ANNA, STELLING-GERMANI

Group Professor Dr. Anne Müller

Institute of Molecular Cancer Research
University of Zürich
Winterthurerstrasse 190
8057 Zürich
stelling@imcr.uzh.ch

https://www.imcr.uzh.ch/en/research/Muller/Team/Stelling.html

KEYWORDS – DLBCL, signaling, mouse models, methylation

MAIN FIELDS OF RESEARCH; ABSTRACT

The sphingosine-1-phosphate receptor S1PR2 and its downstream signaling pathway are commonly silenced in diffuse large B-cell lymphoma (DLBCL), either by mutational inactivation or through negative regulation by the oncogenic transcription factor FOXP1.

We have examined the upstream regulators of S1PR2 expression and have newly identified the TGF-b/TGF-bR2/SMAD1 axis as critically involved in S1PR2 transcriptional activation. Phosphorylated SMAD1 directly binds to regulatory elements in the S1PR2 locus as assessed by chromatin immunoprecipitation, and the CRISPR-mediated genomic editing of S1PR2, SMAD1 or TGFBR2 in DLBCL cell lines renders cells unresponsive to TGF-b-induced apoptosis. DLBCL clones lacking any one of the three factors have a clear growth advantage in vitro, as well as in subcutaneous xenotransplantation models, and in a novel model of orthotopic growth of DLBCL cells in the spleens and bone marrow of MISTRG mice expressing various human cytokines. The loss of S1pr2 induces hyper-proliferation of the germinal center B-cell compartment of immunized mice and accelerates MYC-driven lymphomagenesis in spontaneous and serial transplantation models. The specific loss of Tgfbr2 in murine GC B-cells phenocopies the effects of S1pr2 loss on GC B-cell hyper-proliferation. Finally, we were able to show that SMAD1 expression is aberrantly downregulated in >85% of analyzed DLBCL patients.

The results uncovered an important novel tumor suppressive function of the TGF-b/TGF-bR2/SMAD1/S1PR2 axis in DLBCL, and show that DLBCL cells have evolved to inactivate the pathway at the level of SMAD1 expression. Currently we are examining the epigenetic silencing of SMAD1 in DLBCL via bisulfite sequencing of patient samples and DLBCL cell lines. Furthermore, we are investigating the possibility of targeting epigenetically silenced SMAD1 with drugs in various newly established mouse models of DLBCL.

SPECIAL TECHNIQUES AND EQUIPMENT

CRISPR/Cas9, Chromatin Immunoprecipitation, In vivo mouse models, FACS, bisulfite sequencing