of ROS. Both JNK1/2 activation and migration/chemotaxis were abolished not only by the specific pharmacological inhibitor SP-600125 but also by pretreating cells with rotenone (ROT) or diphenyl-diphenylene-iodonium (DPI), but not by apocynin, a more selective inhibitor of NADPH-oxidase. This suggests that during hypoxia, ROS-related activation of JNK1/2 and migration were dependent by an early increase in intracellular ROS that were mostly released from mitochondria (inhibited by both ROT and DPI).

**Conclusions.** Migration/chemotaxis of human HSC/MFs induced by hypoxia is a complex, at least biphasic, phenomenon that requires an early activation of JNK isoforms by ROS release by mitochondria and a later, HIF-1α-dependent, autocrine/paracrine release of motogenic VEGF.


**COMMON SIGNALLING EVENTS REGULATE MIGRATION AND CHEMOTAXIS OF HEPATIC STELLATE CELLS AND BONE MARROW-DERIVED MESENCHYMAL STEM CELLS**

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**Background and aims.** Myofibroblast-like cells (MFs), key pro-fibrogenic effectors in chronic liver diseases (CLDs), can originate from activated hepatic stellate cells (HSC/MFs), portal (myo)fibroblasts and, as recently proposed, from bone marrow-derived mesenchymal stem cells (MSC) engrafting chronically injured liver. In this study signalling mechanisms regulating migration and chemotaxis in response to key pro-fibrogenic mediators of human bone marrow-derived human MSC and, of comparison human HSC/MFs, have been investigated and compared to those.

**Methods.** Signal transduction was evaluated by integrating morphological, cell and molecular biology techniques, whereas non-oriented migration and chemotaxis were evaluated by using the wound healing assay and the modified Boyden’s chamber assay, respectively.

**Results.** Human MSC, that after transplant can engraft chronically CCL4-injured livers of immunodeficient NOD/SCID mice and differentiate into hepatic MFs, migrate in response to a number of defined stimuli (including PDGF-BB, bFGF, SDF-1, HGF, MCP-1 and superoxide anion) by eliciting signalling mechanisms that are remarkably overlapping those detected for human HSC/MFs. In synthesis: (1) all the mentioned stimuli led to increased migration/chemotaxis by transiently activating c-Jun-NH2-terminal kinase isoforms 1 and 2 (JNK1/2); (2) activation involved mainly 46 kDa JNK1/2 isoforms and was abolished by either treatment with SP-600125 or (for PDGF-BB) siRNA against JNK1/2; (3) JNK activation and migration/chemotaxis by cytokines were modulated by intracellular generation of reactive oxygen species (ROS) by NADPH-oxidase and then abolished by treatment with diphenyl-phenylene iodonium (DPI); (4) generation of intracellular ROS, even in the absence of cytokines, was sufficient to induce migration of human MSC and HSC/MFs.

**Conclusions.** Common mechanisms and signalling events are involved in the recruitment and migration of activated HSC/MFs and of bone marrow-derived MSC by either pro-fibrogenic cytokines and/or ROS that are generated during fibrogenic development of CLDs.


**HOST GENETICS REGULATES LIVER FIBROSIS PROGRESSION IN PATIENTS WITH CHRONIC HEPATITIS C (CHC)**

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**Background and aim.** Fibrosis progression in liver is the main determinant of disease outcome in CHC, being highly variable and influenced by several variables and host factors. Recently, a Cirrhosis Risk Score (CRS) based on seven host single nucleotide polymorphisms (SNPs) has been proposed as genetic marker for development of cirrhosis in CHC. Aim of our study was to assess the role of such CRS in predicting fibrosis progression in CHC.

**Methods.** CRS was measured in genomic DNA derived from peripheral blood cells using a multiplex PCR/Oligonucleotide Ligation Assay based on the Luminex® 200™ System. We investigated 296 untreated patients with CHC having no or minimal fibrosis in the initial biopsy and followed then for at least 60 months. All patients had a 2° liver biopsy taken during follow-up to define fibrosis progression.

**Results.** During this period 34.8% of the cases showed no progression, 65.2% progression by at least 1 META VIR stage, 40.7% by at least 2 META VIR stage and 15.1% by >2 META VIR stage. Mean CRS (ranging from 0 to 1) was significantly higher (p = 0.001) in patients with fibrosis progression compared to those without progression. Mean CRS score was also significantly higher in patients showing progression by 2–3 META VIR stages (0.63 ± 0.01) vs. those with no or minimal progression (0.54 ± 0.02; p = 0.0001). When patients were categorised by CRS levels (low: <0.50, intermediate: 0.50–0.70, high: >0.70) the relative risk for fibrosis progression increased in parallel with increasing CRS values. This was particularly evident in male patients (not significant