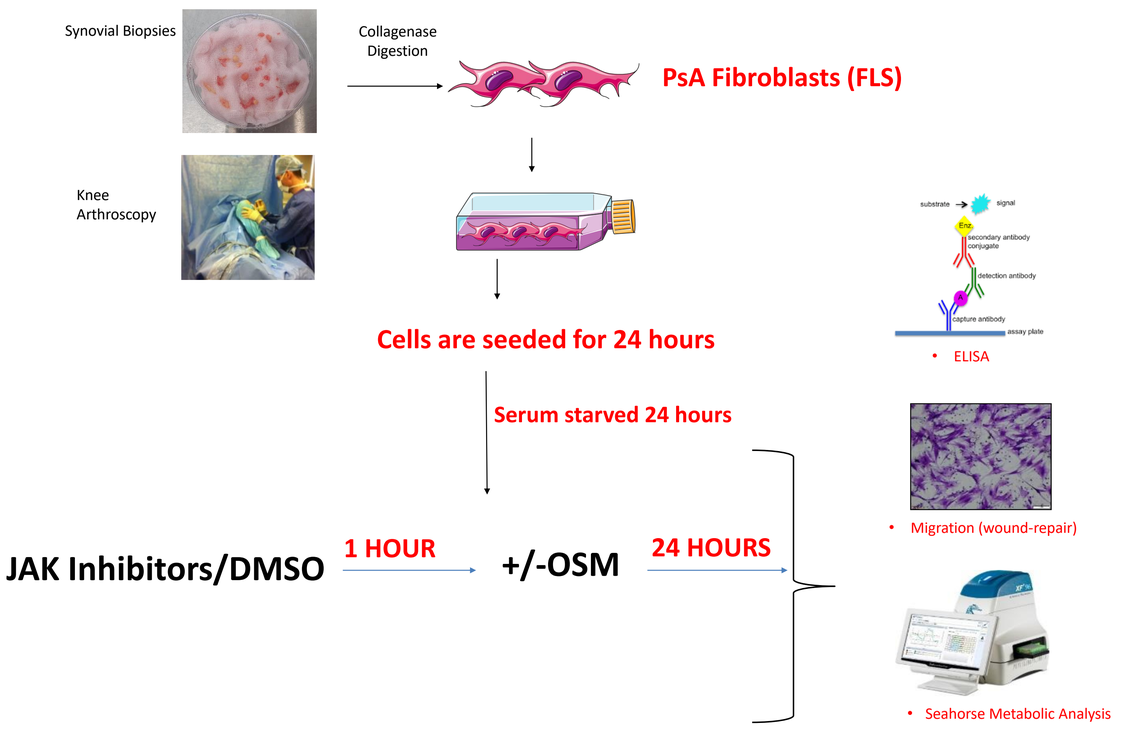
Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis which is associated with psoriasis. Janus Kinase (JAK inhibitors) have emerged as an encouraging class of drugs for the treatment of PsA. Only a few of these inhibitors have been approved for use in PsA patients with others currently in clinical trials. Therefore, it is necessary to identify the role that these JAK inhibitors play in supressing inflammatory mechanisms in this disease. The aim of this study was therefore to examine the effect of JAK inhibitors on primary PsA synovial fibroblasts (FLS) function.

Methods



Synovial tissue biopsies were obtained from PsA patients during arthroscopy. Following collagenase digestion, cells were cultured into flasks to generate fibroblast cell lines. Cells were seeded into appropriate cell culture plates for 24 hours and serum starved in for a further 24 hours (for ELISA and Migration assays only) and then treated with JAK inhibitors or DMSO with or without OSM for 24hours. Supernatants were analysed by ELISA, cell migration was analysed based on wound repair and cellular bioenergetics was determined by seahorse analysis.

Results

Treatment with JAK Inhibitors Supress Cell Migration

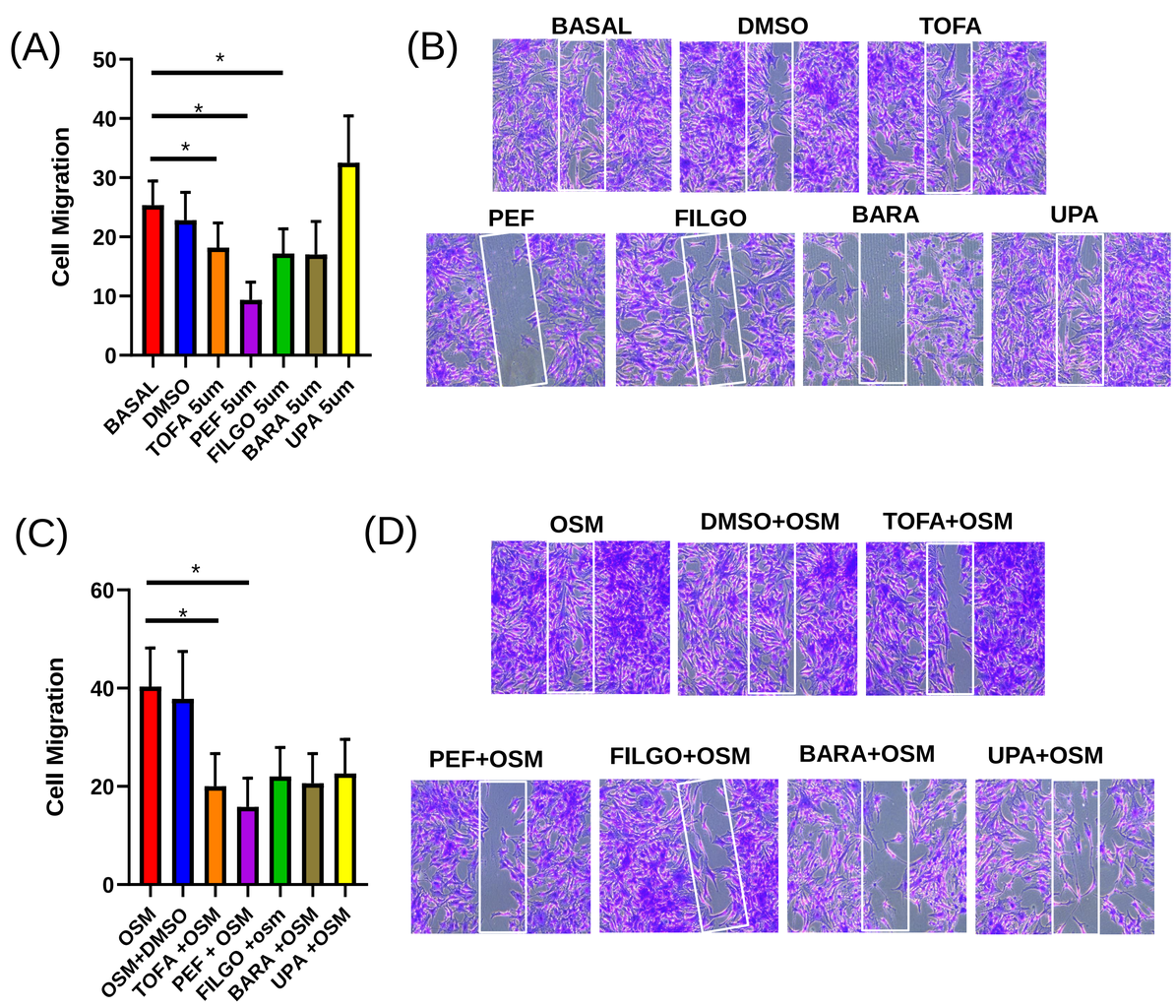


Figure 2: PsA fibroblast migration is supressed following treatment with JAK inhibitors. (A-B) Bar graph and representative wound repair images of cell migration of PsA FLS treated with JAK inhibitors or DMSO for 24 hours following wound formation. (C-D) Bar graph and representative wound repair images of cell migration of PsA FLS treated with JAK inhibitors or DMSO for 1 hour and OSM for 24 hours following wound formation. N=6

Results

JAK inhibitors reduce IL-6 and MCP-1 and increase IL-8 production by PsA FLS

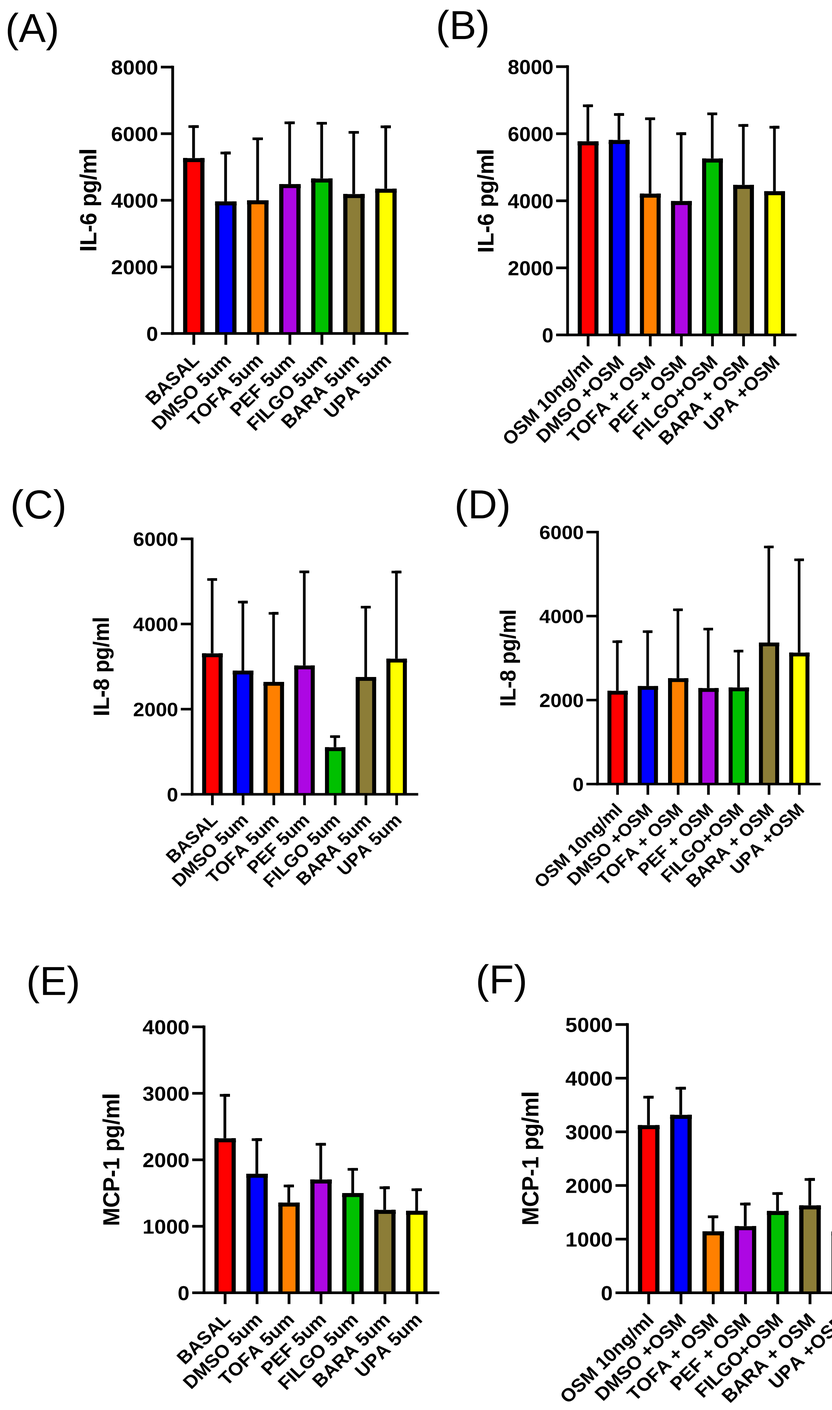


Figure 1: Treatment with JAK inhibitors alters PsA FLS expression of IL-6, IL-8 and MCP-1. (A-F) Bar graphs representing IL-6 (A-B), IL-8 (C-D) and MCP-1 (E-F) expression from PsA FLS treated with JAK inhibitors/DMSO without (A,C,E) or with (B,D,F) OSM for 24hours. N=3

JAK Inhibitors Induce Changes in the Cellular Bioenergetic Profile of PsA FLS by Targeting Glycolysis

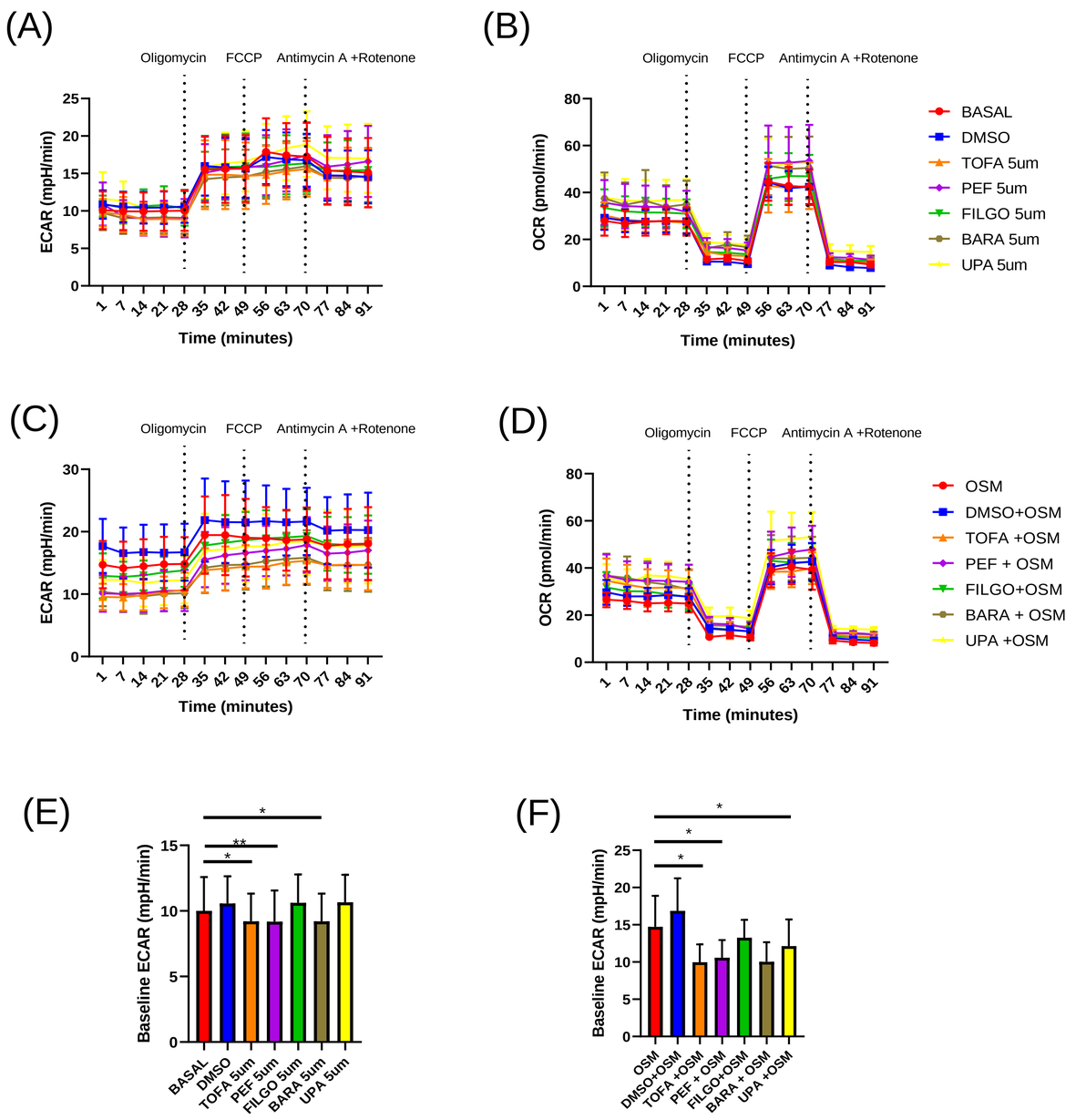


Figure 3: Cellular Bioenergetic profile of PsA FLS following treatment with JAK inhibitors. (A-B) Average seahorse ECAR (A) and OCR (B) traces in PsA fibroblasts either alone or treated with JAK inhibitors/DMSO for 24 hours. (C-D) Average seahorse ECAR (C) and OCR (D) traces in PsA fibroblasts treated with JAK inhibitors/DMSO for 1 hour followed by stimulation with OSM for 24 hours. (E) Bar graph representing baseline ECAR of PsA fibroblasts either alone or treated with JAK inhibitors/DMSO for 24 hours. (F) Bar graph representing baseline ECAR of PsA fibroblasts treated with JAK inhibitors or DMSO for 1 hour followed by stimulation with OSM for 24 hours. N=5

Conclusion

JAK/STAT signaling mediates the complex interplay between inflammation and cellular metabolism in PsA pathogenesis, inhibition of which shows effective suppression of inflammatory mechanisms that drive FLS pathogenic function.

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