Mechanism that induces migration of tumor cells in liver cancer discovered

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Researchers from the Biological clues of the invasive and metastatic phenotype group of the Bellvitge Biomedical Research Institute (IDIBELL) led by Isabel Fabregat have discovered the relationship between the TGFb signalling pathways and CXCR4 in hepatocellular carcinoma (HCC) . The cytokine TGFb is dependent of CXCR4 to induce tumor cell migratory ability.

The results of the study are published in the online edition of the journal *Hepatology*.

Dual function of TGFb

TGFb is a cytokine which in normal conditions and in very early stages of tumorigenesis acts as a tumor suppressor and that inhibits growth and induces cell death. However, as the tumor progresses, the cells acquire mutations or epigenetic alterations that allow them to overcome the suppressive effect of TGFb and respond to this cytokine acquiring a mesenchymal phenotype cells that confers them an increased migratory capacity , very important phenomenon in the tumor metastasis.

"Recently," explained Isabel Fabregat "several research groups are working on finding drugs that inhibit TGFb pathway. But it is important to establish parameters that allow us to predict whether a tumor will respond to TGFb inhibition so as to control tumor progression or whether on the contrary the answer is tumor growth."

TGFb and CXCR4 relationship

In this regard, the study results show that some cell lines of hepatocellular carcinoma (HCC) have overactivated TGFb pathway (by increasing the production of this factor) and always correlate with greater capacity cell migration. An important aspect of the study was the demonstration that this ability depends on another pathway: CXCR4 protein whose expression is dependent on TGFb. The researchers found that inhibition of CXCR4 blocks TGFb induced migration in tumor cells .

The in vitro results were confirmed both in mouse models and in human samples from HCC. "When we analyzed CXCR4 levels in tissues of patients" explained Fabregat "we observed that high levels of this protein correlate always with overactivation of the TGFb pathway and, most interestingly, these patients had a tumor cell phenotype less differentiated, and potentially more aggressive . Moreover, CXCR4 was located preferentially in the areas of tumor invasion."

Future clinical application

"At clinical level," explains the researcher "we believe that patients that reveal an overactivation of TGFb coincident with high expression of CXCR4 in tumor invasion fronts, may be candidates for TGFb inhibitory potential therapies."

This study was conducted in collaboration with Emilio Ramos of liver surgery unit and Teresa Serrano pathology unit of the University Hospital of Bellvitge. "Our group performs a very basic research but through collaboration with clinicians have a more translational aspect because we can corroborate our results not only in animal models but also in human samples and study whether they can have an impact at the

clinical level" said the researcher .

More information: Bertran E., Crosas-Molist E., Sancjo P., Caja L., López-Luque J., Navarro E., Egea G., Lastra R., Serrano T., Ramos E. and Fabregat I. Overactivation of theTGFb pathway confers a mesechymal-like phenotype and CXCR4-dependent migratory properties to liver tumor cells. *Hepatology*. October, 2013

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