1459 ASSOCIATION WITH STEMNESS AND FUNCTIONAL ROLE OF IMMUNORECEPTOR NKG2D EXPRESSION IN ACUTE MYELOID LEUKEMIA

[1,2]Ilona Hagelstein*, [2,3]Sylwia A Stefanczyk, [1]Kim L Clar, [1]Kathrin Rothfelder, [1]Jonas Rieth, [1,2]Jonas S Heitmann, [1,2]Helmut R Salih. [1]*Clinical Collaboration Unit Translational Immunology, German Cancer Consortium (DKTK), Department of Internal Medicine, University Hospital Tuebingen, Tuebingen, Baden-Wuerttemberg, Germany*; [2]*Cluster of Excellence iFIT (EXC 2180) 'Image-Guided and Functionally Instructed Tumor Therapies', University of Tuebingen, Tuebingen, Baden-Wuerttemberg, Germany*; [3]*University Hospital Tuebingen, Tuebingen, Germany*

Background The activating immunoreceptor NKG2D is expressed on cytotoxic lymphocytes (CTL) like NK cells, $CD8^+$ cytotoxic T cells and γδ T cells. It potently stimulates CTL effector functions upon recognition of its ligands (NKG2DL) that are generally absent on healthy tissue, but induced by cellular stress including malignant transformation. Recent studies demonstrated that – somewhat surprisingly - also the NKG2D receptor can be expressed on tumor cells of various origins and may affect cellular functions of the malignant cells like tumor growth and metastasis. Here we report on the role of NKG2D expression in acute myeloid leukemia (AML).

Methods Expression of NKG2D on the cell surface of patient AML cells and its correlation with differentiation/maturation as well as stemness characteristics depending on NKG2D expression were studied. Furthermore, the functional role of NKG2D in AML cells on signaling and stem cell properties was investigated.

Results Primary leukemic cells of AML patients expressed substantial levels of NKG2D on the cell surface in approximately 40% of 156 investigated patients. Within the patient cohort, expression of NKG2D was associated with more differentiated subtypes of AML according to the FAB classification. Notably, within the leukemic cell population of individual patients, NKG2D expression significantly correlated with CD34 negativity. In line, after sorting bulk AML cells of patients according to NKG2D expression, only the subpopulation lacking NKG2D expression showed stemness characteristics like the ability to give rise to colonies in colony forming unit assays. Exposure of NKG2D-positive AML cells to agonistic NKG2D antibody caused release of the cytokines IL-6, IL-8, IL-10 and TNF, which act as growth and survival factors for AML cells and play an important role in disease pathophysiology. NKG2D stimulation further increased engraftment of primary AML cells in NSG mice. Signaling via NKG2D was found to enhance the metabolic activity/viability of AML cells and protected the leukemic cells from treatment with the cytostatic compounds cytarabine and doxorubicin that are routinely used for AML treatment.

Conclusions Taken together, our data implicate that the NKG2D/NKG2DL system, beyond its involvement in immune surveillance, may directly affect AML pathophysiology. Ongoing investigations aim to unravel the NKG2D-mediated signaling pathways, consequences of autocrine/paracrine NKG2D/NKG2DL interaction in AML cells as well as the association of NKG2D negativity with known stemness/differentiation markers and clinical disease course.

Ethics Approval The study was approved by IRB (ethics committee of the Faculty of Medicine of the Eberhard Karls Universitaet Tuebingen and of the University Hospital Tuebingen) and was conducted in accordance with the Declaration of Helsinki; reference number 13/2007V.

Consent Human material was collected after obtaining written informed consent of patients/participants.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1459