Defects in CTLA-4 induction of Regulatory T-cells in COPD

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INTRODUCTION

► Chronic obstructive pulmonary disease (COPD) is characterized by ongoing airway and systemic inflammation
► Little is known about the function of anti-inflammatory pathways in COPD
► T-regulatory cells (Treg) inhibit inflammation via production of regulatory cytokines (e.g. IL-10, TGF-β) and cytotoxic lymphocyte antigen-4 (CTLA-4)
► CTLA-4 is a key anti-inflammatory molecule that inhibits T-cell activation by blocking CD28 signals

Figure 1 – T-cell intrinsic models of CTLA-4 function (Walker and Sansom 2011)

AIM

► To investigate Treg function in COPD

Methodology

Phenotyping of CD4+ T-cell subsets
Flow cytometry

Activation CD4+HLA-DR+

Treg CD4+CD25+CD127low

Peripheral blood mononuclear cells (PBMC)
Isolated by Ficoll density gradient

Non-smokers (NS) n=12
Smokers (S) n=12
COPD patients n=15

Treg depletion by flow
FACS Aria II

Whole PBMC
Treg-depleted PBMC

Culture for 6 hrs ± Staphylococcal enterotoxin-B (SEB)

Total CTLA-4 production in Treg
Flow cytometry

Memory CD4+ T-cell responses
CD4+CD45RO+HLA-DR+
Flow cytometry

Figure 2 – Gating of Treg (CD3+CD4+CD25+CD127hi) cells, pre- and post-depletion

RESULTS

SUMMARY & CONCLUSIONS

► This study is the first to show Treg dysfunction in COPD
(i) Absence of enhanced memory CD4+ T-cell responses when the Treg “brake” was removed:
- Inadequate Treg-mediated suppression in COPD
(ii) Impaired induction of CTLA-4 by SEB in Treg

► Impaired Treg-mediated suppression may explain why...
(i) COPD patients are predisposed to exacerbations associated with bacterial or viral infections
(ii) COPD patients have persistent immune activation driven by ongoing exposure to foreign and/or self antigens

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