154f Proteomic Analysis Reveals Several Hepatic Acute Responses to Injury

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Early after severe injury and trauma, the liver undergoes an acute response characterized by the synthesis of acute phase proteins (APPs) to restore homeostasis. Recent studies have also demonstrated that dysregulated antioxidant functions and apoptosis coupled with hepatic regeneration occur in the liver as a consequence of injury. Thus, many responses which are potentially interrelated to each other occur following severe injury. In this study, we used a proteomics approach to investigate more broadly the effects of severe injury in a small animal model of thermal injury. More specifically, we hypothesized that a change in the liver proteome reflects the diversity of the hepatic responses to injury.

The protein expression profiles of livers from rats 24 h after administration of 40% total body surface area cutaneous burn (n=4) or sham-burn (n=4) under general anesthesia were obtained by two-dimensional gel separation followed by ProteomIQTM blue staining. Image analysis by PDQuest software revealed that 34 different protein spots, representing 30 different proteins identified by matrix-assisted laser desorption/ionization mass spectrometry, were differentially regulated in response to burn injury ($p < 0.05$). Not surprisingly, eleven APPs including the rat major acute phase reactants T-kininogen I and a1-acid glycoprotein were found to be upregulated (positive APPs) and two APPs, albumin and apoliprotein A-1 were downregulated (negative APPs) following burn injury. Many positive APPs such as a1-acid glycoprotein, hemopexin, contrapsin-like protease inhibitor, and fibrinogen could only be detected in the livers from the burn injury group. The change in the positive APP a-antitrypsin was further confirmed using western blot.

Six antioxidant enzymes, among them catalase and superoxide dismutase, were coordinately downregualted, probably due to hypoxia resulting from reduced cardiac output during the early stage after burn injury. To our knowledge, the decreased expression of two enzymes NG, NG-dimethylarginine dimethylaminohydrolase (nitric oxide synthase inhibitor) and biliverdin reductase B (generating potent antioxidant bilirubin from biliverdin) was, for the first time, observed under pathological conditions and may provide an explanation for the impaired protection against reactive oxygen species. Five of seven regulated metabolic enzymes were found to have a lower expression, including ornithine carbamoyltransferase and malate dehydrogenase. This change is consistent with the previous reported hypometabolic phenomena observed at 24 h after burn injury.

An increased expression of the anti-apoptotic chaperone protein glucose-regulated protein 94 (GRP 94) along with GRP 78 could be a positive response to counteract the burn-induced apoptosis and oxidative stress. Finally, the expression levels of two protein synthesis-related proteins elongation factor 2 and protein disulfide isomerase A6 were significantly increased likely to meet the need of the large amount of APP production and hepatic regeneration. All together, the proteomic data offer a fairly comprehensive overview of altered molecular events in liver and provide the basis for identifying new avenues and therapeutic targets for improving clinical outcomes following severe burn injury and trauma.