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POSTER 10: Identification of long non-coding RNAs involved in Acute Myeloid Leukemia chemoresistance

Romain Pfeifer[1], Guillaume Flandin[1], Chloé Bessière[1], Ahmed Zamani[1], Fabienne Meggetto[1], Stéphane Pyronnet[1], Marina Bousquet[1]

1 : Centre de Recherches en Cancérologie de Toulouse (CRCT) - Université Toulouse III - Paul Sabatier, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique – France.

Acute myeloid leukemia (AML) is a blood cancer caused by the acquisition of mutations in hematopoietic stem cells and progenitors resulting in an accumulation of immature cells in the bone marrow. AML patients are treated with a chemotherapy combining cytarabine and anthracycline. However, resistance occurs in 40 to 60% of cases. Therefore, we need to better understand the genetic and molecular mechanisms that contribute to drug resistance of AML.

Until now, studies have focused on protein-coding genes but a major part of the genome is transcribed in the form of non-coding RNAs. Among them, long non-coding RNAs (lncRNAs) are now recognized as key regulators of all biological processes. However, only few articles report the involvement of lncRNA in AML chemoresistance, which leaves a large field of investigation open.

In order to identify new lncRNAs involved in AML chemoresistance, we used public RNAseq datas from 364 AML patients (BeatAML cohort) in order to quantify the expression of all lncRNAs listed in the LNCipedia database (127 802 lncRNAs). Then, using the available clinical data, we identified 995 lncRNAs whose high expression is associated with a poor prognosis. Among them, the lncRNA most correlated with survival of patients is SENCR (p-val<10-8).

Initially, two variants of SENCR were described: one composed of 3 exons (SENCR 1-2-3) and the other composed of exons 1 and 3 (SENCR 1-3). Interestingly, long reads RNAseq and

RACE experiments allowed us to identify a new variant of SENCR composed only of exons 2 and 3 (SENCR 2-3). Moreover, only SENCR 1-3 and SENCR 2-3 are expressed in AML patients. Individual inactivation of each variants using CRISPRi and siRNA suggests that these two variants exert opposing functions on myeloid differentiation and chemoresistance. Indeed, the new variant SENCR 2-3 confers cytarabine resistance and delays myeloid differentiation whereas SENCR 1-3 enhances differentiation.

Through the study of lncRNAs in AML, we aim for a better knowledge of the unknown world of lncRNAs and a better understanding of this new level of complexity in gene regulation. The lncRNA identified in this project could quickly become molecular tool of choice for future therapies, new diagnostic tests and help in prognosis.