Abstract: P275

The expansion of pro-inflammatory CD4+CD28null T lymphocytes in myocardial infarction is driven by homeostatic cytokines interleukin-7 (IL-7) and IL-15 and not by inflammatory cytokines

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Background: We have previously shown that CD4+CD28null (CD28null) T lymphocytes are a unique T lymphocyte subset with pro-inflammatory and cell-lytic phenotype. These cells are apoptosis resistant and expand in patients with myocardial infarction (MI). Of note, MI patients harbouring high numbers of CD28null T cell have increased risk of recurrent MI and poorer prognosis compared to MI patients who don’t exhibit expansion of the CD28null T lymphocyte subset. The pro-inflammatory cytokine tumour necrosis factor-a (TNF-a) has been implicated in CD28null T cell expansion in rheumatoid arthritis. However, the mechanisms that govern CD28null T cell expansion in MI patients remain elusive.

Purpose: We have investigated the effect of inflammatory (TNF-a, IL-1b, IL-6) and homeostatic cytokines (IL-7 and IL-15) on CD28null T cells in MI patients.

Methods: Freshly isolated cells from MI patients were treated with recombinant human cytokines (TNF-a, IL-1b, IL-6, IL-7 and IL-15) and the number, activation, function and proliferation of CD28null T cells were analysed.

Results: We found that pro-inflammatory cytokines TNF-a, IL-1b and IL-6, either alone or in combination, did not affect the number of CD28null T cells. Here we show for the first time that homeostatic cytokines IL-7 and IL-15 triggered expansion of CD28null T cells from MI patients, which was mediated by preferential activation of this cell subset and proliferation. Moreover, we demonstrate that IL-7 and IL-15 increase the cytotoxic function of CD28null T cells. In addition, we present evidence for the preferential sensitivity of CD28null T cells to homeostatic cytokines.

Conclusions: We showed that IL-7 and IL-15 and not pro-inflammatory cytokines are the main drivers of CD28null T cell expansion in MI patients. Our novel findings suggest that anti-inflammatory drugs targeting TNF-a, IL-1 and IL-6 may fail to control CD28null T cell expansion in MI patients and that therapeutic strategies targeting alternative cytokines (IL-7, IL-15) may be beneficial.