HEPATOLOGY *Elsewhere*

JORGE J. GUMUCIO, EDITOR
Department of Internal Medicine
Division of Gastroenterology (111D)
VA Medical Center/University of Michigan
Ann Arbor, Michigan 48105

Starting in January 1994, the new editor of *Elsewhere* will be Dr. Jake Liang. We warmly welcome him. I have been editor of this section for the last three years. It has been an interesting experience. This section allows the editor to select the articles and reviewers and thus to imprint a very personal character on the material published. In my case, I have been very fortunate to work on these endeavors with a group of individuals who provided their time, effort and article assessment to this group enterprise. In particular, I would like to recognize and thank Drs. Rebecca Van Dyke, Richard Moseley, Michael Lucey, Kenneth Lown, Paul Watkins, Peter Traber and Michael McDonnell at the University of Michigan for their continuous support and guidance. Also, I have had the invaluable collaboration of Diana Drescher and, lately, Brenda Vibbart, who put together each issue, arranged permissions and contacted reviewers. Finally, I would like to thank Dr. Paul Berk and Michelle Britton for their support, as well as Kerry Carlyle at Mosby.

JORGE J. GUMUCIO, M.D.

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HEPATOCYTE APOPTOSIS: IS TRANSFORMING GROWTH FACTOR-B1 THE KISS OF DEATH?

Oberhammer FA, Pavelka M, Sharma S, Tietenbacher R, Purchio AF, Bursch W, Schulte-Hermann R. Induction of apoptosis in cultured hepatocytes and in regressing liver by transforming growth factor β1. Proc Natl Acad Sci USA 1992;89:5408-5412.

ABSTRACT

In previous studies hepatocytes undergoing cell death by apoptosis but not normal hepatocytes in rat liver showed immunostaining for transforming growth factor β1 (TGF-β1). Staining was much stronger with antibodies recognizing the pro-region of TGF-β1 than the mature peptide itself. Therefore we investigated the ability of both forms of TGF-β1 to induce apoptosis in primary cultures of rat hepatocytes. Mature TGF-β1 induced rounding up of the cells and fragmentation into multiple vesicles. As revealed by the DNA-specific stain H33258, the chromatin of these cells condensed and segregated into masses at the nuclear membrane; this was obviously followed by fragmentation of the nucleus. Ultrastructurally the cytoplasm was well preserved, as demonstrated by the presence of intact cell organelles. These features strongly suggest the occurrence of apoptosis. Quantification of nuclei with condensed chromatin revealed that mature TGF-β1 was 30-fold more effective than the TGF-β1 latency-associated protein complex. Finally, we administered TGF-β1 *in vivo*using an experimental model in which regression of rat liver was initiated by a short preceding treatment with the hepatomitogen cyproterone acetate. Two doses of TGF-β1, each 1 nM/kg, augmented the incidence of apoptotic hepatocytes 5-fold. Equimolar doses of TGF-β1 latency-associated protein complex were ineffective. These studies suggest that TGF-β1 is involved in the initiation of apoptosis in the liver and that the mature form of TGF-β1 is the active principle.

COMMENTS

Recent studies on the mechanisms of liver growth have emphasized the notion that hepatic growth regulation depends on a balance between stimulatory and suppressor factors (1). As remarkable as the growth of the liver after partial hepatectomy is, equally amazing is the cessation of growth when optimal liver mass is regained. Yet the mechanisms that determine growth termination have not been as intensively studied as the events that trigger regeneration. The beginning and end of the process are, however, likely linked and represent, respectively, disruption of the equilibrium between liver mass and body mass and restoration of the normal equilibrium. Various factors and events have been suggested as signals for growth termination; they may involve, among others, transforming growth factor (TGF)β1 activation, release of other inhibitors such as activin, reexpression of tumor-suppressor genes, attenuation of proliferative stimuli, activation of transcription factors that regulate liver-specific genes, reestablishment of cell/cell contact between hepatocytes and the deposition of laminin after cells undergo one round of replication. Any one of these mechanisms could conceivably be put in motion by an alert signaling system that somehow senses the functional performance of the liver in relationship to the body's needs. It is relatively easy to imagine what this system needs to do when hepatic tissue deficit occurs, but what is to be done when the liver acquires excess functional mass? When this happens, to put it crudely, word goes out that cells must be killed or forced to commit suicide so that order—that is, the appropriate liver mass/body mass ratio—can be restored.

Increases in liver mass above normal in the absence of a compensatory response to tissue deficit can be brought about by drugs and other agents that stimulate liver metabolism, by nutritional shifts, by orthotopic transplantation of a large liver and by heterotopic transplantation. In all of these cases, the excess mass does not persist when the cause of the increase is removed or in the months after transplantation. It is most likely that the mechanism of tissue regression in these conditions involves the selective death of hepatocytes by apoptosis. This type of cell death, in contrast to necrosis, occurs in individual, nonclustered cells. It shows characteristic patterns of chromatin condensation morphologically and formation of DNA ladders detected on gel electrophoresis analysis indicative of DNA cleavage at internucleosomal sites (2). Most important, apoptosis is considered a "programmed" process—that is, it may require gene activation for its triggering. Apoptosis may be controlled by hormones, growth factors, cytokines, calcium and other agents, and in B lymphocytes and other cells it is strongly inhibited by the expression of the bcl-2 gene, which was originally cloned as a chromosomal translocation breakpoint in follicular B-cell lymphomas (3).