Early rheumatoid arthritis...

- A highly heterogeneous condition
- CD4+ T-cells play central role in pathogenesis
- A CD4+ T-cell gene “signature” predicts early (ACPA-neg) RA...
  - STAT3 target gene enriched...

Objectives

1. Understand IL-6 mediated STAT signalling in circulating lymphocytes during early RA.
2. Explore components of Stat3 / Stat1 signalling as biomarkers in early RA..
   - Diagnostic?
   - Therapeutic?

IL-6 Mediated STAT Signalling...

Newcastle Early Arthritis Clinic

Table:

<table>
<thead>
<tr>
<th></th>
<th>ACPA-RA</th>
<th>ACPA-RA</th>
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</thead>
<tbody>
<tr>
<td>Referral (primary care)</td>
<td>NEAC</td>
<td>NEAC</td>
</tr>
<tr>
<td>Diagnosis confirmed</td>
<td>n=8</td>
<td>n=10</td>
</tr>
<tr>
<td>Suspected inflammatory arthritis</td>
<td>ACPA-RA</td>
<td>ACPA-RA</td>
</tr>
<tr>
<td>Age (years)</td>
<td>73 (62-86)</td>
<td>56 (37-75)</td>
</tr>
<tr>
<td>% Female</td>
<td>75</td>
<td>61</td>
</tr>
<tr>
<td>Sympt duration (weeks)</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>ESR (mm/min)</td>
<td>28 (12-52)</td>
<td>29 (12-52)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>15 (8-32)</td>
<td>9 (5-38)</td>
</tr>
</tbody>
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* Values = median (range)
**Methods**

- Phosflow on T cells and B cells - BD Phosflow buffers and antibodies – pStat3(Y705) and pStat1(Y701)

- Surface stains include lineage markers and IL-6R
- IL-6, sIL-6R and sgp130 in serum – MSD and ELISA

**Examples of Phosflow – pStat3(Y705)**

('Fluorescence minus one' gating strategy)

**Basal pStat3(Y705) and pStat1(Y701) in immune cell subsets**

- n = 94 (T cells); n = 78 (B cells)

**Membrane IL-6R expression in lymphocyte subsets**

**Association of basal pStat3(Y705) and pStat1(Y701) and serum IL-6 in immune cell subsets**

**pStat3(Y705) in disease groups**

- CD4+ T cells...
- CD8+ T cells...
- CD19+ B cells...

- (Non-parametric statistics)
Summary

• Basal pSTAT3 and IL-6R expression is maximal in the CD4+ T-cell subset of early arthritis patients.

• A strong correlation between pSTAT3 and serum IL-6 is unique to CD4+ T-cells.

• Basal CD4+ T-cell pStat3 is increased in early ACPA-negative RA patients (reflecting serum IL-6 levels) compared with other diagnoses.

Conclusions.

• Single centre observational dataset.

• Importance of IL-6 mediated STAT3 signalling in CD4+ T-cells, as an early event in RA pathogenesis, confirmed.
  – Especially in ACPA-negative disease.

• Prominent role for classical (rather than trans) signalling implied.

• Future studies will focus on delineating a role for these parameters as diagnostic / therapeutic biomarkers.

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Evidence Based Medicine

