EDITORIAL

Surgical Stress and Tumor Behavior: Impact of Ischemia-Reperfusion and Hepatic Resection on Tumor Progression

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In this issue of *Liver Transplantation*, the article from the University of Hong Kong by Man et al.[1] introduces potentially important concepts related to the mechanisms involved in tumor progression associated to surgical stress, specifically hepatic ischemia-reperfusion and major hepatic resection. This study attempted to determine the molecular mechanisms involved in enhanced tumor progression exhibited in the remnant liver following ischemia-reperfusion and major hepatic resection. To study the effects of ischemia-reperfusion and major hepatic resection, the expression of mitogenic/cell cycle–associated molecules (Rho-associated coil-containing protein kinase [ROCK], Cdc42, proliferating cell nuclear antigen [PCNA]), adhesion-associated molecule (FAK), and angiogenic factors (early growth response-1 [Egr-1]/VEGF) in tumor tissues and cells were evaluated. The data generated on the expression of these markers have provided evidence which indicates that hepatic surgical stress, such as ischemia-reperfusion and major hepatic resection, stimulate tumor cell invasion, migration, and metastasis. However, it is clear that further studies are needed to address the precise significance of the expression of these molecules in relation to tumor progression. The mechanisms of tumor progression are complex. Therefore, the results of the experiments reported in this study must be regarded as preliminary. Nevertheless, the findings in this study may help to elucidate the mechanisms involved and the nature of tumor progression; and, in addition, the findings suggest future therapeutic approaches.

TWO INCONSISTENT ASPECTS OF ISCHEMIA-REPERFUSION OF ORGANS

Much attention has been devoted to understanding the mechanisms of postischemic liver damage. In this context, oxidative stress-mediated cell/tissue damage must be considered. Oxidative stress during ischemia-reperfusion was first studied in the early 1980s.[2-4] Since then, xanthine oxidase-/neutrophil-induced oxidative stress has been extensively studied as a major cause of organ damage after reperfusion.[4,5] In the 1990s, more attention has been paid to harmful cellular reactive oxygen species (ROS), and their origin. Cellular ROS of nonphagocytic cells are believed to originate in mitochondria[6,7] and/or membrane-associated Nox (nicotineamide adenine dinucleotide phosphate [NADPH]-oxidases) oxidase.[8,9] It has been established that redox-sensitive molecules play major roles in various pathophysiological processes,[10-13] with the result that the concept of oxidative stress to cells and organs has undergone dramatic changes. In general, ROS from: 1) NADPH oxidase (neutrophils/phagocytes); 2) the mitochondrial respiratory complex[14]; and 3) Nox oxidase (nonphagocytic cells) can explain the mediation of oxidative stress during ischemia and after reperfusion. ROS from the first 2 of these sources are considered to be important in mediating cell damage (apoptosis or

Abbreviations: ROS, reactive oxygen species.

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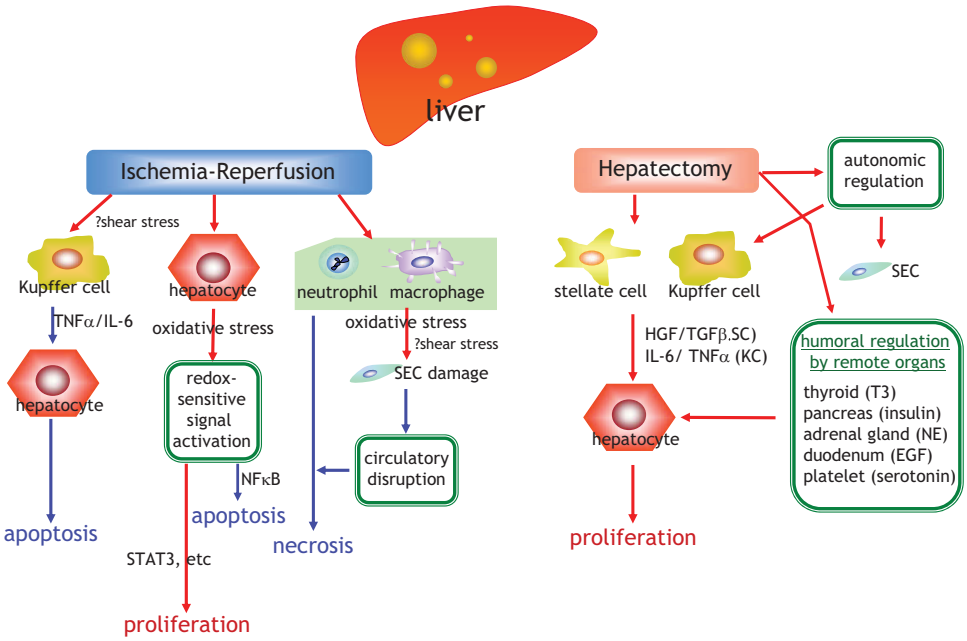

Figure 1. Schematic scheme illustrating the effects of hepatic ischemia-reperfusion and major hepatic resection on liver cell injury and proliferation.

necrosis), and ROS from the third source may be responsible for redox-dependent signal transduction that leads to apoptosis and proliferation (Fig. 1).

Cellular ROS activate some redox-dependent signals and may regulate certain cell functions.[15] Rac1 small guanosine triphosphatase (GTPase) and the gp91 component of NADPH oxidase/Nox are essential for activation of oxidase[10]; the former is definitely responsible for the regulation of oxidase activity.[16,17] Rac1, if bound to guanosine triphosphate, activates Nox and mediates oxidative stress in cells; this process may lead to malignant transformation in some cells.[8,9,18,19]

In general, tumor cells possess antiapoptotic/antioxidant properties, which appear to be unique characteristics that facilitate their survival.[20-22] Potentially, tumor cells are more likely to survive ischemia-reperfusion–induced damage than normal liver cells (Fig. 2). When angiogenic EGR-1/VEGF and adhesion-associated FAK are upregulated in tumor tissue, and the microvascular environment is disrupted in peritumor liver tissue, as reported in this study by Man et al.,[1] further invasion of the tumor and metastasizing of the tumor to remote organs will be facilitated.

HEPATIC RESECTION AND TUMOR PROGRESSION

Liver regeneration after hepatic resection has also been extensively studied. In particular, the mechanisms underlying the initiation, maintenance, and termination of liver regeneration have been investigated in vivo using animal models.[23-26]

After hepatic resection, various molecules are induced and/or secreted that promote regeneration by various cells and organs, including the liver. In the liver, gut-derived factors, such as lipopolysaccharide, are upregulated after hepatic resection and are delivered to the liver via the portal venous system. These factors activate hepatic nonparenchymal cells (including Kupffer cells and stellate cells). Kupffer cells and stellate cells secrete interleukin-6/tumor necrosis factor-alpha and hepatocyte growth factor/tumor growth factor-beta, respectively, in response to hepatic resection. With regard to extrahepatic organs, the thyroid, pancreas, adrenal gland, and duodenum secrete triiodothronine, insulin, norepinephrine, and epidermal growth factor, respectively, and, in addition, platelets secrete serotonin[23] (Fig. 1). It appears that the autonomic nervous system must be involved in liver regeneration though the exact mechanism is still unclear. There are many reports describing an inhibitory effect of vagotomy on liver regeneration.[27,28] In this context it may be relevant that acetylcholine (Ach) receptors have been reported on hepatocytes, Kupffer cells, and hepatic sinusoidal cells.[29-31]

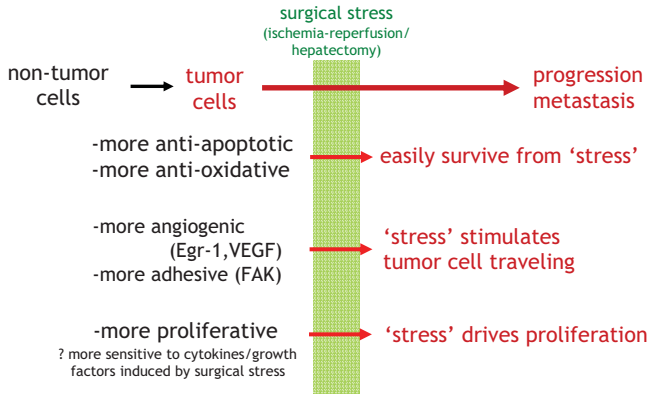

Figure 2. Putative mechanisms of tumor cell survival, progression, and metastasis after surgical stress to the liver (ischemia-reperfusion, major resection).

Tumor progression may be influenced by humoral

regulation, which may be mediated by hormones, growth factors, and cytokines. Some tumors, such as those arising in lung, breast, prostate, liver, colon, and rectum appear to be subject to humoral regulation of their growth. Hence these tumors may be suitable targets for cancer therapy with antihumoral regimens.[32-40] Thus, proinflammatory cytokines induced by ischemia-reperfusion and hormones released from extrahepatic organs after hepatic resection may promote progression of liver tumors and metastasizing of these tumors.

In conclusion, ischemia-reperfusion tends to disrupt normal liver tissue, including the microvasculature, and to create an environment that may promote tumor progression. Antiapoptotic/antioxidative tumor cells will be induced by direct oxidative mitogenic stimuli as well as by indirect proinflammatory cytokine stimuli. In addition, hepatic resection will induce tumor cells to become more aggressive by promoting production of cytokines by nonparenchymal liver cells and/or secretion of hormones by extrahepatic tissues (Figs. 1 and 2). The study by Man et al.[1] may lead to an improved understanding of the steps of tumor progression in various surgical settings.

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REFERENCES

1. Man K, Ng KT, Lo CM, Ho JW, Sun BS, Sun CK, et al. Ischemia-reperfusion of small liver remnant promotes liver tumor growth and metastases—activation of cell invasion and migration pathways. Liver Transpl 2007;13: 1669-1677.
2. Granger DN, Rutili G, McCord JM. Superoxide radicals in feline intestinal ischemia. Gastroenterology 1981;81:22-29.
3. Chambers DE, Parks DA, Patterson G, Roy R, McCord JM, Yoshida S, et al. Xanthine oxidase as a source of free radical damage in myocardial ischemia. J Mol Cell Cardiol 1985;17:145-152.
4. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med 1985;312:159-163.
5. Jaeschke H. Xanthine oxidase-induced oxidant stress during hepatic ischemia-reperfusion: are we coming full circle after 20 years? Hepatology 2002;36:761-63.
6. Taylor DE, Ghio AJ, Piantadosi CA. Reactive oxygen species produced by liver mitochondria of rats in sepsis. Arch Biochem Biophys 1995;316:70-76.
7. Littauer A, de Groot H. Release of reactive oxygen by hepatocytes on reoxygenation: three phases and role of mitochondria. Am J Physiol 1992;262(Pt 1):G1015–G1020.
8. Lambeth JD. NOX enzymes and the biology of reactive oxygen. Nat Rev Immunol 2004;4:181-189.
9. Suh YA, Arnold RS, Lassegue B, Shi J, Xu X, Sorescu D, et al. Cell transformation by the superoxide-generating oxidase Mox1. Nature 1999;401:79-82.
10. Irani K, Xia Y, Zweier JL, Sollott SJ, Der CJ, Fearon ER, et al. Mitogenic signaling mediated by oxidants in Ras-transformed fibroblasts. Science 1997;275:1649-1652.
11. Terui K, Haga S, Enosawa S, Ohnuma N, Ozaki M. Hypoxia/re-oxygenation-induced, redox-dependent activation of STAT1 (signal transducer and activator of transcription 1) confers resistance to apoptotic cell death via hsp70 induction. Biochem J 2004;380(Pt 1):203-209.
12. Ozaki M, Haga S, Irani K, Amemiya H, Suzuki S. Overexpression of redox factor-1 protects against postischemic liver injury by reducing oxidative stress and NF-kappa B activity. Transplant Proc 2002;34:2640-2642.
13. Haga S, Terui K, Zhang HQ, Enosawa S, Ogawa W, Inoue H, et al. Stat3 protects against Fas-induced liver injury by redox-dependent and -independent mechanisms. J Clin Invest 2003;112:989-998.
14. McLennan HR, Degli Esposti M. The contribution of mitochondrial respiratory complexes to the production of reactive oxygen species. J Bioenerg Biomembr 2000;32:153-162.
15. Sundaresan M, Yu ZX, Ferrans VJ, Irani K, Finkel T. Requirement for generation of H2O2 for platelet-derived growth factor signal transduction. Science 1995;270:296-299.
16. Ozaki M, Deshpande SS, Angkeow P, Bellan J, Lowenstein CJ, Dinauer MC, et al. Inhibition of the Rac1 GTPase protects against nonlethal ischemia/reperfusion-induced necrosis and apoptosis in vivo. FASEB J 2000;14:418-429.
17. Ozaki M, Deshpande SS, Angkeow P, Suzuki S, Irani K. Rac1 regulates stress-induced, redox-dependent heat shock factor activation. J Biol Chem 2000;275:35377-35383.
18. Lesurtel M, Graf R, Aleil B, Walther DJ, Tian Y, Jochum W, et al. Platelet-derived serotonin mediates liver regeneration. Science 2006;312:104-107.
19. Sorescu D, Weiss D, Lasseque B, Clempus RE, Szocs K, Sorescu GP, et al. Superoxide production and expression of nox family proteins in human atherosclerosis. Circulation 2002;105:1429-1435.
20. Monks NR, Biswas DK, Pardee AB. Blocking anti-apoptosis as a strategy for cancer chemotherapy: NF-kappaB as a target. J Cell Biochem 2004;92:646-650.
21. Kren L, Brazdil J, Hermanova M, Goncharuk VN, Kallakury BV, Kaur P, Ross JS. Prognostic significance of anti-apoptosis proteins survivin and bcl-2 in non-small cell lung carcinomas: a clinicopathologic study of 102 cases. Appl Immunohistochem Mol Morphol 2004;12:44-49.
22. Chiou SK, Jones MK, Tarnawski AS. Survivin - an anti-apoptosis protein: its biological roles and implications for cancer and beyond. Med Sci Monit 2003;9:PI25-PI29.
23. Taub R. Liver regeneration: from myth to mechanism. Nat Rev Mol Cell Biol 2004;5:836-847.
24. Diehl AM, Rai RM. Liver regeneration 3: regulation of signal transduction during liver regeneration. FASEB J 1996;10:215-227.
25. Diehl AM, Rai R. Review: regulation of liver regeneration by pro-inflammatory cytokines. J Gastroenterol Hepatol 1996;11:466-470.
26. Brenner DA. Signal transduction during liver regeneration. J Gastroenterol Hepatol 1998;13(Suppl):S93–S95.
27. Sakaguchi T, Liu L. Hepatic branch vagotomy can block liver regeneration enhanced by ursodesoxycholic acid in 66% hepatectomized rats. Auton Neurosci 2002;99:54-57.
28. Ohtake M, Sakaguchi T, Yoshida K, Muto T. Hepatic branch vagotomy can suppress liver regeneration in partially hepatectomized rats. HPB Surg 1993;6:277-286.
29. Vatamaniuk MZ, Horyn OV, Vatamaniuk OK, Doliba NM. Acetylcholine affects rat liver metabolism via type 3 muscarinic receptors in hepatocytes. Life Sci 2003;72:1871-1882.
30. de Jonge WJ, van der Zanden EP, The FO, Bijlsma MF, van Westerloo DJ, Bennink RJ, et al. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. Nat Immunol 2005;6:844-851.
31. Serobyan N, Schraufstatter IU, Strongin A, Khaldoyanidi

SK. Nicotinic acetylcholine receptor-mediated stimulation of endothelial cells results in the arrest of haematopoietic progenitor cells on endothelium. Br J Haematol 2005;129: 257-265.

32. Rossmanith W, Schulte-Hermann R. Biology of transforming growth factor beta in hepatocarcinogenesis. Microsc Res Tech 2001;52:430-436.
33. Budhu A, Wang XW. The role of cytokines in hepatocellular carcinoma. J Leukoc Biol 2006;80:1197-1213.
34. Durai R, Yang W, Gupta S, Seifalian AM, Winslet MC. The role of the insulin-like growth factor system in colorectal cancer: review of current knowledge. Int J Colorectal Dis 2005;20:203-220.
35. Ahmed SM, Salgia R. Epidermal growth factor receptor mutations and susceptibility to targeted therapy in lung cancer. Respirology 2006;11:687-692.
36. Sledge GW. VEGF-targeting therapy for breast cancer. J Mammary Gland Biol Neoplasia 2005;10:319-323.
37. van Horssen R, Ten Hagen TL, Eggermont AM. TNF-alpha in cancer treatment: molecular insights, antitumor effects, and clinical utility. Oncologist 2006;11:397-408.
38. Jaouen G, Top S, Vessieres A, Leclercq G, McGlinchey MJ. The first organometallic selective estrogen receptor modulators (SERMs) and their relevance to breast cancer. Curr Med Chem 2004;11:2505-2517.
39. Carruba G. Estrogens and mechanisms of prostate cancer progression. Ann NY Acad Sci 2006;1089:201-217.
40. Peant B, Diallo JS, Lessard L, Delvoye N, Le Page C, Saad F, Mes-Masson AM. Regulation of I{kappa}B kinase {varepsilon} expression by the androgen receptor and the nuclear factor-{kappa}B transcription factor in prostate cancer. Mol Cancer Res 2007;5:87-94.