Changes in Lipoprotein Binding and Uptake by Hepatocytes During Rat Liver Regeneration

A. Trentalance, G. Bruscalupi, L. Conti DeVirgiliis, S. Leoni, M. T. Mangiantini, L. Rossini, S. Spagnuolo and S. K. Erickson

Received October 11, 1988

The binding and uptake of cholesterol enriched lipoproteins by isolated hepatocytes was decreased at 16 hours after partial hepatectomy, with a tendency to return to control values as the regeneration proceeds. The number of lipoprotein binding sites of total cellular membranes remained similar to control at 16 and 24 hours. The plasma lipoprotein pattern, determined by electrophoretic analysis, showed a lower per cent of very low density lipoproteins (VLDL) and a higher per cent of low density lipoproteins (LDL) at 16 and 24 hours post-partial hepatectomy. At these times, plasma lecithin:cholesterol acyltransferase (LCAT) activity was decreased. It is intriguing to suggest that the regenerating liver could regulate the blood lipoprotein pattern and the uptake of lipoproteins by modulating the surface expression of the receptors.

KEY WORDS: lipoprotein metabolism; regenerating liver; apo E receptor; apo B, E receptor.

INTRODUCTION

During liver regeneration several changes in hepatic lipid metabolism have been observed. These include increased intracellular cholesterol concentration (Leoni et al., 1982), decreased cholesterol synthesis not paralleled by a similar decrease of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase activity (Trentalance et al., 1984), increased dolichol production (Marino et al., 1986), and decreased glycoprotein synthesis (Leoni et al., 1987). As regards lipoprotein metabolism, Narayan et al. (1968) and Van Tol et al. (1987a, b) reported changes...
in serum lipoprotein pattern during regeneration, while Bruscalupi et al. (1987) observed an altered secretion of very low density lipoproteins (VLDL).

These variations could be both the cause and the effect of changes in some of the functional activities of the cell membranes during the proliferative process. Qualitative and quantitative modifications of cell receptors have been observed during liver regeneration at various phases of the cell cycle following partial hepatectomy in the rat. For example, the number of transferrin receptors on isolated hepatocytes is doubled at 2 days of regeneration (Tei et al., 1984), the EGF receptors on plasma membranes decrease at 24 hours (Barghava et al., 1980), the cell surface asialoglycoprotein receptors decrease at 24 and 48 hours (Howard et al., 1982), and the glucocorticoid receptors show a decrease at 6 hours (Loeb and Rosner, 1979).

Rat liver proliferation requires cholesterol for synthesis of new cell membranes and structures, but the primary source of this cholesterol is still unclear. The need for cholesterol could be met either by endogenous synthesis or by exogenous cholesterol derived from plasma lipoproteins.

In quiescent rat liver, two types of lipoprotein receptors have been described (Brown and Goldstein 1983): an apo B, E receptor which recognizes apo B and apo E containing lipoproteins, and an apo E receptor recognizing only apo E containing lipoproteins. The apo B, E or LDL receptor can be regulated by cholesterol availability (Kovanen et al., 1981; Windler et al., 1980) while the chylomicron remnant or E receptor appears not to be (Cooper and Yu, 1978; Arbeeny and Rifici, 1984). The binding of lipoproteins to specific cell surface receptors is followed by internalization of the ligand-receptor complex in endocytic vesicles, sequestration of receptor from ligand, fusion with lysosomes, degradation of the ligand and recycling of the receptor to the cell surface via a still unknown pathway (Brown and Goldstein, 1983). A receptor mediated endocytotic pathway has also been described for chylomicron remnants (Jones et al., 1984). The activity of the receptor could be modulated by changes in its synthesis and degradation or by changing its intracellular traffic (Wileman et al., 1985).

Some information is available about the plasma LDL clearance in the partially hepatectomized rat (Chao et al., 1979; Koelz et al., 1982); however, little is known about the detailed response of lipoprotein receptors during liver regeneration. Therefore, we studied the capacity of hepatocytes to bind and take up lipoproteins at two time points during the first cell cycle after partial hepatectomy: at the onset of S phase (16 hours) and at the onset of mitosis (24 hours). We also examined hepatocytes at the 48 hour time point. Cholesterol-enriched lipoproteins (hcVLDL) from rat serum were used as a ligand. These lipoproteins are recognized by both apo B, E and apo E receptors because of their apo E content (Hui and Innerarity, 1983). In addition, the total number of binding sites was measured in cell membrane preparations. The serum lipoprotein distribution and lecithin:cholesterol acyl transferase (LCAT) activity were also measured to check the influence of eventually changed receptor function on lipoprotein metabolism.