CIC bioGUNE
Biozientzietako Ikerkuntza Kooperatiboko Zentroa
Centro de Investigación Cooperativa en Biociencias

NOTA DE PRENSA

Research published in Hepatology

When fat meets inflammation: NK cells are to blame

- *Researchers from the Center for Cooperative Research in Biosciences, CIC bioGUNE (Bizkaia), led by Dr. Naiara Beraza, have found that NK cells play a key role in promoting liver inflammation at early stages of non-alcoholic steatohepatitis (NASH), a critical step previous to cirrhosis and hepatocarcinoma development.*

- *This study, recently published in Hepatology, underlines the therapeutic potential of NK cell inactivation and inhibition of TRAIL expression to counteract the progression of NASH*

(Bilbao, 5th of June, 2012).- Obesity, considered nowadays as epidemic in the Western countries, is strongly linked to liver steatosis. Fat accumulation in the liver (steatosis), can be considered as a benign condition in patients and might be chronified for life. However, steatosis may lead to esteatohepatitis; the chronic inflammation of the liver. This condition has strong detrimental consequences for the liver and is considered as the 'point-of-no-return' of non-alcoholic steatohepatitis (NASH disease) progression.

Inflammation promotes fibrogenesis, cirrhosis and finally hepatocellular carcinoma (HCC). HCC represents the third leading cause of death in cancer patients. All these urge the need to identify the molecular mechanisms leading to chronic inflammation in the context of NASH progression and the identification of new molecular targets for early diagnosis and treatment.

Researchers led by Dr. Naiara Beraza have developed a work in the Metabolomics Unit Lab of Biogune, directed by Dr. Martinez Chantar, that highlights the role of NK cells as the main promoters of inflammation at early stages of NASH development. Moreover, they proved that TRAIL strongly mediates the detrimental role of NK cells.

This work has been published in the journal 'Hepatology', and uncovers a new mechanism by which TRAIL-producing NK cells promote liver inflammation in steatotic livers from Glycin-N-Methyl-Transferase (GNMT) deficient mice. S-adenosylmethyonine (SAMe) is the main methyl donor of the

body and GNMT is the enzyme that catabolizes it. Interestingly, patients with cirrhosis show downregulation of GNMT, which expression is completely absent in HCC.

"*TRAIL is a well-know therapeutic tool to treat several types of tumors in patients as this cytokine, produced by NK cells, kills only transformed or virally infected cells*. *However, our work highlights the detrimental effect of NK cell activation and TRAIL production in steatotic livers as this promotes hepatocyte cell death leading to chronic inflammation; the pathogenic condition that precedes cirrhosis and HCC development. Moreover, our work shows that hepatocytes lacking GNMT, which accumulate lipids, actively express ligands of NK cells leading to the recognition of those hepatocytes as damaged or transformed and thus promoting their death through TRAIL-mediated mechanisms*", explains Dr. Beraza.

- **Complex process**

The pathogenesis of NASH is a complex process involving many cellular events; lipid accumulation, apoptosis, inflammation, fibrogenesis and tumorigenesis among others. An important part of the pathogenesis of NASH involves bacterial overgrowth and permeabilisation of the gut, which exposes the liver to a great amount of endotoxin.

"*Macrophages are classically described as the main cell compartment to counteract endotoxin-mediated liver injury",* explains Dr. Beraza. "*Interestingly, we have found that GNMT deficiency sensitizes the liver to endotoxin-mediated liver damage and that this injury is mediated by TRAIL-expressing NK cells whereas macrophages seem to play a less important role in this process. In this direction, we have proven that inactivation of NK cells and/or impairment of TRAIL production protects the liver against bacterial insult at early stages of fatty liver disease"*.

Overall, the work of the researchers lead by Dr. Beraza defines the essential role of TRAIL-producing NK cells in mediating liver injury when GNMT is absent and points to this cell compartment as potential mediator of chronic inflammation in the onset of NASH progression. Also, data suggest the therapeutic potential of early detection of NK cell activation and further blockade of TRAIL production and activity of these immune cells to counteract liver inflammation in the scenario of liver steatosis. "*We have provide further evidences of the relevance of the innate immune system in the biology of the liver and the important role of NK cells in the pathogenesis of NASH*", concludes Dr. Beraza.

References for the study:

- *Inhibition of NK cells protects the liver against acute injury in the absence of GNMT.*

Gomez-Santos L, Luka Z, Wagner C, Fernandez-Alvarez S, Lu SC, Mato JM, Martinez-Chantar ML, Beraza N. Hepatology. 2012 Mar 5. [Epub ahead of print]