ImmunoTools *special* Award 2013

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Measuring the release of auto-antigens following major liver surgery

Background

Major liver surgery often is the only treatment option for patients with a benign of malignant liver tumor. During liver resection, it is routinely required to temporarily halt the hepatic blood supply to prevent excessive blood loss. This period of ischemia however predisposes the liver to a massive inflammatory response that is initiated by the reintroduction of blood (i.e., reperfusion). These harmful consequences of vascular inflow occlusion (VIO) are collectively known as ischemia/reperfusion (IR) injury and in most severe cases culminate in liver failure. In spite of the severe consequences, few therapeutic options are currently available to treat hepatic IR injury in patients. A fresh look on the pathophysiology of hepatic IR injury is therefore required to develop novel intervention modalities. In that respect, it has recently been postulated that hepatic IR injury is triggered by endogenous self-antigens, known as damage-associated molecular patterns (DAMPs), which are leaked into the circulation by liver cells unable to cope with the ischemic insult. These DAMPs are regular components of healthy cells (e.g., histones, mitochondrial DNA) that become potent activators of the immune system when released extracellularly.

Although the pivotal role of DAMPs has been demonstrated in various animal studies, clinical data on this subject is scarce. The aim of this research therefore is to monitor the release of DAMPs in patients following major liver surgery.

Methods

In this currently-recruiting, observational study (NCT#01700660), the release of DAMPs is measured in patients following a major liver resection (≥3 Couinaud segments). Liver resection is performed either with VIO (IR group) or without VIO (control group). Because the decision to apply VIO is made during surgery, based on the course of the operation, patients will be allocated to the control or IR group peroperatively. Patient recruitment will continues until both study arms comprise a minimum of 15 subjects.

During surgery, blood samples are drawn from a central line immediately after induction of general anesthesia (baseline) and 1hr and 6hrs after reperfusion (IR group) or removal of the resection specimen (control group). Plasma and serum samples are assayed for the following DAMPs: mitochondrial DNA (qRT-PCR), HMGB-1 (ELISA), and histones (ELISA). The extent of DAMP release will next be correlated to the extent of hepatocellular injury (i.e., serum alanine aminotransferase and liver fatty acid-binding protein) and decrease in liver function (i.e., serum bilirubin and prothrombin time).

ImmunoTools

The most important role of DAMPs is to notify the host of tissue injury. To do so, DAMPs bind directly to immune receptors on the surface of various leukocytes of the innate immune system (e.g., macrophages, dendritic cells). In response, these leukocytes release an array of chemokines and cytokines that amplify the inflammatory response by chemoattracting and activating cytotoxic leukocytes such as neutrophils, inflammatory monocytes, and T-cells. Accordingly, these leukocytes are responsible for the majority of liver damage during hepatic IR injury.

Considering that cytokine production is a direct consequence of DAMP signaling, it would be of great value correlate DAMP release to the production of cytokines and chemokines during hepatic I/R injury. To that end, we would like to use the ImmunoTools ELISA sets specified below to measure the plasma levels of IL-4, IL-6, IL-8, IL-12p40, and TNFa in patients that have undergone majot liver surgery.

ImmunoTools *special* AWARD for **Rowan van Golen** includes 17 reagents

recombinant human cytokines rh G-CSF, rh GM-CSF, rh GRO-alpha, rh IL-17A, rh IL-22, IP-10 /CXCL10, rh MCP1 / CCL2, rh MCP2 / CCL8, rh MIP-1α/ CCL3, rh RANTES / CCL5, rh TNFα, rh TRAIL / CD253,

human IL-4 ELISA-set, human IL-6 ELISA-set, human IL-8 ELISA-set, human IL-12p40 ELISA-set, human TNF alpha ELISA-set,

DETAILS