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Extending into glioma invasion: a role for albumin?

Glioblastoma multiforme (GBM) is the most common and deadly glioma with survival typically less than a year, regardless of therapy. There are vigorous ongoing efforts to understand pathologic mechanisms related to this aggressive biological behavior. The characteristic ‘ring-enhancing’ appearance of GBM on neuroimaging is owing to a peripheral zone of active cell proliferation and angiogenesis. The neovascularization forms a leaky barrier to fluid and serum proteins, including albumin, leading to the peritumoral edema and mass effect characteristic of these tumors. A pathogenetic role of transudates composed of plasma proteins in glioma invasion is an intriguing possibility. In this issue, **Beckner *et al***¹ (p. 1103) provide evidence that albumin may associate with pseudopodia (cell processes at the leading edge of migrating cells) to promote glioma invasion. The authors previously developed a novel method that permits analysis of the 2D electrophoretic proteome of tumor cell pseudopodia protruding through filters with 3 μ m pores.² One finding of that study was that exogenously added bovine serum albumin (BSA) was highly expressed among a group of proteins forming a ‘pseudopodial proteome’. In the current study, the association of albumin with pseudopodia of U87 and LN229 glioma cells was studied. Tumor cells treated with hepatocyte growth factor (HGF) in the presence of 0.1% BSA showed enhanced cell migration. Lysates prepared from pseudopodia of migrating cells contained increased BSA compared to control unemigrated cells when analyzed by immunoblot. The BSA levels of pseudopodia of migrating cells reached or exceeded those observed for known pseudopodial proteins. Fluorescein (F)-labeled BSA, which was added to the cell cultures, colocalized with HGF to the tips of pseudopodial plasma membranes. These results suggest a mechanism in which the leaky blood–brain barrier of malignant gliomas may allow serum albumin to alter the microenvironment in a manner that promotes brain tumor infiltration. Further studies in this area may lead to a better understanding of the role of plasma proteins in glioma biology.

References

- 1 Beckner ME, Zhang Z, Agostino NR, *et al*. Albumin marks pseudopodia of astrocytoma cells responding to hepatocyte growth factor or serum. *Lab Invest* 2006;86:1103–1114.

- 2 Beckner ME, Chen X, An J, *et al*. Proteomic characterization of harvested pseudopodia with differential gel electrophoresis and specific antibodies. *Lab Invest* 2005;85:316–327.

Take a deep breath: endotoxin-induced lung inflammation

The Toll-like receptors (TLR) constitute the interface by which the innate immune system detects microbial products. The ensuing responses depend on an intricate network of adaptor proteins that activate distinct signaling pathways. The identification of which adaptor proteins are necessary in a specific inflammatory process opens the door to which signaling pathway is mobilized. In this issue, **Togbe *et al***¹ (p. 1126) use a battery of gene knock-out mouse strains to examine the downstream molecular events following TLR4 engagement by endotoxin, which induces acute inflammation in the airway. They found that endotoxin triggers a cascade of signaling events that is dependent on MyD88 and TIRAP in a nonredundant fashion, but not on TRIF. They further show that IL-1R1, IL-18R and caspase 1, which also use MyD88, were not involved. This implies that endotoxin-induced acute lung injury depends on early NF- κ B and MAP kinase activation, which are induced by MyD88 and TIRAP, but not on the interferon α pathway that depends on TRIF recruitment. These data add a significant piece to the ever-expanding puzzle of signaling events occurring in response to recognition of microbial product by TLRs in the clinically relevant context of inhaled endotoxins.

Reference

- 1 Togbe D, Aurore G, Noulin N, *et al*. Non-redundant roles of TIRAP and MyD88 in airway response to endotoxin, independent of TRIF, IL-1 and IL-18 pathways. *Lab Invest* 2006;86:1126–1135.

Impaired regeneration of the steatotic liver in the *ob/ob* mouse

The *ob/ob* mouse is deficient in leptin, a peptide that regulates energy homeostasis, lipid metabolism, and immunological function. Identification and elucidation of the roles of leptin in intermediary metabolism and adipose tissue homeostasis has been of enormous value. One of the curiosities about this mouse is impaired liver regeneration after partial hepatectomy. At face value, liver regeneration is one of the most time-honored features of

mammalian regenerative biology: after extirpation of liver tissue, a brisk regenerative response ensues, and liver mass is restored within weeks in small animals, and several months in larger animals (and humans). Apparent failure of successful regeneration in the *ob/ob* mouse is an enigma, and suggests a role for leptin in regenerative biology over-and-above its role in metabolism. A critical first step in testing this possibility is to determine whether leptin replacement in the *ob/ob* mouse restores the liver capacity for regeneration. The results of such experimentation are reported herein, performed by **Leclercq *et al***¹ (p. 1161). Because of the high mortality of the traditional 70% partial hepatectomy in *ob/ob* mice, a modified 55% partial hepatectomy was performed (which carried a 6% mortality). Compared to lean, wild-type mice, liver regeneration in *ob/ob* mice after this modified partial hepatectomy was severely delayed, and at 7 days after the procedure, regeneration was incomplete. Contrary to expectations, exogenous administration of leptin at the time of surgery and for the week after surgery did not rescue the defective liver regeneration. Likewise, correction of the metabolic syndrome, obesity, and hepatic steatosis by prolonged administration of leptin or food restriction did not restore liver regeneration. In exploring whether activation of the hepatic progenitor compartment, oval cells, played a role in the partial hepatic regenerative response, the authors were able to demonstrate that there were increased oval cells in the naive livers of *ob/ob* mice. However, oval cells decreased in

number following partial hepatectomy, and did not play a role in the blunted regenerative response. These results raise a remarkable panoply of questions, pertinent to the pathophysiology of obesity, and potentially also relevant to the important clinical entity of non-alcoholic steatohepatitis (NASH). Most obvious is, what is the cause of the impaired hepatic regenerative response in leptin-deficient mice, if not absence of leptin? Second, does impaired hepatocellular regeneration and the absence of an oval cell response in the metabolic syndrome of obesity have relevance to the risk of developing cirrhosis in the steatotic liver? Third, does an impaired response of the steatotic *ob/ob* liver to loss of hepatocellular mass have clinical relevance for such human conditions as alcoholic liver disease, NASH, and drug-induced hepatic steatosis? Fourth, is it clinically relevant to be concerned about correcting the hepatic regenerative response in steatotic states? Absent mechanistic answers to the first question, we are left to speculate about how impaired health of the ancient seat of the soul (the liver) may affect the overall health of the obese individual. We look forward to such deliberations.

Reference

- 1 Leclercq IA, Vansteenberghe M, Lebrun V, *et al*. Defective hepatic regeneration after partial hepatectomy in leptin-deficient mice is not rescued by exogenous leptin. *Lab Invest* 2006;86:1161–1171.