

New therapeutic target to combat liver cancer discovered

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Spanish researchers at CIC Biogune, the Cooperative Centre for Research into Biosciences and led by Dr. Maria Luz Martinez Chantar, have found a strong relationship between high levels of Hu antigen R (HuR) protein and the malignancy of Hepatocellular Carcinoma, through a novel molecular process in the investigation of this pathology and known as neddylation. The project provides new opportunities for making advances in the quest for personalised therapeutic applications in the treatment for Hepatocarcinoma.

Hepatocellular Carcinoma (HCC) is the cause of most liver cancers, the fifth most frequent cancer worldwide and the third after lung and gastric cancers. HCC is a tumour with a [poor prognosis](#), even in developed countries; its incidence is similar to its death rate, most patients dying within months of diagnosis, despite diagnostic and therapeutic advances. It is a highly heterogeneous tumour and so the scientific community is redoubling its efforts to establish personalised and highly specific therapeutic targets.

Researchers from the Metabolomic Unit at CIC bioGUNE and led by Dr. Martinez, have gone one step further with this type of tumour and have revealed a hitherto unknown molecular mechanism that is involved in the development of CHC, showing that the [malignancy](#) of this illness may be linked to the [overexpression](#) of the HuR protein.

The research work, published in the *Hepatology* journal, and which has obtained a mention in the Cancer section of the prestigious *Nature*

Reviews Gastroenterology & Hepatology journal, showed the relation between high levels of HuR protein and the malignancy of [Hepatocellular Carcinoma](#) by means of a [molecular mechanism](#) – neddylation - totally novel in these kinds of tumour and effectively opens up new opportunities for the future development of potential therapeutic applications for patients with this pathology. The route also proved to have an application in cancer of the colon, given the high correlation between both types of tumour.

"Neddylation is an enzymatic reaction which, in the biological context, avoids the degradation of the protein modified with the NEDD8 molecule. Just as the ubiquitination marks the proteins to order them to be degraded, neddylation marks them in order to stabilise them and, in theory, these proteins are important for the tumour to proliferate and develop", explained Dr Martínez, lead researcher in the project.

In this way, the strategy followed has been to maintain the HuR protein at high levels of expression through its modification by neddylation, thus encouraging its proliferation and the malignancy of the HCC, in such a way that, "when we block the neddylation action or regulate the levels of HuR protein in liver tumours and in in vitro and in vivo hepatoma lines, cell death is induced and tumour regression takes place", stated Dr Martínez.

The options of conventional oncological treatment for Hepatocellular Carcinoma are limited, given that it is a highly chemoresistant tumour, usually arising from a cirrhotic liver. Approximately 40% of the patients diagnosed with HCC are in at an advanced stage and whose short-term prognosis produces a survival rate of 1 year in 29% of cases and of 2 years in 16%. This neoplasia is a unique situation in oncology and, despite its high incidence and poor prognosis, has not had an effective therapeutic option to date. A possible explanation for this is the wide-ranging heterogeneity in the molecular mechanisms involved in the

development of this tumour.

The following step in this long and complex process of research is to find a potential therapeutic application for the formula found. This is why Dr Martínez has come to an agreement with the pharmaceutical Millenium: the Takeda Oncology Company to apply new neddylation inhibitors, marketed by this company and currently being tested in other types of tumours, to in vivo Hepatocellular [Carcinoma](#) models (mice), in order to explore this new therapeutic solution.

"Now that we have discovered that neddylation can play an important role in the development and progress of HCC, the next step is to undertake an in-depth study of possible therapeutic applications", concluded Dr Martínez.

Provided by Elhuyar Fundazioa

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