Oxidative stress and inflammation in liver carcinogenesis

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Inflammation is a common response in the human liver. It is involved in chronic hepatitis, cirrhosis, steatosis, ischemia-reperfusion damage, hepatocarcinomas and in the development of metastasis. Reactive oxygen species (ROS) production is part of the inflammatory processes. It is implicated in many physiological and pathological situations and can induce mutations in key cancer genes. Normally, this process is prevented by DNA repair enzymatic systems that maintain sequence fidelity during DNA replication. However, overproduction of free radicals in chronic inflammatory diseases is thought to saturate the ability of the cell to repair DNA damage prior to replications.

Inflammation-induced genetic damage is not unique to the liver, and it might contribute to the development of mutations in several organs. An example is the chronic inflammatory response in ulcerative colitis that ultimately could lead to neoplasia.

There is compelling evidence to suggest that most known environmental risk factors for HCC development lead to generation of reactive oxygen species (ROS). Indeed, hepatitis C virus (HCV), alcohol and hepatitis B virus (HBV) have all been associated with oxidative stress. Direct production of oxidative stress by HCV core protein has been shown. A link between oxidative stress and liver pathogenesis is also supported by the successful use of antioxidant therapy to treat liver injury caused by chronic HCV infection, although it is not currently used for effective therapy. Ethanol metabolism via the alcohol dehydrogenase pathway and microsomal ethanol oxidizing system contribute substantially to the production of acetaldehyde and generation of ROS. HBx via its association with mitochondria has been shown to induce oxidative stress which in turn leads to activation of a series of transcription factors. Moreover, in addition to direct production of ROS by these pathogens, liver infiltration by activated phagocytic cells provides an additional source of ROS production that promotes oxidative stress via interleukin or NO production that can damage proteins, lipids and DNA.

Nuclear MSI was demonstrated first in familial hereditary colorectal cancer (HNPCC) and then in sporadic cancers, primarily digestive tract cancers such as colorectal, gastric and pancreatic cancers.In HCC, although nuclear MSI has been shown in some studies (15,18), there is as yet no direct evidence of alteration of the MMR genes and the biological and the clinicopathological significance of the low-level MSI seen in HCC is unclear. MSI has also been shown to occur in inflammatory tissues such as chronic hepatitis and cirrhosis as well as in ulcerative colitis, chronic pancreatitis and in non digestive inflammatory diseases such as rheumatoid arthritis.

Recently, the role of mitochondria in carcinogenesis has been under numerous investigation, in part because their prominent role in apoptosis, ROS production and other aspects of tumour biology. The mitochondrial genome is particularly susceptible to mutations because of the high level of ROS generation in this organelle, coupled with a relatively low level of DNA repair. Somatic mutations of mitochondrial DNA (mtDNA) have been shown in HCC as was also observed MSI. These findings suggest a potential role for mitochondrial genome instability in the early steps of tumorigenesis.

Ischemia-reperfusion injury can occur in several situations and is a major cause of cell damage during surgery. Cells and tissues subjected to hypoxia by prolonged ischemia become acidic, which protects against hypoxic cell death. Restoration of normal pH following reoxygenation triggers rapid necrosis. Cells from liver and other organs also undergo apoptosis after ischemia reperfusion. In particular, ischemic injury of parenchymal cells results in a loss of mitochondrial respiratory chain activity and consequently ATP depletion. Ischemic preconditioning could protect cirrhotic liver from ischemia-reperfusion injury by diminishing apoptosis through up-regulation of anti-apoptotic proteins such as Bcl-2 and regulating inflammation through overexpression of anti-inflammatory factors as IL-1Ra. The molecular mechanisms could be regulated by nitric oxide production through increased nitric oxide synthase expression .Moreover, this could be a protective mechanism in a series of liver biopsies from patients previously treated for colon cancer with chemotherapeutic agents.

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