UNA4CAREER

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Research Topic

Functional contribution of microRNAs to oncogenic B cell transformation: Molecular mechanisms responsible of miR-28 anti-tumoral activity and impact of AID mutagenic activity on miRNA repertoire.

Most of the lymphomas arise from the malignant transformation of mature B lymphocytes that have germinal center (GC) experience. GCs are unique structures where somatic remodeling of immunoglobulin (Ig) genes takes place, thus allowing the generation of high affinity antibodies and a proficient immune response. Activation Induced Deaminase (AID) initiates these remodeling events by deaminating cytosines on the DNA of Ig genes. However, AID specificity for Ig genes is not perfect and can promote mutations and chromosomal translocations on other sites of the genome. In addition, other networks including post-transcriptional regulation of GCs by microRNAs (miRNAs) contribute to B cell propensity to malignant transformation.

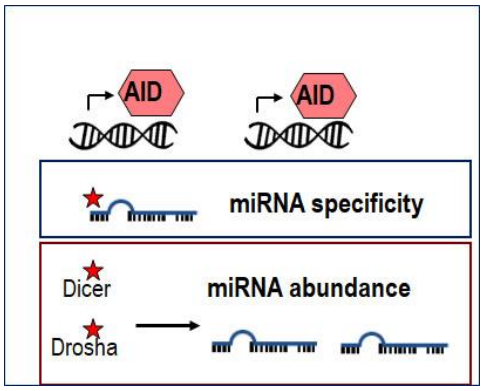
Hypothesis and general objectives

We want to characterize two aspects about the contribution of miRNAs to oncogenic B cell transformation to use this knowledge for the design of new miRNA-based effective therapies to treat aggressive human mature B cell lymphomas.

The first objective is to determine the role of miR-28, a GC-specific miRNA, in GC B cell biology and to unveil the molecular mechanisms responsible for the anti-tumoral activity of miR-28. Our hypothesis is that the administration of miR-28 analogs in combination with other synergic-targeted therapies will be more effective, less toxic and **reduce the generation of resistances** to aggressive mature B cell malignancies treatments. We have developed a novel mouse model that will enable to determine the physiological role of miR-28 in the GC reaction and affinity maturation, the identification of miR-28 targets in GC B cells and to test the impact of miR-28 loss immature B cell lymphoma development. In addition, we will screen for miR-28 synergic therapeutic target genes with a genome wide CRISPER Cas9 approach and assess miR-28-based lymphoma therapy protocols in patient-derived *in vivo* models. We aim at generating the **scientific knowledge required for the development of a new and more specialized therapeutic approach to mature B cell malignancies based on the combined administration of synthetic miR-28 analogs with synergic-targeted therapies.**

The second objective is to determine the impact of **AID mutagenic activity on miRNA repertoire and its contribution to mature B cell transformation through the loss of microRNA-**

mediated regulation. Our hypothesis is that AID mutagenic activity can affect miRNA posttranscriptional regulations in two ways. AID mutagenic activity in activated B cells can target protein-coding genes involved in microRNA biogenesis, and mutations in these genes will provide a growth advantage and/or be an oncogenic event for B cell lymphomas. In addition, AID can mutate non-coding miRNA genes transcribed in activated B cells. Mutations within miRNA seed sequences will alter mRNA-target specificity. These AID-induced alterations of miRNA regulation of GC gene expression will be selected when they confer a selective advantage, and thus contribute to B cell neoplastic transformation (Figure 3). We plan to determine the impact of AID mutagenic activity on miRNA levels and specificities and to characterize the effect of AID-induced miRNA mutations frequently found in DLBCL lymphomas. This will enable the design of specific strategies based on the restauration of the expression of miRNAs with key roles in GC transcriptome regulation or the inhibition of miRNAs with AID-induced aberrant specificities.



Hypothesis model on the contribution of AID mutagenic activity to B cell transformation through microRNA gene expression control escape mechanisms. AID-induced mutations can alter miRNA specificities if the mutation alters the “miRNA seed” sequences leading to: 1) the disruption of the physiological regulation of miRNA-target genes, and 2) an aberrant downregulation of the expression of a new set of genes. In addition, AID can contribute to global miRNA downregulation through the introduction of loss-of-function mutations in the genes or the regulatory sequences required for the expression of the miRNA-processing enzymes Drohsa and Dicer.