Το σύστημα ιστικού παράγοντα/θρομβίνης ρυθμίζει την αλληλεπίδραση υμενοκυττάρων και ουδετεροφίλων στη ρευματοειδή αρθρίτιδα

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ΔΗΜΟΚΡΙΤΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΡΑΚΗΣ | DEMOCRITUS UNIVERSITY OF THRACE

ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΛΕΞΑΝΔΡΟΥΠΟΛΗΣ

Ρέθυμνο, 5 Οκτωβρίου 2025

Introduction

- Rheumatoid arthritis (**RA**) is a chronic autoimmune disease characterized by persistent synovial inflammation
- Fibroblast-like synoviocytes (**FLS**), the key stromal cells of the joint, play an integral role in the pathogenesis of the disease

- Dysregulated crosstalk between immune and stromal cells
- Neutrophils cause tissue damage through the release of neutrophil extracellular traps (**NETs**)

- Coagulation factors like **Thrombin** & **Tissue Factor** can activate FLS → cytokine production

1. Nygaard G, Firestein GS. Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes. Nat Rev Rheumatol. 2020 Jun;16(6):316-33.
2. Kaplan MJ. Role of neutrophils in systemic autoimmune diseases. Arthritis Res Ther. 2013 Oct 2;15(5):219.
3. Ohba T, Takase Y, Ohhara M, Kasukawa R. Thrombin in the synovial fluid of patients with rheumatoid arthritis mediates proliferation of synovial fibroblast-like cells by induction of platelet derived growth factor. J Rheumatol. 1996 Sep;23(9):1505-11.
4. Chiu YC, Fong YC, Lai CH, Hung CH, Hsu HC, Lee TS, et al. Thrombin-induced IL-6 production in human synovial fibroblasts is mediated by PAR1, phospholipase C, protein kinase C alpha, c-Src, NF-kappa B and p300 pathway. Mol Immunol. 2008 Mar;45(6):1587-99.

Methods

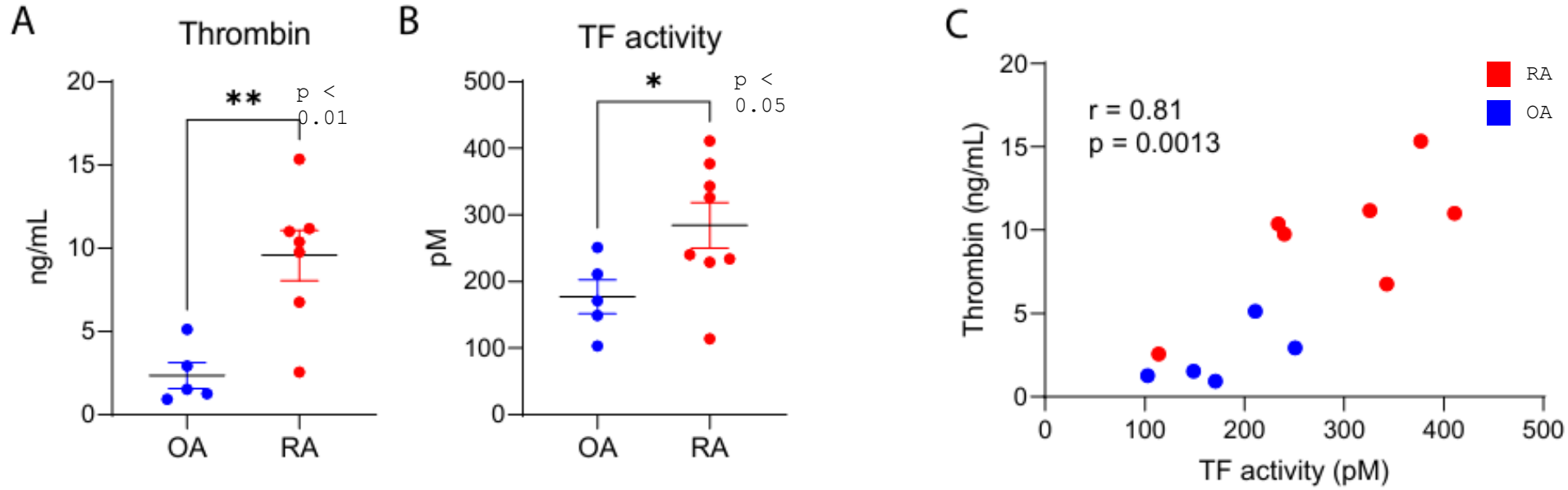
- 9 RA patients, 8 OA patients, 5 healthy donors were recruited
- Isolation of serum, neutrophils and NETs from the above-mentioned groups
- Isolation of synovial fluid (SF), SF-derived neutrophils & FLS from RA & OA patients through arthrocentesis or orthopedic surgery
- Immunofluorescence staining in primary FLS, peripheral blood & SF-derived neutrophils
- Quantification of Thrombin & TF activity in SF using commercially available kits
- Measurement of CitH3 and IL-8 in SF and FLS supernatants was performed
- Neutrophil chemotaxis was assessed with *in vitro* transwell migration assay

Patient characteristics

	Ctrls	OA	RA
Number of samples	5	8	9
Per cent female	80%	87.5%	87.50%
Age mean	27	66.7	63
Age range	(21; 35)	(60; 73)	(50; 78)
Per cent RF positive	nd	nd	3
Per cent ACPA positive	nd	nd	9
CRP mean (mg/dl)	0.64	1.73	4.85
ESR mean (mm/hr)	19.2	22.2	40.8
Patients on corticosteroids	nd	nd	4
Mean steroid dose (prednisolone equivalent)	nd	nd	5mg/d
Patients on DMARDs	nd	nd	5
Methotrexate	nd	nd	3
Leflunomide	nd	nd	3
Hydroxychloroquine	nd	nd	1
Patients on biologicals	nd	nd	1
Tumour necrosis factor inhibitors	nd	nd	2
DAS28	nd	nd	4.9
SF samples	nd	8	9
Isolation of FLS	5	5	5

Increased tissue factor activity and thrombin generation in RA

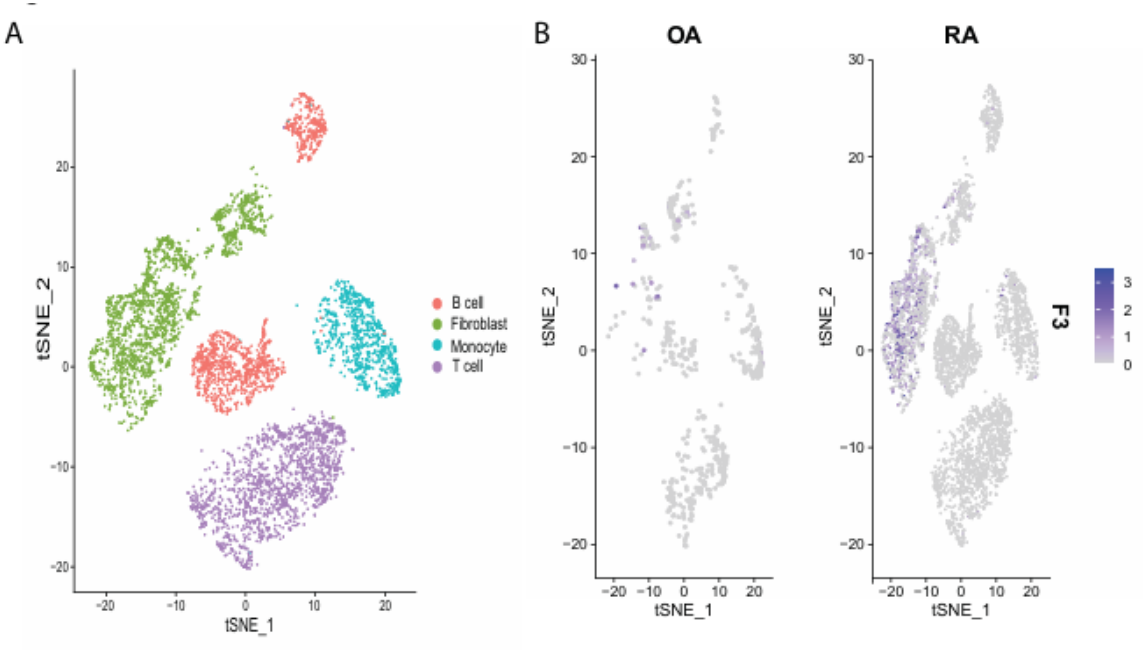
Synovial fluid



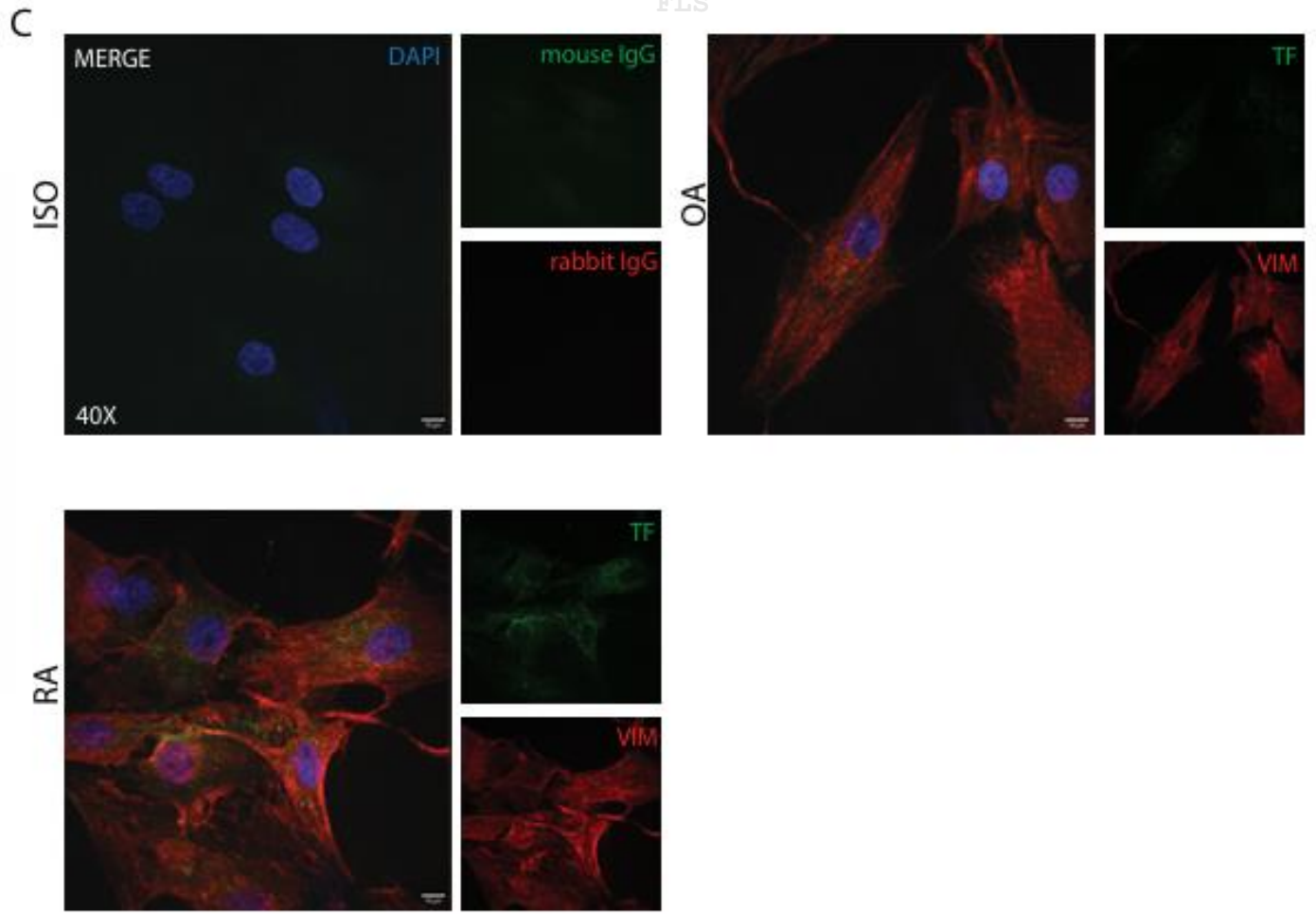
1. Ohba T, Takase Y, Ohhara M, Kasukawa R. Thrombin in the synovial fluid of patients with rheumatoid arthritis mediates proliferation of synovial fibroblast-like cells by induction of platelet derived growth factor. J Rheumatol. 1996 Sep;23(9):1505-11
2. Chen L, Lu Y, Chu Y, Xie J, Ding W, Wang F. Tissue factor expression in rheumatoid synovium: a potential role in pannus invasion of rheumatoid arthritis. Acta Histochem.

FLS constitute a source of tissue factor

scRNAseq

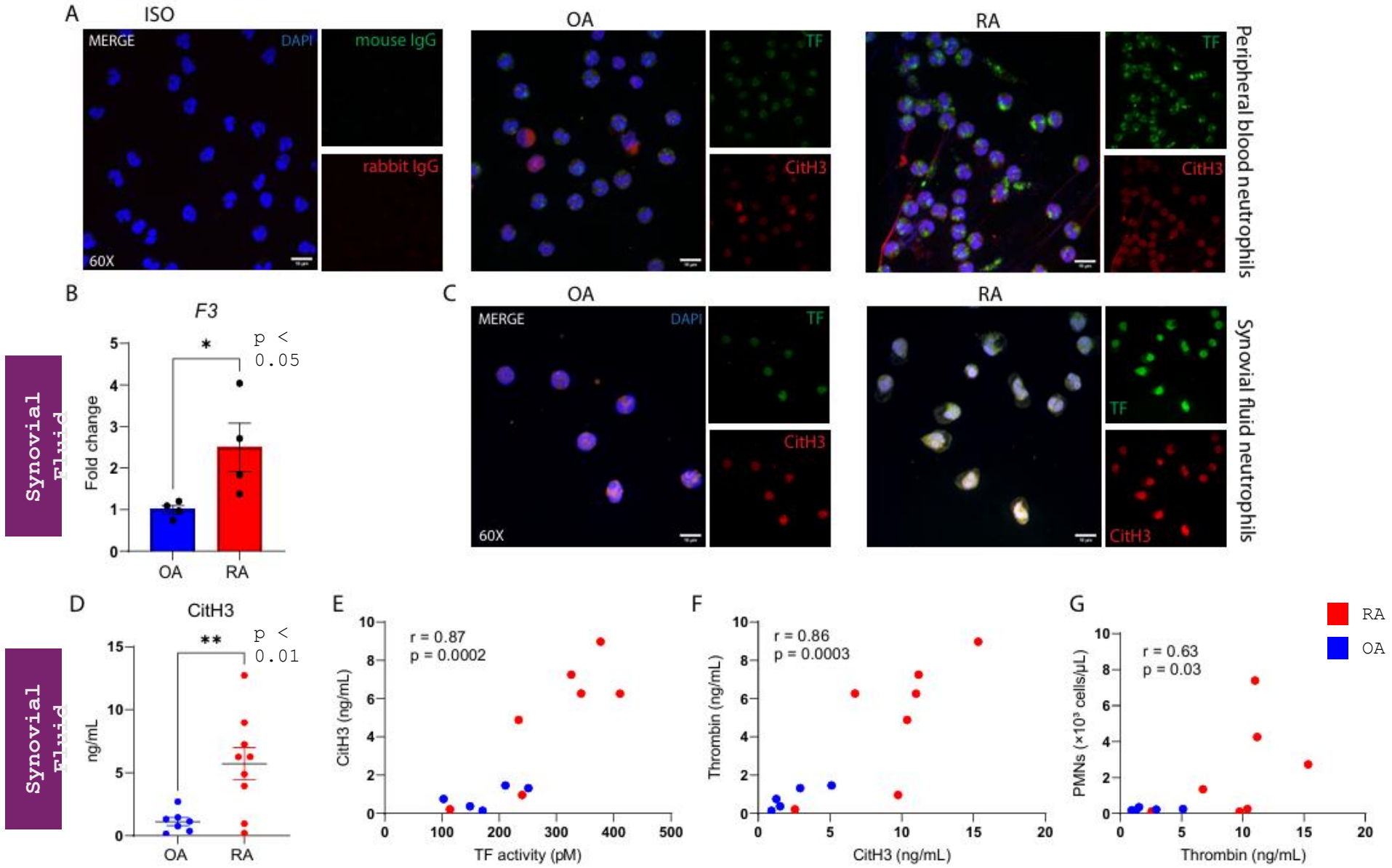


Primary FLS

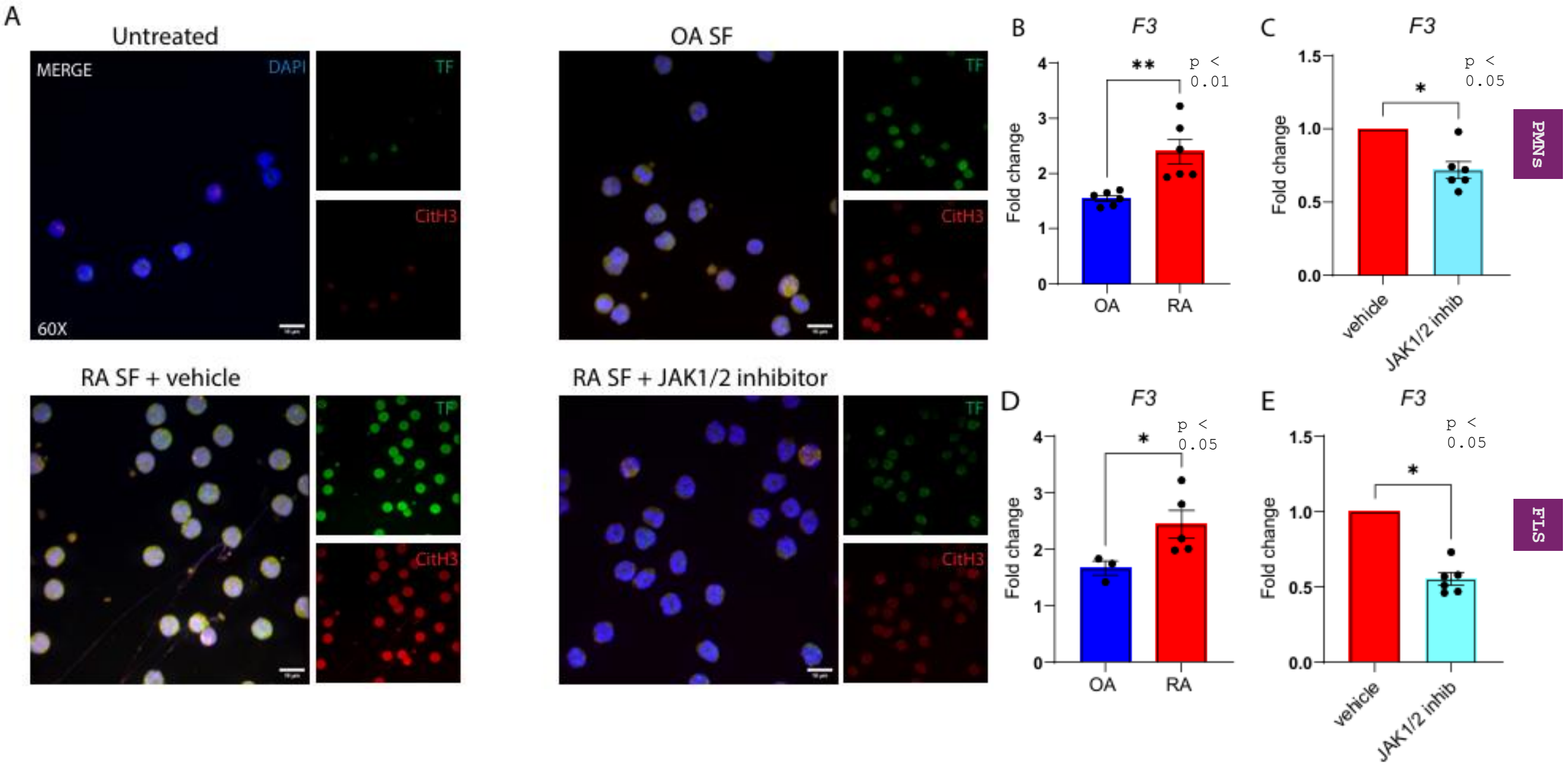


Zhang F, Wei K, Slowikowski K, Fonseka CY, Rao DA, Kelly S, et al. Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry. Nat Immunol. 2019 Jul;20(7):928–42.

Increased neutrophil-derived TF expression correlates with NETosis

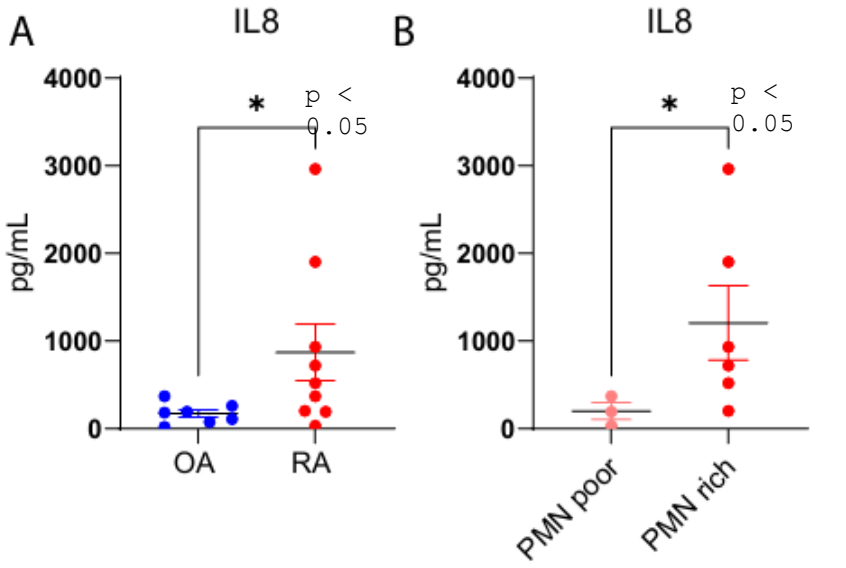


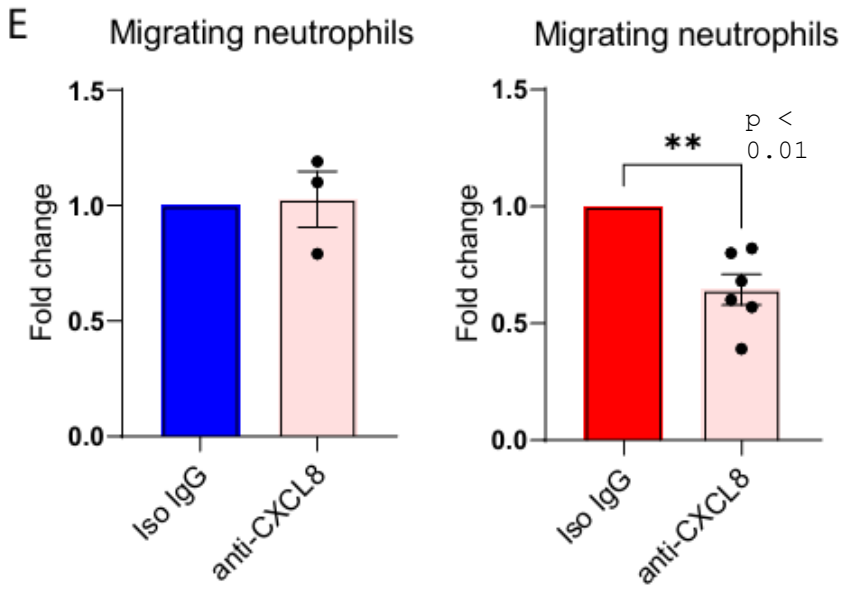
JAK1/2 inhibition attenuates tissue factor expression in RA



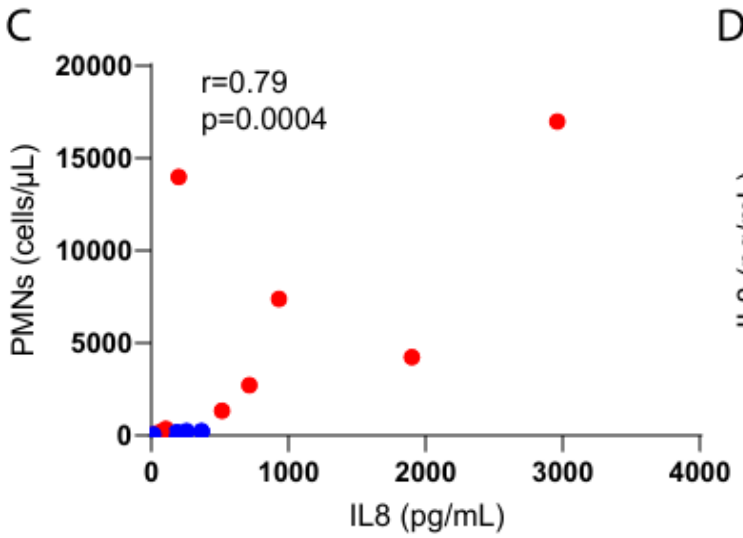
IL-8 promotes neutrophil recruitment

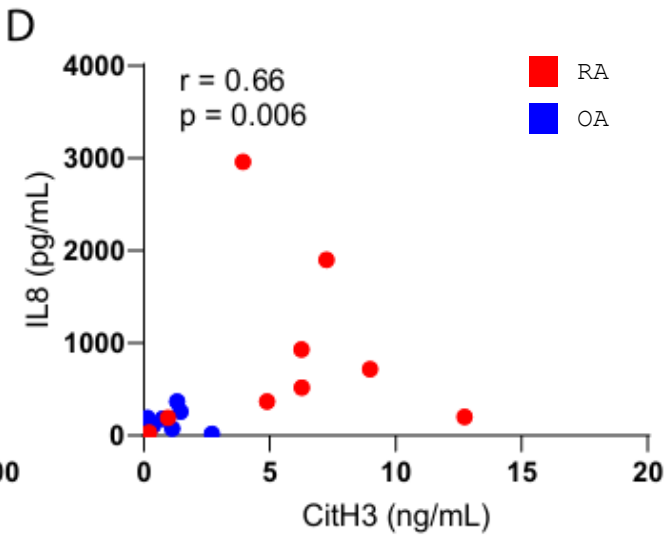
Synovial fluid



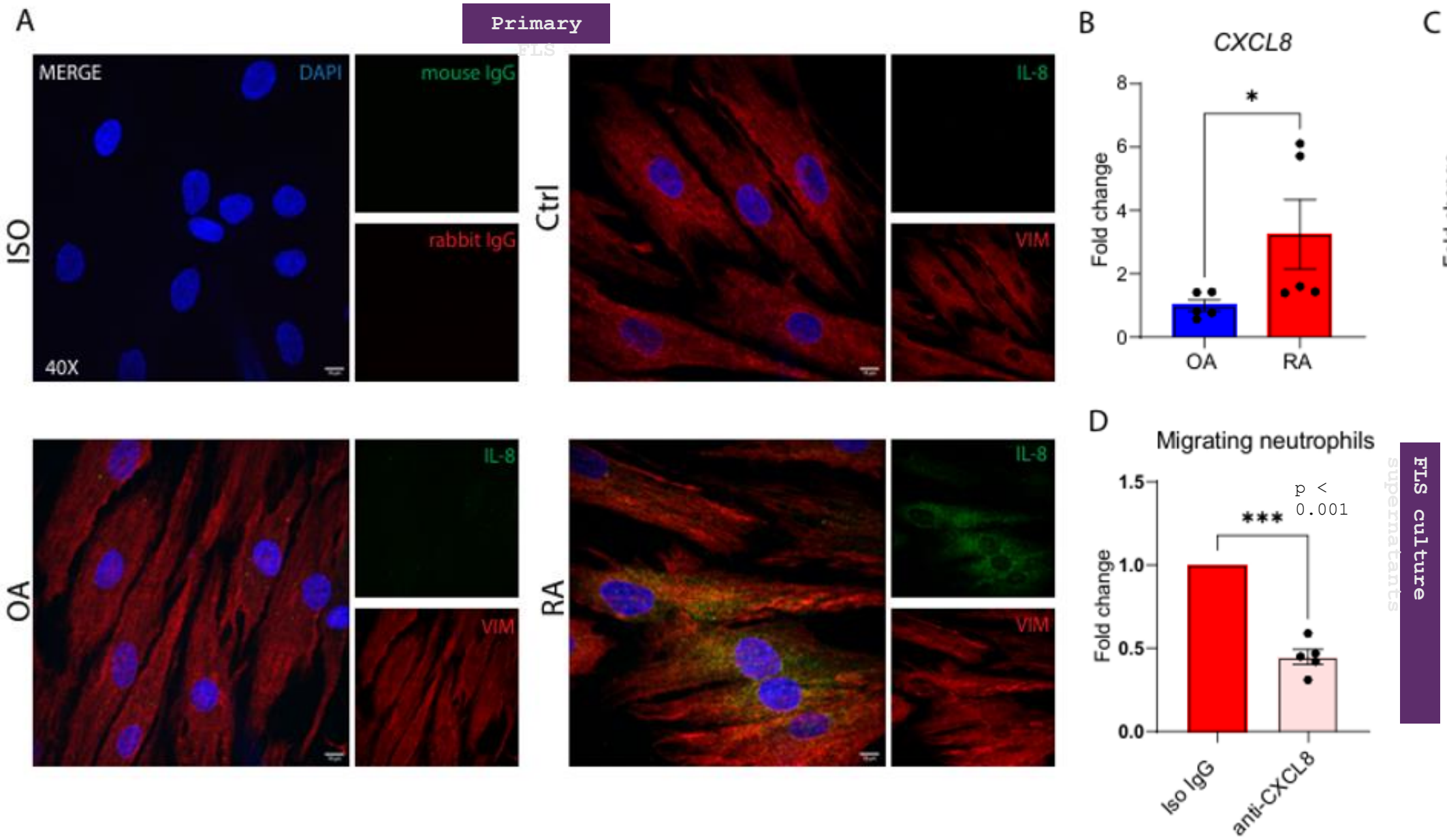


Correlations

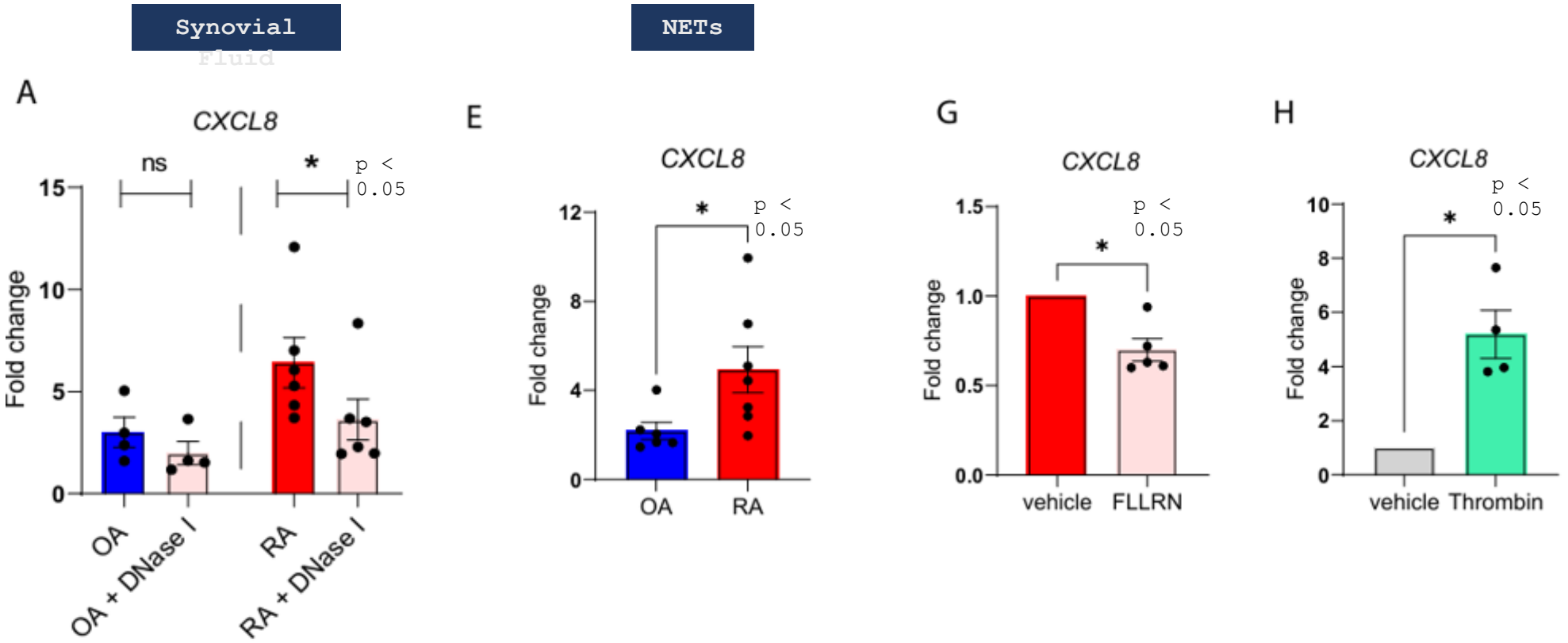




IL-8 promotes neutrophil recruitment

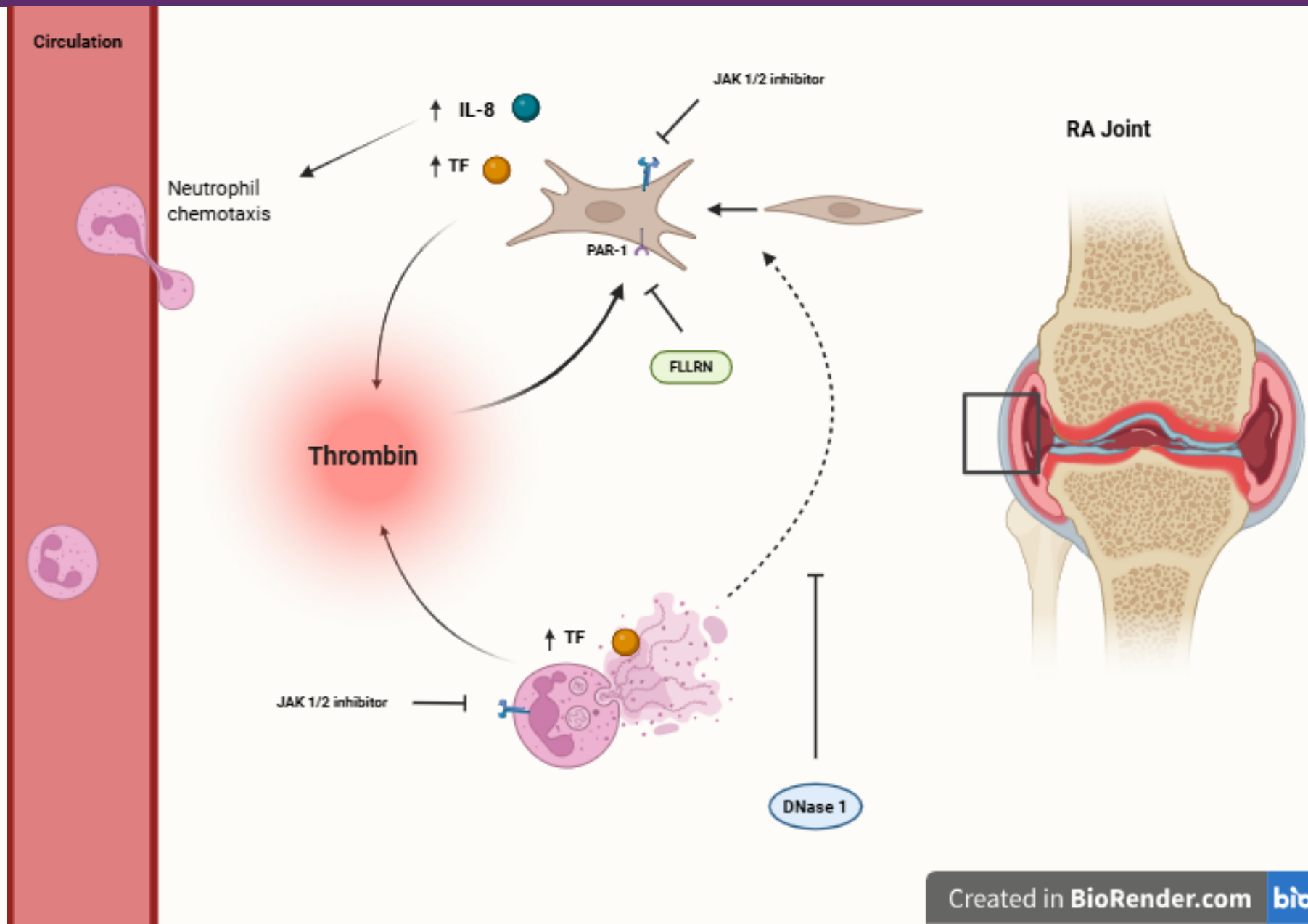


NET components and thrombin/PAR-1 signaling amplify CXCL8 expression in FLS



Conclusions

- **FLS & neutrophils** cooperate to drive a self-sustaining inflammatory loop
- **RA SF** amplifies inflammation via JAK/STAT → TF & IL-8 expression
- **Thrombin** promotes Il-8 expression from FLS
- **NETs** further activate FLS to produce IL-8



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