LS18-111 - Ultra-high-risk pediatric cancer - combinatorial drivers and therapeutic targets for precision medicine

Abstract

Although cure rates of children, adolescents and adults with cancer have improved considerably through research and therapy optimization studies, patients are frequently ill-served by conventional therapies, such as combination chemotherapy, and often relapse and succumb to the disease. These patients are commonly referred to as ultra-high-risk and require therapies that are focused on specific genetic or epi-genetic targets. In our study we focus on childhood cancer, specifically neuroblastoma, as a model for overly aggressive disease. Neuroblastoma is a tumor affecting the peripheral nervous system. It affects mainly young children and despite intensive treatment, the chances to be cured are still below 50% in high-risk cases. The underlying genetic and epigenetic alterations and cellular pathways responsible for the aggressive phenotype are not well understood. Therefore, we investigated genetic mutations in neuroblastoma, specifically in the ATRX gene, which is often found in patients with ultra-high-risk neuroblastoma. In addition, we studied ATRX's role in metastasis. Single cell sequencing allowed us to understand the exact molecules and cellular programs active in tumor cells that metastasize to the bone marrow and how tumor cells and immune cells interact. We found that tumor cells with ATRX mutations weaken the immune system by signalling to monocytes and turning them into allies that further promote disease progression. Using CRISPR- and drug screens, we identified new and more specific treatment approaches, which are promising to be tested in further pre‐clinical and early clinical trials. Finally, we developed a zebrafish model for ATRX mutated neuroblastoma, the first animal model for this type of neuroblastoma, by implanting ATRX mutated human tumor cells into zebrafish larvae. The fish larvae carrying tumors were then tested for drug effectiveness. Fluorescently labelled tumor cells in the transparent fish can be visualized in an automated microscopy platform that measures their growth or shrinkage. This platform will be important to test novel drugs and may help determine whether patients will respond to treatments in personalized precision medicine. The combination of the knowledge gathered on relevant molecular pathways and personalized test models will provide oncologists a solid basis for informed therapy decisions.

Scientific disciplines:
Translation studies (60%) | Oncology (20%) | Cancer research (20%)

Keywords:
cancer, neuroblastoma, ATRX, CRISPR screen, (epi-)genetics, synthetic lethality, zebrafish, patient-derived drug testing, personalized medicine

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Further links to the persons involved and to the project can be found under
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