Homeostatic cytokines interleukin-7 (IL-7) and IL-15 drive the expansion and activation of CD4+CD28null T cells in patients with myocardial infarction

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Background and Aim: We have previously shown that $CD4^{+}CD28^{null}$ ($CD28^{null}$) T cells, a unique T lymphocyte subset with pro-inflammatory and cell-lytic phenotype that are apoptosis resistant, expand in patients with myocardial infarction (MI). MI patients harbouring high $CD28^{null}$ T cell numbers have increased risk of recurrent severe acute coronary events and unfavourable prognosis. The mechanisms that govern $CD28^{null}$ T cell expansion in MI remain elusive. The pro-inflammatory cytokine tumour necrosis factor-α (TNF-α) has been implicated in $CD28^{null}$ T cell expansion in rheumatoid arthritis. We investigated the effect of inflammatory and homeostatic cytokines on $CD28^{null}$ T cells in MI patients.

Methods: Freshly isolated cells from MI patients were treated with recombinant human cytokines (TNF-α, IL-1β, IL-6, IL-7 and IL-15) and the number, activation, function and proliferation of $CD28^{null}$ T cells were analysed.

Results: We found that pro-inflammatory cytokines TNF-α, IL-1β and IL-6 did not have any effect on $CD28^{null}$ T cell number. Strikingly, homeostatic cytokines IL-7 and IL-15 triggered expansion of $CD28^{null}$ T cells from MI patients, which was mediated by cell proliferation. Moreover, we demonstrate for the first time that IL-7 and IL-15 activate $CD28^{null}$ T cells and increase their cytotoxic function.

Conclusions: We showed that IL-7 and IL-15 and not pro-inflammatory cytokines are the main drivers of $CD28^{null}$ T cell expansion in MI patients. Our novel findings suggest that anti-inflammatory drugs targeting TNF-α, IL-1 and IL-6 may fail to control $CD28^{null}$ T cell expansion in MI patients and that therapeutic strategies targeting alternative cytokines (IL-7, IL-15) may be beneficial.