ID: 02341
Type: Poster
Topic: New frontiers in treatment/Precision medicine

Decoding Translation: Leveraging its power for hepatocellular carcinoma treatment

Laura Contreras-Bernal[1,4] , Alfonso Rodriguez-Gil[2,4] , Stefano Biffo[3] , Jordi Muntané[2,4] , Jesus De la Cruz[1,4]

1) Department of Genetic. 2) Departament of Medical Physiology and Biophysic. 3) Department of Biosciences, National Insitute of Molecular Genetic (INGM). University of Milan, Italy. 4) Institute of Biomedicine of Seville (IBiS). University of Seville, Spain.

Translation is a crucial step in the regulation of gene expression. The information contained into mRNAs is decoded into proteins that ultimately determines the cellular context. The relationship between translation and cancer has been extensively described. The number of publications highlighting its involvement in tumoral transformation and therapy resistance has increased over the last decade; numerous therapies targeting translation machinery have been studying for clinical use in the last years. In this work, we evaluate the role of translation during the cellular response to Sorafenib treatment in hepatocellular carcinoma (HCC), one of the most deadly cancers worldwide.

Despite the high incidence and mortality of HCC, systemic therapies for advanced HCC have yet to be truly effective. Sorafenib has been the sole therapeutic option for more than a decade and is currently the recommended option for a significant proportion of patients. However, its clinical benefits are limited due to resistance mechanisms and the fact that not all patients respond equally. Sorafenib is a multikinase inhibitor that targets the two main pathways controlling translation: the mTORC1 and MAPK pathways. Indeed, it is well known that Sorafenib reduces the phosphorylation levels of MAPK downstream effector called eukaryotic initiation factor 4E (eIF4E). This factor is the main limiting factor of the so-called cap-dependent complex, also consisting of eIF4A and eIF4G. This complex controls the translation of most cap-containing mRNAs but, interestingly, defects on its activity drive translation of different subset of uncapped and capped-mRNAs, usually stress-related ones. Throughout creation of different stable HCC cell lines and translation assays, we have demonstrated that reduced Phospho-eIF4E in Sorafenib-treated cells caused a selective translation inhibition of pro-tumoral mRNAs in an initial response (1 h). Not much later (3 h), other components of the translation machinery were also affected, further enhancing the translation inhibition across a broad spectrum of mRNAs. Moreover, we demonstrated that the overexpression of a phosphomimetic eIF4E suppressed the cell cycle arrest induced by Sorafenib, highlighting its significant role in the cellular response to Sorafenib treatment.

In a cellular context where global protein synthesis is inhibited, various mechanisms allow the translation of different subset of mRNAs. This process, known as translational reprogramming, is based on intrinsic features within the mRNAs and factors involved in their recognition. Through this process, cells are able to rapidly respond to environmental stresses, leading them to death or survival. Thus, using massive analysis from a translational study and an enrichment analysis, we have constructed a translational map, illustrating the changes in the translational behaviour of different subset of mRNAs, the features that could determine them and the cellular programs related to Sorafenib-associated translational reprogramming.

In summary, we have demonstrated that the translational machinery has an important role in the anti-tumoral activities of Sorafenib in HCC. Additionally, we propose that this machinery could modulate the cellular response to the treatment according to the translational profile, ultimately determining cells' fate. Finally, we hypothesized that a deeper understanding of the Sorafenib-associated translational reprogramming, as well as the translation profile of different HCC tumours will indeed be very powerful for (i) classifying HCC patients, (ii) predicting their response to the treatment and, (iii) developing new biomarkers.