

neuroblastoma may provide new opportunities for therapy of aggressive neuroblastoma.

Recent evidence has revealed a substantial role of microRNAs (miRNAs) in multidrug resistance in various cancer types. MicroRNAs are small (18–24 nucleotides) non-coding RNA molecules that regulate the expression of genes at the post-transcriptional level by either direct cleavage of target mRNAs or repression of translation. Several studies indicate that deviant expression of certain miRNAs correlate with poor clinical outcome in neuroblastoma. However, the role of miRNAs in neuroblastoma cell resistance to chemotherapeutic drugs is poorly understood.

Methods To explore the role of miRNAs in the resistance of neuroblastoma cells to anticancer drugs, we generated miRNA cDNA libraries from six isogenic human neuroblastoma cell line pairs established from the same patients at the time of initial diagnosis and relapse following therapy. To analyse expression patterns of miRNAs, a deep sequencing analysis (SOLiD sequencing) was performed using the miRNA cDNA libraries.

Results Deep sequencing analysis (SOLiD sequencing) revealed differential expression patterns of miRNAs before and after treatment. Systematic analysis of these miRNA expression patterns identified potential alterations in pathways associated with drug resistance suggesting that dysregulation of miRNAs might influence sensitivity to therapy.

Conclusion We anticipate that our findings will provide new insights into the molecular mechanisms of drug resistance in neuroblastoma.

0-090 FOXO3 IS ACTIVATED IN HIGH-RISK NEUROBLASTOMA AND CONTRIBUTES TO CHEMOTHERAPY-RESISTANCE AND ANGIOGENESIS

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Background FOXO transcription factors control programmed cell death, stress resistance and longevity in normal and malignant cells. We investigated the expression, subcellular localization and phosphorylation of FOXO3 in tumour sections of *post* chemotherapy neuroblastoma (NB) patients and analysed the effects of FOXO3 in cultured NB cells.

Methods Paraffin-embedded sections from patients were analysed for FOXO3 expression, localization and phosphorylation. Effects of chemotherapeutics on FOXO3 subcellular shuttling were assessed by live cell fluorescence imaging in ECFP-FOXO3 transgenic cells. To study how FOXO3 modulates survival we generated cell lines expressing a conditional PKB-independent FOXO3 allele (FOXO3(A3)ERtm) that can be activated by 4OH-tamoxifen and studied the effects of FOXO3-activation *in vitro* by clonogenic survival and propidium iodide FACS-analyses and *in vivo* by xenograft transplantation into nude mice.

Results We found that FOXO3 was localised in the nucleus in tumour sections from high-risk NB patients. FOXO3 nuclear localization and phosphorylation significantly correlated with reduced patient survival. The chemotherapeutics etoposide and doxorubicin led to rapid nuclear accumulation and increased phosphorylation of FOXO3. After low activation of FOXO3 increased clonogenic survival was observed in NB8/FOXO3 cells in combination with chemotherapeutic drugs whereas NB15/

FOXO3 cells underwent spontaneous apoptosis. When transplanting NB15/FOXO cells into nude mice, basal FOXO3 activity induced angiogenesis of NB tumours *in vivo*, whereas full activation eradicated the tumour.

Conclusions The combined data suggest that FOXO3 is activated in high risk NB tumours and depending on the level of its activation, contributes to chemotherapy resistance and tumour angiogenesis or acts as a tumour suppressor.

0-091 WITHDRAWN

0-092 WITHDRAWN

0-092a LEFT VENTRICULAR FUNCTION IN CHILDREN WITH ACUTE LEUKAEMIA RECEIVING HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Hematopoietic stem cell transplantation (HSCT) is a curable therapy for paediatric cancer. Cardiovascular complications are the leading cause of late morbidity and mortality in long-term childhood cancer survivors. However, cardiac function in children after HSCT is not well known. We assessed left-ventricular (LV) function in children after HSCT for acute leukaemia by using tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE). Forty consecutive patients (median 11.9 years) who had HSCT for acute leukaemia between 2011 and 2014 had undergone an echocardiographic assessment before and after (median 9.2 month) HSCT. LV function parameters, including conventional, TDI, and STE data, were collected from patients' echocardiographic data, and were compared with those of controls (n = 39, median age 9 years). All patients had anthracycline as a pre-HSCT chemotherapy. At post-HSCT, patients had decreased LV ejection fraction (p = 0.06), rate-corrected velocity of fibre shortening (p = 0.04), and mitral septal annular E' velocity (p = 0.03) compared with controls. STE parameters also decreased in patients; mid LV global circumferential strain (p < 0.01), and mid LV global circumferential systolic strain rate (SR, p = 0.01). There was no significant change in LV function parameters after HSCT compared with pre-HSCT study. Patients with anthracycline cumulative dose > 400 mg/m² showed significantly lower mid LV global circumferential strain (p < 0.05) and mid LV global circumferential diastolic SR (p < 0.05). Patients who received HSCT for acute leukaemia had sub-clinical cardiac dysfunction, which may be associated with pre-HSCT anthracycline exposure with little effect of conditioning regimens. Serial monitoring of cardiac function is mandatory in all children following HSCT.

0-093 ENERGY EXPENDITURE IN WHITE ADIPOSE TISSUE IS ACTIVATED IN RESPONSE TO BRAIN TUMOUR GROWTH

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