Title: Alu RNAs as novel therapeutic targets and biomarkers in colorectal cancer

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Introduction: The Alu repeat elements are the most abundant short interspersed repeated elements (SINEs) in human genome. Recently, we showed that Alu RNAs accumulation linked to DICER1 deficit is responsible of geographic atrophy, one of the main causes of human blindness. This is the first evidence showing the involvement of Alu RNAs in a human disease. Interestingly, increased levels of Alu RNAs and reduced DICER1 expression have been observed in several cancers, although no correlation has yet been established. Also, it has been demonstrated that tumors-derived exosomes are enriched for Alu sequences. Furthermore, we recently demonstrated that Alu RNA accumulation induces epithelial-to-mesenchymal transition (EMT) and it is associated with colorectal cancer (CRC) progression (1).

Results: We showed that Alu RNAs expression correlated with tumor progression in two colorectal cancer cell lines derived from primary (SW480) and metastatic (SW620) site of the same patient (1). In order to gain a better understanding of their action in tumor progression, we generated stable clones in which Alu RNAs expression is inhibited or over-expressed. Analysis of proliferation, invasion and ability to grow independently from the anchorage strongly suggest that Alu sequences have a potential role in tumorigenesis. Since extracellular vesicles (EVs) play an important role within the tumor microenvironment during cancer progression moving bioactive molecules between tumor and non-tumor cells, we purified EVs both in vitro from cell cultures and in vivo from plasma of xenotransplanted mice with human CRC cells, demonstrating that Alu RNAs is transported in exosomes and its abundance correlates with tumor progression.

Objectives: Based on these findings, the main objective of the present project is to dissect the role of Alu RNAs in CRC pathogenesis. More specifically, this project is focused on four aims: 1) to address the functional role of Alu RNAs in CRC pathogenesis; 2) to study the role of Alu RNAs in vivo; 3) to evaluate the potential use of Alu RNAs as cancer biomarker; and 4) to identify novel compounds inhibiting Alu RNAs signaling in vivo.

Future perspectives: This project will provide new insights into the CRC field, since a complete study of the role of Alu RNAs in cancer is still lacking. More specifically, the ultimate goals are to 1) clarify the mechanism underlying Alu RNAs function necessary to identify small chemical compounds able to inhibit Alu RNAs signaling and 2) identify a new cancer biomarker.


Keywords: Alu RNAs, colorectal cancer, exosomes.

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