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Molecular subtyping of gastric cancer

Gastric cancer is one of the leading causes of cancer death. Traditionally, it is subclassified into the intestinal and diffuse types based on their morphology (Lauren classification). The recently published WHO (World Health Organization) classification also follows this rule, but with some modifications. Under these classifications, however, the correlations between the tumor phenotypes and their clinical behaviors are not appreciated. Thus, effort has been made to identify molecular markers in gastric cancers, which are more biologically and clinically relevant. Among those, molecular subtyping by reverse transcription-polymerase chain reaction combined with immunohistochemical stain of certain markers seems to have a better correlation with prognosis. Microsatellite instability (MSI) study has also identified a subgroup of gastric cancers with distinct clinicopathological features and relatively favorable prognosis. However, interpretation and extrapolation of data from studies using single or a limited set of gene markers has serious drawbacks, because gastric cancers develop through accumulation of multiple genetic lesions that involve oncogenes, tumor suppressor genes and DNA mismatch repair genes. Moreover, the pathways of carcinogenesis in diffuse and intestinal types are known to be different, even when both are associated with *Helicobacter pylori* infection. Therefore, meaningful molecular subtyping may only be accomplished by global genetic alteration or expression study.

A recent study by **Tay *et al***,[1] using a combination of comparative genomic hybridization and global gene expression profiling analyses, identified unique molecular signatures in gastric cancers, which were associated with distinct clinical profiles and biological behaviors. Based upon their molecular signatures, gastric cancers were categorized into three groups: tumorigenic, reactive, and gastric-like types. Patients with the gastric-like type had significantly longer survival, independent of other parameters such as age of diagnosis, sex, tumor site, Lauren classification, or clinical stage, when compared the other two groups. The prediction by molecular signatures correlated well with the clinical stage in each subtype, especially in early and late tumor stages (stages 1 and IV). This study demonstrates that molecular signatures of gastric cancer may serve as a better indicator for prognosis and be a sound base for more clinically relevant classification.

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Effects of hepatitis C virus core on hepatic stellate cells

Hepatitis C virus (HCV) infects a number of cell types, including hepatocytes, macrophages, lymphocytes and salivary gland cells. Among cells that are involved in liver fibrogenesis, only hepatocytes and lymphocytes are susceptible to HCV. Depending on the target cell type, HCV core and nonstructural proteins exert different biologic actions, which may play a role in the pathogenesis of chronic liver disease. The known receptors for HCV are CD81 and low-density lipoprotein (LDL). Recent evidence indicates that core protein binds to complement 1q (C1q) receptors that are present in target cells (such as lymphocytes) and activates the generation of free radicals, stimulates mitogen-activated protein kinases (MAPK), and activates NF-κB. In contrast, the extensively studied nonstructural protein NS3 mainly regulates cell growth/differentiation and is essential for virus replication.

To date, the mechanisms underlying hepatitis C virus (HCV)-induced fibrosis are largely unknown. It has been hypothesized that the continuous chronic inflammation from the infection of hepatocytes stimulates the neighboring hepatic stellate cells (HSC). Persistent indirect activation of HSC would then lead to the accumulation of extracellular proteins and progressive fibrosis.

A newly published study in *Gastroenterology* by **Bataller *et al***[1] investigated whether different HCV proteins can directly interact with HSC and exert profibrogenic actions. The researchers used two different approaches. The first was incubation of HSC with recombinant core and NS3 proteins to investigate the acute effects of HCV proteins on HSC. The second was assessment of a variety of HSC functions that are associated with fibrogenesis after gene transfer using adenoviral vectors and expression of the HCV proteins.

The study found that quiescent human HSC, HSC activated in culture, and HSC freshly isolated from cirrhotic livers all expressed both CD81 and LDL-receptor mRNA. mRNA expression of C1q was seen in cultured and *in vivo*-activated HSC, but not in quiescent HSC, indicating that the expression of this receptor was activation dependent. Incubation of activated but not quiescent human HSC with

recombinant core and NS3 protein increased intracellular calcium concentration and reactive oxygen species production, as well as stimulated intracellular signaling pathways. Furthermore, expression of core protein increased cell proliferation in Ras/ERK- and PI3K/AKT-dependent manner. In contrast, NS3–NS5 protein expression preferentially induced proinflammatory actions, such as increased chemokine secretion and expression of intercellular cell adhesion molecule type 1 (ICAM-1) through the NF-κB and c-Jun N-terminal kinase pathways. The investigators also found that infection of freshly isolated rat HSC with adenovirus-encoding core protein resulted in accelerated cell activation, as assessed by α-smooth muscle actin expression. In addition, NS3–NS5 proteins increased the secretion of bioactive TGFβ1 and procollagen α1.

The findings in this study suggest that HSC are potential targets for HCV infection and provide evidence that HCV proteins differentially regulate key biologic functions of HSC in liver fibrogenesis. Whether HSC are infected by HCV in patients with chronic liver disease is still largely unknown, but core protein can be easily detected in serum of patients with chronic hepatitis C. 'The results suggest that a direct interaction between HCV and HSC may participate in the pathogenesis of HCV-induced liver fibrosis' commented Ramon Bataller, investigator of this study.

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References

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Companion paper in this issue of *Laboratory Investigation*:

Borkham-Kamphorst E, Herrmann J, Stoll, D *et al*. Dominant-negative soluble PDGF-ß receptor inhibits hepatic stellate cell activation and attenuates liver fibrosis. Lab Invest 2004;84:766–777.