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Immunomodulation of antigen-specific $CD8^+$ T cells by everolimus and mesenchymal stem cells

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Everolimus, a derivative of sirolimus, is a novel inhibitor of mammalian target of ra-pamycin (mTOR) that is recently used off-label for patients after hematopoietic stem cell transplantation (HSCT) and is useful in reducing cyclosporine-related ne-phrotoxicity. We demonstrate here that everolimus strongly hampers Cytomegalo-vi-rus (CMV)-specific CD8+ T cells. Proliferation of CD8+ T cells after stimulation with pp65 peptides and the frequency of CMV-specific T cells stained with pp65 te-tramers were suppressed by low doses of everolimus in a dose-dependent manner. When we added everolimus at a concentration corresponding to the therapeutical range of the drug (3-8 ng/ml), CD8+ T cells were strongly suppressed (by 90%). Be-yond proliferation, everolimus had a strong impact on the cell number of CD8+ T cells expressing the activation marker CD137 and the secretion of cytokines. In addi-tion we studied the influence of everolimus on T cells after stimulation with staphy-lococcal enterotoxin B (SEB) or phytohemagglutinin (PHA). Again, proliferation of T cells was inhibited in a dose-dependent manner. As reactivation of CMV plays a piv-otal role for the outcome of patients after HSCT, attention must be paid to early detec-tion and pre-emptive treatment of CMV reactivity in patients treated with everolimus.

Mesenchymal stem cells (MSCs) have a potential to differentiate into different cell types such as adipocytes, chondrocytes and muscle cells. Moreover MSCs constitute key players of the immune system. Therefore MSCs have been considered for cellular therapies for patients with graft versus host disease (GVHD) after HSCT. We demon-strated that platelet lysate (PL) -cultured MSCs have similar immunomodulatory ca-pacities when compared to MSCs culturate containing fatal calf serum and cytokines (6S). Both MSCPL and MSC6S showed an immunosuppressive effect on the prolifer-ation of peripheral blood mononuclear cells stimulated with mitogen and mixed lym-phocyte reaction (MLR). The immunomodulatory effects of MSCs on CMV-specific CD8+ T cells were studied in mixed lymphocyte peptide culture. When co-cultured with either MSCPL or MSC6S, the proliferation of CMV-specific CD8+ T cells was inhibited, as well as the frequencies of CD8+CMVtetramer+ T cells and CD137+CMVtetramer+ T cells were reduced. Moreover in enzyme-linked immuno-spot (ELISPOT) assays, MSCs suppressed the number of CMV-specific IFN-γ- and granzyme B-producing cells. In this work, the immunosuppressive potential in terms of inhibition of proliferation, immunophenotype and function of T cells was paradig-matically demonstrated for antigen-specific CD8+ T cells.