Abstract:

The dark matter of the genome: Long non-coding RNA & Cancer

The majority of the human genome is transcribed into RNA, while only 2% are protein-encoding inducing a paradigm shift towards the recognition of RNA as functionally important entity – beyond serving as messengers for protein-encoding genes. Long non-coding RNAs (lncRNAs) fulfill important functions ranging from epigenetic gene regulation to scaffolding functions in the cytoplasm. Thus, the cell contains many more RNAs than anticipated and many lncRNAs just await their discovery as functionally important molecules. Since cancer is – in most cases – a disease of the genome caused by deregulated oncogenes and tumor suppressors, we are convinced that all products of the human genome are important to study in tumor biology.

Our research focuses on the role of lncRNAs in cancer. We elucidate their expression patterns, regulatory mechanisms and cellular and molecular functions. The fascination as well as the major challenge in lncRNA research is driven by the fact that each lncRNA can have a different function and a different mechanism, so that many important discoveries and insights into the molecular mechanisms underlying tumorigenesis can be expected from this field.

After profiling the expression of thousands of lncRNAs in three tumor entities – lung, liver and breast cancer – we elucidate the cellular and molecular function of deregulated lncRNAs. We use innovative techniques like Genome Editing to silence lncRNAs in human cancer cells and RNA Affinity Purification to identify their interactomes. To further generate hypotheses o lncRNA functions, we use bioinformatic guilt-by-association studies.

One example illustrates our research approach: the lncRNA MALAT1 (Metastasis-Associated in Lung Adenocarcinoma Transcript 1) is a biomarker associated with the development of distant metastasis in lung cancer (Oncogene 2003). We developed a novel approach to quantitatively silence this lncRNA in lung cancer cells by genome editing (Genome Res 2011). This loss-of-function unraveled that MALAT1 was essential for cell migration and metastasis in a xenograft mouse model. Joining forces with ISIS Pharmaceuticals, we developed an inhibitor for MALAT1, an Antisense Oligonucleotide (ASO), which effectively reduced MALAT1 in the mouse model and suppressed lung cancer metastasis (Cancer Res 2013). At the molecular level, we identified MALAT1 as an epigenetic regulator inducing a signature of metastasis-associated genes. In summary, MALAT1 can serve as a biomarker and is an essential player and promising therapeutic target for metastasis prevention in lung cancer.

CV Sven Diederichs

Since 2008, Sven Diederichs leads the research group “Molecular RNA Biology & Cancer” at the German Cancer Research Center DKFZ and the Institute of Pathology at the University of Heidelberg. His research is focused on the one hand side microRNA biogenesis and the improvement of RNA interference - on the other hand, he investigates the expression and function of long non-coding RNAs in cancer.

Previously, he was a postdoctoral fellow with Daniel Haber at Harvard Medical School / MGH Cancer Center here in Boston. In 2004, he received his PhD in Biochemistry from the University of Muenster in Germany. His scientific work has been recognized by several awards including AACR Scholar-in-Training Awards, the Young Scientist Award of the German National Academy of Scientists Leopoldina and most recently the Innovation Award of the Society of Cell Biology and the Hella Bühler-Prize for Cancer Research endowed with 100.000 Euro.

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CV table:

Since 2008: Group Leader „Molecular RNA Biology & Cancer“, German Cancer Research Center DKFZ & Institute of Pathology, University of Heidelberg, Germany

2005-2008: Postdoctoral Fellow Harvard Medical School / Massachusetts General Hospital Cancer Center, Boston

2002-2004: PhD in Biochemistry, University of Muenster & University of Witten / Herdecke, Germany

1996-2001: Studying Biochemistry, University of Tuebingen & University of Witten / Herdecke, Germany

Several Awards including AACR Scholar-in-Training Awards & Young Scientist Award of the German National Academy of Scientists Leopoldina

Summary:

The majority of the human genome is transcribed into non- coding RNA. We investigate the role of long ncRNAs in cancer by profiling the expression of 17000 ncRNAs in three major tumor entities - lung, liver and breast cancer. In addition, we identified the lncRNA MALAT1 as a marker, active player and potential therapeutic target in lung cancer metastasis using a novel approach to create human knockout cells.