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Co-stimulation dependent CD8 T cell activation protects vein graft disease

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Introduction Vein grafts are frequently used conduits for arterial reconstruction in patients with cardiovascular disease. Unfortunately, diminished patency rates are caused by vein graft disease (VDG). Components of the innate immune system are known to contribute to VGD. However, the role of T cells and T cell activation as part of the adaptive immune system in VGD has yet to be established. T cells can be activated by antigen presenting cells via a combination of different signals of the T cell receptor (TCR), co-stimulation, or a bystander effect.

Purpose To investigate the role of T cells and T cell activation pathways via TCR, co-stimulation and bystander effect in VGD.

Methods Vein graft surgery was performed in C57BL/6 mice, after depletion of T cells with anti-CD8, anti-CD4, both, or control IgG injection. To establish the role of the TCR in T cell activation, vein graft surgery was performed in OTI mice, because of their transgenic TCR. Mice were sacrificed after 28d and vein graft, blood, spleen, (non)draining lymph nodes were used for FACS analysis.

CD80/86-/- mice were used to investigate the CD28-CD80/86 T cell co-stimulation pathway, CD70-/- mice for the CD27-CD70 T cell co-stimulation pathway and CD80/86/70-/- mice for both pathways. Vein graft surgery was performed and after 28d vein grafts were harvested for immunohistochemical analysis. In vitro T cell activation via co-stimulation and the bystander effect was investigated using CD8 T cells, cultured with either agonistic antibody-CD3, CD27, CD28, IFN-β, or a combination thereof.

Results Vein graft patency of CD8 and CD4/CD8 depleted mice was only 10% and 12.5% respectively compared to >70% in both CD4 depleted and control mice after 28d, suggesting a protective role of CD8+ T cells in VGD. Vein grafts contained significantly more activated T cells (CD3+KLRG1+CD62L-) compared to other organs. Interestingly, 28d after surgery, similar patency rates were observed in control mice and OTI mice (75 vs 100%, ns). Moreover, the percentage of activated CD8 T cells (CD8+KLRG1+CD62L-) was also similar, indicating that CD8 T cells activation in vein grafts is TCR independent.

In vivo analysis showed that intimal thickening in vein grafts was decreased in CD80/86/70-/- mice compared to controls, but CD70-/- mice and CD80/86-/- mice showed no differences.

For prominent in vitro CD8 T cells activation a co-stimulation signal was essential. Besides, more T cells were activated with a combination of CD3-CD28 agonist compared to CD3-CD27 agonist, suggesting a prominent role of the CD28-CD80/86 T cell co-stimulation pathway.

Conclusions T cells play a role in VGD, with a specific protective role of CD8 T cells. T cell activation in vein grafts is TCR independent and co-stimulation dependent, with a prominent role of the CD28-CD80/86 T cell co-stimulation pathway, giving rise to potential new strategies to use the CD28-CD80/86 T cell co-stimulation pathway in a therapeutic approach to prevent VGD.