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CANCER

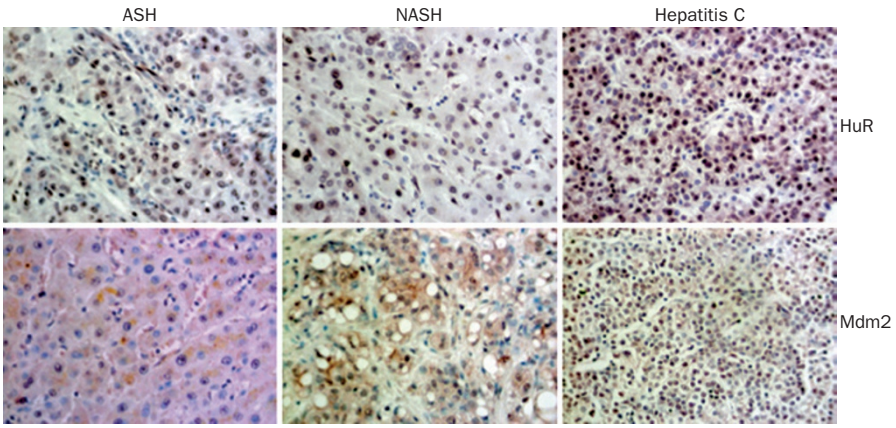
Mdm2-regulated stabilization of HuR by neddylation in HCC and colon cancer—a possible target for therapy

Hu antigen R (HuR) is essential for the differentiation, proliferation and survival of hepatocellular carcinoma (HCC) and colon cancer cells. Neddylation of HuR by Mdm2 protects it from degradation—a process that could be exploited therapeutically.

Maria Martinez-Chantar and colleagues, at the Center for Cooperative Research in Biosciences (CIC bioGUNE), Spain, had previously shown that HuR controls proliferation and differentiation of liver cells. "We thought that the increased levels of HuR in HCC could be a hallmark of malignant transformation," explains Martinez-Chantar. Now the researchers have uncovered a key pathway that controls HuR expression. Neddylation stabilizes proteins by conjugating them to NEDD8. Raised levels of Mdm2, which promotes neddylation, correlated with increased HuR expression in HCC and metastatic colon cancer, suggesting that the Mdm2–NEDD8–HuR pathway could regulate malignant transformation.

The researchers are now exploring this mechanism in HCC of various etiologies (image). They also plan to test a drug that prevents the activation of NEDD8 and could, therefore, disrupt the mechanism that leads to HuR overexpression.

Andy McLarnon



Sections of human hepatocellular carcinoma of different etiologies—alcoholic steatohepatitis (ASH), nonalcoholic steatohepatitis (NASH) and hepatitis C—stained with antibodies to Mdm2 and HuR. Courtesy of M. Martinez-Chantar.

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