Exploring PIM1 as a measurable therapeutic target in early rheumatoid arthritis.

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Background: We previously showed that PIM1 kinase gene expression is strikingly up-regulated amongst circulating CD4+ T cells of treatment-naïve early RA (eRA) patients compared with disease controls[1,2]. PIM1 has a recognised role in T cell development and has been implicated in the pathogenesis of autoimmunity[3]. Oral PIM kinase inhibitors are in clinical development in oncology; for example PIM1 was recently identified as a promising target in triple-negative breast tumours[4]. We hypothesised that, amongst a readily-identifiable subgroup of eRA patients, PIM1 overexpression in CD4+ T cells is a targetable early event in pathogenesis that lies downstream of STAT3-mediated IL-6 signalling.

Methods: Peripheral blood was obtained from consenting healthy donors or eRA patients and CD4+ T cells were isolated. PIM1 knock-down (SMARTpool siRNA, Dharmacon) or protein inhibition (small molecule inhibitor TCS-PIM-1 1, Tocris) was undertaken in primary CD4+ T cells of healthy donors. Flow cytometric analysis was then used to assess its potential role in activation and proliferation following CD3/CD28-mediated stimulation.

Results: Both PIM1 knock-down and PIM1-specific inhibition decreased the activation and proliferation of healthy donor CD4+ T cells and increased their expression of FoxP3 *in vitro*. The production of pro-inflammatory cytokines was decreased by PIM1-specific inhibition, although not by siRNA knock-down, potentially as the latter also significantly increased PIM2 and PIM3 expression. In eRA, CD4+ T cells exhibited an activated, hyper-proliferative phenotype compared with those isolated from healthy donors, which could also be reduced via PIM1 inhibition.

Conclusions: Taken together, these data implicate PIM1 as prominent among genes whose induction may “pre-programme” CD4+ T cells to function aberrantly in disease. Conceivably, targeting PIM1 kinase may prove an attractive approach to regulating aberrant CD4+ T cell effector function in an identifiable sub-population of early RA patients, with fewer “off-target” effects than currently available IL-6 pathway-directed approaches. Ongoing *in vivo* work will explore this further.

1. Pratt AG et al, *Ann Rheum Dis* 2012; 71(8) 1374-81
2. Anderson AE et al Ann Rheum Dis 2016; 75(2):466-73
3. Li Z et al J Biol Chem 2014; 289(39):26872-81
4. Horiuchi D et al Nature Medicine 22(11):1321-9