Serum isolated after autologous transplantation stimulates proliferation and \textit{in vitro} expansion of human CD34$^+$ hematopoietic stem- and progenitor cells

T. Walenda$^1$, G. Walenda$^1$, E. Jost$^2$, O. Galm$^2$, A. Schellenberg$^1$, C.M. Koch$^1$, D.M. Piroth$^3$, W. Drescher$^4$, T.H. Brümmendorf$^2$, W. Wagner$^1$

Abstract

After hematopoietic stem cell transplantation (HSCT), regeneration of the hematopoietic system requires activation of the stem cell pool. So far, the mechanisms that recruit these cells into proliferation and self-renewal are scarcely understood. Here, we have addressed the question if activation of hematopoietic stem and progenitor cells (HPC) after autologous HSCT is mediated by systemically released cytokines and growth factors. Serum was taken from patients before chemotherapy, during neutropenia and after hematopoietic recovery. Subsequently, it was used as supplement for \textit{in vitro} culture of CD34$^+$ cord blood HPC. Serum samples that were isolated during hematopoietic stress between 4 and 11 days after HSCT significantly enhanced HPC-proliferation and maintained primitive immunophenotype (CD34$^+$, CD133$^+$, CD38$^-$, CD45$^-$) over more cell divisions.

The frequency of colony forming units (CFU) as well as the number of cobblestone area forming cells (CAFC) was also increased. More than 2 weeks after HSCT when hematopoietic recovery was almost completed, this stimulating effect declines to normal levels as observed with samples from before chemotherapy. Chemokine profiling revealed down-regulation of several growth factors after HSCT including platelet-derived growth factors PDGF-AA, PDGF-AB and PDGF-BB, whereas expression of monocyte chemotactic protein-1 (MCP-1) increased. Metabolomic profiling was used for identification of 46 metabolites that are currently tested for their functional relevance in HPC expansion. Taken together, these results demonstrate that systemically released factors stimulate hematopoiesis after autologous HSCT. This feedback mechanism opens new perspectives for \textit{in vivo} stimulation of the stem cell pool.