IL-8, GRO and MCP-1 produced by hepatocellular carcinoma microenvironment determine the migratory capacity of human bone marrow-derived mesenchymal stromal cells without affecting tumor aggressiveness

Bayo J.

Real A.

Fiore E.J.

Malvicini M.

Sganga L.

Bolontrade M.

Andriani O.

Bizama C.

Fresno C.

Podhajcer O.

Fernandez E.

Gidekel M.

Mazzolini G.D.

García M.G.

New therapies are needed for advanced hepatocellular carcinoma (HCC) and the use of mesenchymal stromal cells (MSCs) carrying therapeutic genes is a promising strategy. HCC produce cytokines recruiting MSCs to the tumor milieu and modifying its biological properties. Our aim was to study changes generated on human MSCs exposed to conditioned media (CM) derived from human HCC fresh samples and xenografts. All CM shared similar cytokines expression pattern including CXCL1-2-3/GRO, CCL2/MCP- 1 and CXCL8/IL-8 being the latter with the highest concentration. Neutralizing and knockdown experiments of CCL2/MCP-1, CXCL8/IL-8, CXCR1 and CXCR2 reduced in vitro MSC migration of ?20%. Simultaneous CXCR1 and CXCR2 neutralization resulted in 50% of MSC migration inhibition. MSC stimulated with CM (sMSC) from HuH7 or

HC-PT-5 showed a 2-fold increase of migration towards the CM compared with unstimulated MSC (usMSC). Gene expression profile of sMSC showed ~500 genes differentially expressed compared with usMSC, being 46 genes related with cell migration and invasion. sMSC increased fibroblasts and endothelial cells chemotaxis. Finally, sMSC with HuH7 CM and then inoculated in HCC tumor bearing-mice did not modify tumor growth. In this work we characterized factors produced by HCC responsible for the changes in MSC chemotactic capacity with would have an impact on therapeutic use of MSCs for human HCC. Copyright: Bayo et al.

Human hepatocellular carcinoma

Human mesenchymal stromal cells

IL-8

Migration

Tumor microenvironment

chemokine receptor CXCR1

chemokine receptor CXCR2

CXCL1-2-3 protein

cytokine

interleukin 8

monocyte chemotactic protein 1

unclassified drug

animal experiment

animal model

Article

bone marrow cell

cell invasion

cell migration

conditioned medium

controlled study

endothelium cell

fibroblast

gene expression

human

human cell

human tissue

in vitro study

liver cell carcinoma

male

mesenchymal stroma cell

mouse

nonhuman

tumor growth

tumor microenvironment