DKMS Stiftung Leben Spenden

Project Summary

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Mechanisms and therapeutic targets of endothelial damage during GvHD

Dr. rer. nat. Katarina Riesner

Acute graft-versus-host disease (aGVHD) remains a major reason for mortality after allogeneic hematopoietic stem cell transplantation and there is an urgent medical need for new therapeutic approaches. Clinical studies demonstrated that endothelium related factors predict mortality after aGVHD diagnosis, raising interest in the endothelium as a therapeutic target in this setting. In our preliminary work, we found extensive endothelial damage, structural changes and endothelial dysfunction in GVHD target organs. Therefore, we see a strong rationale for the use of endothelium-targeting and protective therapeutic approaches during aGVHD. As a first example for such an approach, we detected reduced GVHD mortality and target organ damage in experimental GVHD by administration of the endothelium protective agent sildenafil, a phosphodiesterase-5 (PDE5) inhibitor. Additionally, in search for new targets, we have generated preliminary data identifying new candidate genes that are differentially regulated in damaged endothelial cells during aGVHD. A specifically promising pathway is the pentose phosphate pathway (PPP), which is important for the metabolic regulation of endothelial cell function.

The objective of this study is to study mechanisms of endothelial damage and identify suitable therapeutic targets to protect the endothelium during GVHD.

Our specific aims are: 1) To study the effects and mechanisms of endothelial-specific PDE5- and PPP inhibition in vitro, and 2) To analyze the influence of PDE5 and PPP inhibition on endothelial damage during GVHD in vivo.