Patterns and molecular determinants of NK cell mediated killing of melanoma cells

Sabrina Cappello[1], Carsten Kummerow[2], Adina Vultur[1], Patricia Bradford[3], Tobias J. Legler[4], Meenhard Herlyn[3], Markus Hoth[2] and Ivan Bogeski[1]

[1]Molecular Physiology, Institute for Cardiovascular Physiology, University Medical Center, Georg August University Göttingen, Göttingen, 37073, Germany.

[2]Biophysics, Center of Integrative Physiology and Molecular Medicine, School of Medicine, Saarland University, Homburg, 66421, Germany.

[3]Program of Cellular and Molecular Oncogenesis, Melanoma Research Center, The Wistar Institute, Philadelphia, PA, USA.

[4]Department of Transfusion Medicine, University Medical Center Göttingen, Robert-Koch-Str. 40, 37075, Göttingen, Germany.

Malignant melanoma is the most deadly form of skin cancer. Due to its genetic heterogeneity and high potential to metastasize, the treatment of melanoma is challenging. Despite the promising result of T-cell based therapeutic strategies in combination with targeted therapies, therapeutic resistance or relapse occur. Natural killer (NK) cells, which show an innate ability to recognize and kill cancer cells without prior sensitization, could be a useful additional therapeutic tool in melanoma immunotherapy. To investigate the therapeutic potential of NK cells, we assessed the cytotoxicity of primary NK cells as well as the NK-92 cell line to genetically diverse human melanoma cell lines. We observed a broad range of susceptibility of different melanomas to activated NK cells, while non-stimulated NK cells showed reduced cytotoxicity against the same cells. Subsequent proteome analyses (RPPA) of melanoma cells identified single proteins as well as signalling pathways influencing NK killing. Furthermore, by using the melanoma proteomic signature, we successfully predicted the NK cell susceptibility of additional and untested melanoma cell lines. In summary, our study reveals new insights in the potential use of NK cells in melanoma treatment by identifying novel prognostic immunotherapy-response biomarkers for melanoma.