Projects

We currently have two major lines of investigation: We are exploring the functional relevance of miRNAs and long non-coding RNAs in cancer and development; and in parallel, we are developing and applying novel methods of modeling human cancers in mice using somatic genome editing. Here you will find a brief outline of ongoing projects.

In vivo chromosome engineering using the CRISPR-Cas9 system

Chromosomal rearrangements are common events in human cancers, but have proven extremely difficult to engineer in mice. To overcome this limitation, we have recently developed a CRISPR-based strategy to induce chromosomal inversions, deletions, and translocations in somatic cells of adult mice (Maddalo et al., *Nature* 2014). We have used this strategy to generate a new mouse model of Eml4-Alk driven non-small cell lung cancer and we show that this model closely recapitulates the biological properties of human EML4-ALK-driven lung cancers, including a remarkable sensitivity to ALK-inhibitors.

We are using this model to investigate the role of downstream pathways and as a pre-clinical platform for drug discovery and drug development. In addition, we are applying the general strategy we have developed to model *in vivo* other tumor types driven by chromosomal rearrangements and to explore the tumor suppressive potential of selected long non-coding RNAs.

Genetic dissection of the miR-17~92 cluster and of its paralogs.

We have previously generated conditional and constitutive loss of function alleles for three related miRNA clusters in the mouse (Ventura et al., Cell 2008). These clusters are miR-17~92, miR-106b~25 and miR-106a~363. MiR-17~92 is also known as oncomir-1 because of its oncogenic properties in humans and mice. Our initial characterization of these null alleles in the mouse has revealed a critical role of miR-17~92 in controlling B cell survival and B cell development, as well as in regulating lung and heart development. Experiments performed on compound mutant animals for miR-17~92 and miR-106b~25 (one of its two paralogs) also suggest that these two miRNA clusters strongly synergizes in regulating early embryonic development.

By using spatially and temporally regulated Cre-expressing mice in combination with the conditional miR-17~92 allele, we are investigating the functions of this cluster in specific tissues and developmental stages. By employing a combination of gene targeting and in vitro experiments we are attempting to identify the functions of individual members of each miRNA clusters.

Role of miR-17~92 in the pathogenesis of Feingold syndrome.

We have recently reported that a subset of patients affected by Feingold Syndrome -a rare autosomal dominant syndrome characterized by short stature, skeletal defects, learning disabilities and gastro-intestinal defects- harbor hemizygous germline deletions of the entire miR-17~92 cluster (De Pontual et al., Nature Genetics 2011). The role of miR-17~92 in the pathogenesis of

this condition is confirmed by the fact that miR-17~92+/- mice display many of the key developmental defects observed in humans affected by Feingold Syndrome. We are currently investigating the molecular mechanisms through which reduced miR-17~92 dosage affects skeletal development and patterning.

MiR-19 in tumorigenesis

We have recently demonstrated that miR-19a and miR-19b, two miRNAs encoded by the miR-17~92 cluster, are necessary and sufficient to confer oncogenic potential in the context of a mouse model of B cell lymphomas (Mu et al., G&D 2009).To investigate the molecular mechanisms of miR-19 function and to determine its role in tumor progression, we have generated mice carrying selective targeted deletion of miR-19a and miR-19b. The characterization of these animals is providing important information regarding the roles of these two miRNAs in mammalian development and their contribution to a variety of mouse model of human cancers.

p53-dependent and independent functions of the miR-34 family of miRNAs

Three miRNAs (miR-34a, miR-34b and miR-34c) have been shown to be transcriptional targets of the p53 tumor suppressor protein and have been suggested to act as tumor-suppressor themselves. To investigate their biology, we have recently reported the generation of mice carrying targeted deletion of all three members of the miR-34 family (TKO mice). The characterization of these mice has indicates the miR-34 is not essential for the tumor-suppressive function of p53 and suggest the existence of additional, p53-independent, functions for this important miRNA family (Concepcion et al., PlOS Genetics 2012). We are currently investigating both the p53-dependent and p53-independent functions of miR-34 by using HITS-CLIP, RNAi screens and in vivo methods.

Identification of oncogenic and tumor-suppressive lincRNAs

We have recently launched an effort to identify long-intergenic non-coding RNAs that possess oncogenic or tumor suppressor properties. To achieve this goal we are combining mouse models of human cancers, human tumor samples, RNAseq and RNAi-based screenings. The function of lincRNAs identified using this approach will be further examined by generating gain- and loss-of-function alleles in the mouse.

Novel strategies to identify and validate miRNA targets.

Identifying and functionally validating miRNA targets remains one of the main obstacles to fully understand the functions of miRNAs in biological processes. We are developing a novel method to identify bona fide miRNA-targets from whole tissues or from specific cell populations within a tissue. By combining the information gained through this approach with novel genome-editing technologies such as Talens, we hope to define a general strategy for the identification and in vivo validation of miRNA targets.

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