Hepatic Stellate Cells and their Effect on Tumor Growth in Primary Liver Cancer

Denise Rauer

Hepatocellular carcinoma (HCC) is the most common form of liver cancers. Every year, more than 700,000 new cases are diagnosed, which makes it the seventh most common cancer worldwide and the second most common contributor to cancer related death. HCC almost exclusively develops in a background of liver fibrosis. This is caused by underlying chronic liver diseases, such as viral infections, alcohol abuse and non-alcoholic fatty liver disease, which elicits a wound healing response of the liver. This wound healing response is characterized by inflammation, cell death, formation of new blood vessels and the deposition of extracellular matrix proteins (ECM). The extracellular matrix is a non-cellular 3D structure present in unique compositions in all tissues. It provides physical support for cells, is involved in cell adhesion and migration, and influences essential cell behaviors such as cell differentiation and proliferation. The most abundant ECM protein is collagen, which forms a relaxed network. In the liver, extracellular matrix proteins are secreted by hepatic stellate cells. Hepatic stellate cells serve as the main storage of vitamin A in the healthy liver, but they are activated by transforming growth factor beta (TGFβ) to increasingly secrete ECM proteins in a chronically injured liver. Abnormal deposition of collagen influences tumor progression and invasion, as well as tumor cell survival and proliferation. ECM proteins have also been found to be essential components of the stem cell niche and it is possible that deregulated ECM dynamics lead to an over-expression of cancer stem cells and a loss of differentiation of cancer cells. These cancer stem cells are the driving form of tumorigenesis (cancer formation) and metastasis in cancer. There are three hypotheses on how cancer stem cells form: either adult tissue stem cells or progenitor cells have regained the potential for self-renewal and therefore lost regulated cell division, or differentiated (cancer) cells were de-differentiated and obtained the potential for self-renewal along the way.

The aim of this project was to determine how hepatic stellate cells affect tumor growth, migration and de-differentiation of cells in hepatocellular carcinoma, and how this could be inhibited. For this, two different compounds were used. One, cis-4-hydroxy-L-proline, inhibits the synthesis of collagen, whereas the other compound, TC-I 15 inhibits the interaction of collagen with integrin expressed on HCC cells. These integrins form the direct link between extracellular matrix and the cell and are important in passing on signals from the outside, changing the behavior of the cell.

Using *in vitro* methods we could show that the activation of hepatic stellate cells contributes to cancer cell migration, proliferation and de-differentiation to a more stem cell like phenotype. Inhibition of hepatic stellate cells with the collagen synthesis inhibitor LHP decreased migration, proliferation and stem cell marker expression, whereas the integrin signaling inhibitor TC-I 15 was only effective in reducing migration and stem cell marker expression.

Degree Project in Biology, Master of Science (2 years), 2015
Examensarbete i Biologi, 45 hp till masterexamen, Uppsala University, 2015
Biology Education Centre and Department of Medical Cell Biology
Supervisor: Femke Heindryckx