Early up-regulation of MMP-2/MMP-9 in a rat model of Non-Alcoholic Fatty Liver Disease (NAFLD)

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Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the Western world characterised by the accumulation of triglycerides in the liver. NAFLD includes a spectrum of histopathological findings, including simple fatty liver, non-alcoholic steatohepatitis (NASH), the more aggressive form of fatty liver disease, fibrosis and ultimately cirrhosis, which may progress to hepatocellular carcinoma. NAFLD has been considered as the hepatic manifestation of metabolic syndrome which is defined as a clustering of numerous age-related metabolic abnormalities, such as obesity, high blood pressure, high blood glucose and dyslipidaemia, that together increase the risk for cardiovascular disease (CVD) and type 2 diabetes. Despite of this evidence, the mechanism behind the pathogenesis and the progression of this pathology is still not fully understood. Our study was aimed to evaluate the effect of hyperlipidemia alone or in combination with hyperglycemia in the onset and development of NAFLD. In our experimental conditions, we observed an increase of cholesterol levels in hyperglycemic/hyperlipidemic rats as compared to hyperglycemic or hyperlipidemic rats. Rats fed with an hyperlipidemic diet also showed an increase in triglycerides levels as compared to controls, which was associated to lipid accumulation in liver. In contrast, in hyperglycemic/hyperlipidemic rats, a progression in hepatic degeneration caused by lipid accumulation was observed although the triglycerides levels were lower as paragoned with hyperlipidemic rats. Although fat infiltration is commonly attributed to triglyceride, free fatty acids and cholesterol, recent evidence has pointed to an emerging role for cholesterol in the progression from steatosis to steatohepatitis (NASH) as it sensitizes hepatocytes to inflammatory cytokines with a consequent free radicals overproduction. Lipid accumulation in liver, which couples with lower anti-oxidative capacities and higher liver damage/inflammatory indices, causes chronic inflammation and extracellular matrix (ECM) remodeling by matrix metalloproteinases (MMPs) finally leading to fibrosis. For liver fibrogenesis, the infiltration of blood-derived macrophages, in addition to the activation of liver-resident Kupffer cells appears essential. In hyperglycemic/hyperlipidemic rats the progression in hepatic degeneration was associated with MMP-2/MMP-9 activation as compared to hyperglycemic or to rat fed with a normocaloric diet. This activation was also observed in liver of hyperlipidemic rats, but not in hyperglycemic rats. It has been demonstrated that hyperglycemia alone is not sufficient to stimulate macrophage proliferation in lesions of atherosclerosis or in isolated macrophages. In contrast, hyperlipidemia in concert with hyperglycemia induces accumulation of proliferating lesion macrophages. Moreover, glucose-oxidized LDL significantly stimulates macrophage proliferation, suggesting that a combination of hyperglycemia and hyperlipidemia may contribute to enhance macrophage proliferation in diabetes. Our results suggest that, in liver, hyperglycemia associated with hyperlipidemia first enhances macrophage activation and proliferation and subsequently oxidative damage. In this process MMP-2/MMP-9 activation is an early event, probably triggered by cholesterol-induced mitochondrial dysfunction, as demonstrated by liver response to a hyperlipidemic diet. In addition, together with the blood markers of both hyperlipidemia and liver dysfunction, we hypothesize the use of MMP-2/MMP-9 as an early biomarker of NAFLD and predictive of metabolic syndrome.

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