CHARACTERIZATION OF THE 5'UTR ELEMENTS REGULATING B-CATENIN TRANSLATION IN CANCER

JAVIER ROL MORENO [1], ANGELITA SIMONETTI [1], NATACH ENTZ-WERLÉ [2], EAMONN ROONEY [3], OLIVER BROOM [3], E. ENNIFAR [1],

[1]Architecture et Reactivite de l'ARN, IBMC, CNRS/Université de Strasbourg, Strasbourg,
[2]Service Onco-Pediatrie des Hôpitaux Universitaires de Strasbourg/UMR CNRS 7213, Illkirch,
[3]Sanofi Open Innovation Plateform, Strasbourg

In humans, β-catenin (CTNNB1 gene) is a multifunction protein involved in cell proliferation, adhesion and migration. Aberrant accumulation of this protein in several types of cancer has significantly been associated with poor prognosis, chemotherapy resistance and malignant cell invasion. Notably, the expression of β-catenin increased under stress conditions without corresponding changes in mRNA abundance and the presence of an IRES (Internal Ribosome Entry Site) has been proposed[1]. However, little progress has been achieved towards the targeting of the β-catenin protein due to its undruggability[2].

Here, we show that CTNNB1 5'UTR is composed of two main elements: a GC-rich three-way junction and an AU-rich less-structured region. We demonstrate that the cap structure is needed for translation in both standard and stress culture conditions. Besides, the GC-rich element is involved in the enhancement of reporter translation during hypoxic stress. Finally, were able to produce native translation initiation complexes of cancer cell lines in hypoxic conditions. The CryoEM structure of this complex provides mechanistic insights into the translation regulation of β-catenin expression in cancer cells and opens promising therapeutic targets for a new family of anticancer drugs.

1. β-catenin expresión is regulated by an IRES-dependent mechanism ans stimulated by paclitaxel in human ovarian cancer cells. Fu Q, Chen Z, Gong X et al.; Biochem. Biophys. Res. Commun. 2015; 461(1): 21-7

2. Is β-catenin a Druggable Target for Carcer Therapy? Cui C, Zhou X, Zhang W et al. Trends Biochem. Sci. 2018; 43(8): 623-34.