In vitro, exposure of TCR-stimulated early RA CD4+ T cells to pim kinase inhibitors restrained their activation and proliferative capacity; diminished pro-inflammatory cytokine production (IFN-γ and IL-17) and an expanded CD25hi FoxP3+ regulatory T cell (Treg) fraction were also observed in treated versus un-treated cells. Finally, administration of pim inhibitors robustly attenuated clinical scores of arthritis in the CIA model, with reduced cartilage loss observed in animals treated with a pan-PIM inhibitor compared with vehicle control (Figure 2).

Figure 1. A. Correlation between CD4+ T cell PIM1 readouts of flow cytometric assay and real-time PCR. B. HM1 transcript in circulating RA and disease control CD4+ T cells. Quantitative immunofluorescence staining for pim-1 in (C) nucleated (DAPh+) synovial cells and (D) CD3+CD4+ T cells in particular.

Figure 2. A. Significantly reduced arthritis severity amongst CIA mice treated with pan-pim inhibitor (n=15) compared with vehicle control (Vh; n=16). B. Representative images depicting preserved ankle joint cartilage layer (safranin O) following pan-pim kinase inhibition (day 50; separate experiment).

Conclusion: Our data highlight pim kinases as plausible therapeutic targets for a subgroup of early RA patients that may be identifiable using tractable in vitro assays. Pim kinase inhibitors could simultaneously target immune inflammation and RASF dysregulation; consideration should now be given to their repurposing for this condition.

References:

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SAT0014 ENDOTHELIAL PROGENITOR CELLS: ROLE IN ENDOTHELIAL DAMAGE OF INTERSTITIAL LUNG DISEASE ASSOCIATED TO RHEUMATOID ARTHRITIS V. Pulito-Cueto1, S. Remuzgo-Martinez2, F. Genre1, V. M. Mora-Cuesta1, D. Iturbe Fernandez2, S. Fernandez-Rozas3, L. Lera-Gomez4, P. Alonso Lecue1, R. Rodriguez-Carro1, V. Portilla1, D. Merino5, R. Blanco1, A. Corrales1, J. M. Cifrian-Martinez1, R. Lopez-Mejias1, M. A. Gonzalez-Gay1,4,5. 1Research Group on Genetic Epidemiology and Atherosclerosis in Systemic Diseases and in Metabolic Bone Diseases of the Musculoskeletal System, IDIVAL, Hospital Universitario Marqués de Valdecilla, Santander, Spain; Santander, Spain; Santander, Spain; 2Department of Functional Biology, Immunology Area, Faculty of Medicine, Universidad de Oviedo, Oviedo, Spain; 3Health Research Institute-IDIVAL, Santander, Spain; 4School of Medicine, Universidad de Cantabria, Santander, Spain; 5Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Background: Interstitial lung disease (ILD) is one of the most significant comorbidities of rheumatoid arthritis (RA), increasing the mortality in these patients [1,2]. Although the pathogenesis of ILD associated to RA (RA-ILD) remains poorly defined [1], it is known that vascular tissue plays a crucial role in lung physiology [3]. In this context, a population of cells termed endothelial progenitor cells (EPC) is involved in vasculogenesis and endothelial tissue repair [4]. Previous reports suggest the implication of EPC in different conditions such as RA and idiopathic pulmonary fibrosis (IPF), the most common and destructive ILD [5,6]. Nevertheless, little is known about their specific role in RA-ILD.

Objectives: The purpose of this study was to shed light on the potential role of EPC in endothelial damage in RA-ILD.

Methods: Peripheral venous blood was collected from a total of 68 individuals (18 with RA-ILD+, 17 with RA-ILD-, 19 with IPF and 14 healthy controls). All subjects were recruited from the Rheumatology and Pneumology departments of Hospital Universitario Marqués de Valdecilla, Santander, Spain. Quantification of EPC was analyzed by the expression of surface antigens by flow cytometry. The combination of antibodies against the stem cell marker CD34, the immature monocyte marker CD14, and the common leukocyte antigen CD45 was used. EPC were considered as CD34+, CD45low, CD309+ and CD133+. All statistical analyses were performed using Prism software 5 (GraphPad).

Results: EPC frequency was significantly increased in patients with RA-ILD+, RA-ILD- and IPF compared to controls (p=0.001, p=0.002, p< 0.0001, respectively). Nevertheless, patients with RA, both RA-ILD- and RA-ILD+, showed a lower frequency of EPC than those with IPF (p= 0.048, p= 0.006, respectively).

Conclusion: Our results provide evidence for a potential role of EPC as a reparative compensatory mechanism related to endothelial damage in RA-ILD+, RA-ILD- and IPF patients. Interestingly, EPC frequency may help to establish a definitive diagnostic between patients with IPF and those who have an underlying autoimmune disease (RA-ILD-).

References:

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