

ONLINE RESEOURCE 7

ELECTRONIC SUPPLEMENTARY MATERIAL (ESM-7)

INFLAMMATION RESEARCH

The role of CD8+ T lymphocytes in chronic obstructive pulmonary disease: a systematic review.

Maya Williams, Ian Todd, Lucy C. Fairclough

Corresponding author: Dr Lucy C. Fairclough, School of Life Sciences, The University of Nottingham, Life Sciences Building, University Park, Nottingham NG7 2RD, United Kingdom.

Email: lucy.fairclough@nottingham.ac.uk

Table S6: Studies investigating the role of CD8+ T lymphocytes in acute exacerbations of COPD. Four studies investigated CD8+ T lymphocytes at acute exacerbation of COPD, three of which examined the CD8+ T lymphocyte subpopulations.

Publication	Title	Subjects	COPD diagnosis	Sample	Conclusions
Chen et al [45] Human 2016	Imbalance between subsets of CD8+ peripheral blood T cells in patients with chronic obstructive pulmonary disease	24 stable COPD (SCOPD), 14 acute exacerbation of COPD (AECOPD), 14 healthy non-smokers (HNS)	Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria AECOPD – symptoms diagnostic for COPD exacerbation without any new therapeutic intervention	Peripheral blood	A higher percentage of CD8+ T cells in peripheral blood of AECOPD patients than the other two groups. The proportions in SCOPD and HNS were similar. Tc1 cells were elevated in AECOPD and SCOPD compared to HNS and were the predominant CD8+ T cell subset. Tc17 cells were also increased at AECOPD. Tc2 cells were reduced in SCOPD compared to AECOPD and controls The anti-inflammatory CD8+ T cells (Tc10) were decreased in both COPD groups compared to controls.
Freeman et al [46] Human 2015	Acute exacerbations of chronic obstructive pulmonary disease associated with decreased CD4+ and CD8+ T cells and increased growth & differentiation factor-15 (GDF-15) in peripheral blood	Subjects with COPD and history of previous AE- COPD were followed up for up to 3 years. Of 33 enrolled subjects, 13 participated in multiple stable visits and had at least 1 AE- COPD visit, which generated 18 total AE-COPD events	GOLD AECOPD – change above baseline in respiratory symptoms plus addition by a study physician of antibiotics, oral steroids, review of history, physical examination, chest radiographs AECOPD diagnosis was made prior to collection of samples	Peripheral blood Sputum	In AECOPD there is a marked decrease in the absolute number and the percentage of CD8+ T cells in the peripheral blood compared to the relative stable visit. This is followed by a rebound back to normal levels at the next stable visit CD8+ T cells correlated significantly and inversely with CRP (inflammatory marker) In some patients whose stable visit was shortly before their AECOPD, the decline in cell frequency could be observed before the exacerbation – therefore, immune activation may precede symptoms

<p>Makris et al [47]</p> <p>Human 2008</p>	<p>Tc2 response at the onset of COPD exacerbations</p>	<p>24 COPD examined at the onset of exacerbation and in stable condition</p>	<p>GOLD</p> <p>Initiation of symptoms diagnostic for COPD exacerbation in past</p> <p>72h, abstention from any new therapeutic intervention, absence of signs suggestive of severe exacerbation requiring hospitalisation</p>	<p>Induced sputum taken at exacerbation and at stable condition (>8 weeks after exacerbation)</p>	<p>Percentage of CD8+ T cells amongst lymphocytes was significantly increased during exacerbations compared to stable condition</p> <p>The percentage of CD8+ IFN-g+ cells was no different at stable or exacerbation whereas the percentage of CD8+ IL-4+ cells was significantly increased, suggesting that the cells are polarized towards Tc2 profile at AECOPD</p> <p>No statistically significant relationship between CD8+ T cell subpopulation ratios and exacerbation type, age, sex, pack years, smoking status or FEV₁% predicted change between exacerbation and stable condition</p>
<p>Tsoumakidou et al [48]</p> <p>Human 2005</p>	<p>Changes in sputum T-lymphocyte subpopulations at the onset of severe exacerbations of chronic obstructive pulmonary disease</p>	<p>12 COPD at onset of acute severe exacerbation and on stable condition</p>	<p>GOLD</p> <p>Severe exacerbation – use of accessory respiratory muscles, paradoxical chest wall movement, respiratory failure breathing room air and/or requiring hospital admission</p>	<p>Induced sputum taken at exacerbation and 16 weeks after remission</p>	<p>There was a lower CD4/CD8 + T cell ratio at the onset of exacerbation which suggests that there are more CD8+ T cells.</p> <p>There is also a lower CD8+ IFN-g/CD8+ IL-4 positive cell ratio at the onset of exacerbation which suggests that there is a Tc2 mediated immune response at the onset of severe COPD exacerbation.</p>

