Stem cell pathways in development and oncogenesis

Various tumors have been shown to contain subpopulations of so-called cancer stem cells (CSCs), which are thought to be responsible for disease initiation, maintenance, metastasis and escape after conventional anti-tumor therapies. We hypothesize that pathways that regulate stem cells during development can reactivate during oncogenesis and specifically in CSCs. For example, we show that enhanced expression of the pluripotency-related embryonic protein SOX2 associates with stemness, disease aggressiveness and therapy resistance in putative ovarian and breast CSCs. In breast carcinoma, SOX2 protein expression strongly relies on pAKT activity, suggesting AKT-inhibitors as promising drugs for targeting SOX2-expressing CSCs.

In our developmental studies, we previously identified the BMP-WNT-CDX-HOX signaling pathway as an essential regulator of embryonic hematopoiesis. Later on, involvement of CDX genes was demonstrated in human leukemia. Gene expression arrays performed on CDX2-modified leukemic cells confirmed HOX genes as targets but also revealed the transcription factor EVI (Ectopic viral integration site 1) as a putative downstream molecule. EVI1 has been mostly studied in acute myeloid leukemia (AML), where high expression predicts adverse clinical outcome.

We showed that EVI1 also expresses in lymphoblastic leukemia cells where it regulates apoptosis sensitivity, and furthermore plays important roles as an oncogene in breast as well as prostate carcinoma, where it regulates cell growth and migration independently of estrogen and HER2 signaling, and respectively appears to control disease progression and therapy resistance at the stem cell level.

Using zebrafish to study hematopoiesis and tumor biology

EVI1 also plays important roles during development, amongst other regulating nascent hematopoietic stem cells (HSCs). Using in vivo live imaging studies on transgenic zebrafish embryos, we could show that evi1 suppression impairs HSC emergence by altering Notch levels in endothelial cells of the ventral dorsal aorta (VDA, the fish equivalent of the mammalian aorta-gonado-mesonephros region) and thereby impairing their transition to hematopoietic fate (Konantz et al., 2016). Zebrafish are also used to xenograph human tumor cells and monitor tumor-induced angiogenesis, invasiveness, and response to a range of treatments in vivo and in real-time. Moreover, our laboratory aims to generate transgenic zebrafish leukemia models by inducing EVI1, RAS and p53 expression in specific cell types of the hematopoetic compartment; these models are currently being characterized in detail on the functional and molecular levels and in the near future shall be used for drug screens. Finally, in a project sponsored by the Roche Postdoctoral Program (RPP), we recently showed that double transgenic gata1/egfp;lyz:dsRed fish can be used to model erythroid lineage toxicity and regeneration; a small molecule screen allows identifying novel compounds that can be used to target RAS induced leukemias.

Figure: Using xenograph and zebrafish models to model human disease and identify new treatments.

A. Small molecule screens in zebrafish leukemia models. In transgenic fli.1;RAS flx (Alghisi et al., 2013), the caudal hematopoietic tissue – the equivalent to the mammalian fetal liver – is expanded due to malignant transformation. Phenotypic analysis after treatment with small molecules allows identifying novel compounds that can be used to target RAS-induced leukemias.

B. Functional validation of genomic screening hits. Gene X was identified by whole exome sequencing as a novel mutation in neutropenia. Shown are two representative time points for control (left) and knockdown (right) transgenic Tg fli.1:RAS;mpx:eGFP;lyz:DsRed embryos in which the migration of double positive neutrophils to the blood stream area varies over time. For each time point, merged images are shown. Dotted lines indicate the localization of the tail fin amputation.

C-D. Human AML engraft NSG mice with latency depending on the molecular risk group of the xenotransplanted AML. Favorable risk AML, which in patients associates with improved survival rate, requires longer latency to engraft and induce leukemia in NSG mice, when compared to intermediate or adverse risk AML.

E. Leukemia induction in mice faithfully mimics human disease showing bone marrow (BM) and organ infiltration with leukemic cells with conserved expression of leukemic antigens. (From Alghisi et al., 2013).

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