In vivo hematopoietic Myc activation directs a transcriptional signature in endothelial cells within the bone marrow microenvironment.

Cancer pathogenesis involves tumor-intrinsic genomic aberrations and tumor-cell extrinsic mechanisms such as failure of immunosurveillance and structural and functional changes in the microenvironment. Using Myc as a model oncogene we established a conditional mouse bone marrow transduction/transplantation model where the conditional activation of the oncoprotein Myc expressed in the hematopoietic system could be assessed for influencing the host microenvironment. Constitutive ectopic expression of Myc resulted in rapid onset of a lethal myeloproliferative disorder with a median survival of 21 days. In contrast, brief 4-day Myc activation by means of the estrogen receptor (ER) agonist tamoxifen did not result in gross changes in the percentage/frequency of hematopoietic lineages or hematopoietic stem/progenitor cell (HSPC) subsets, nor did Myc activation significantly change the composition of the non-hematopoietic microenvironment defined by phenotyping for CD31, ALCAM, and Sca-1 expression. Transcriptome analysis of endothelial CD45-Ter119-cells from tamoxifen-treated MycER bone marrow graft recipients revealed a gene expression signature characterized by specific changes in the Rho subfamily pathway members, in the
transcription-translation-machinery and in angiogenesis. In conclusion, intra-hematopoietic Myc activation results in significant transcriptome alterations that can be attributed to oncogene-induced signals from hematopoietic cells towards the microenvironment, e. g. endothelial cells, supporting the idea that even pre-leukemic HSPC highjack components of the niche which then could protect and support the cancer-initiating population.