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INSIDE LAB INVEST

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Wound repair: more collagen breakdown in males than in females

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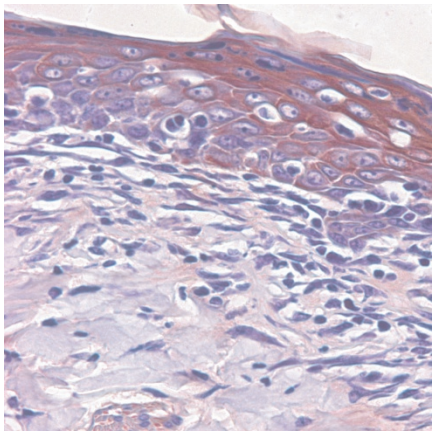

The healing of skin wounds is significantly delayed in the elderly, with aged men being at greater risk of developing chronic venous ulcers than their female counterparts. Studies have suggested that the sex hormones play a major role in the wound-healing process, with estrogens enhancing and accelerating healing while androgens appear to inhibit and retard recovery from injury. Despite this, androgens have been shown to stimulate matrix synthesis, which is an important part of the wound-repair process.

This apparent contradiction has now been investigated by Gilliver and colleagues by examining the effect of castration and synthetic androgen treatment on matrix synthesis and protease activity in rat skin wounds. Wound levels of collagen I and fibronectin were increased in castrated rats compared with controls; this despite the fact that androgens increase type I collagen in rat fibroblasts. However, investigations concerning levels of matrix metalloproteinase (MMP) and activity revealed that, although the fibrillar collagenases MMP-1 and MMP-13 were initially increased in response to wounding, their levels were significantly decreased at later timepoints in castrated wounds. Furthermore, both MMP-2 and MMP-9 expression and activity were significantly reduced in castrated rat wounds.

These results support the contention that increased collagen deposition in androgen-deprived wounds results from reduced matrix degradation rather than enhanced matrix synthesis. These data support a critical role for proteolysis as a contributing factor in impaired wound healing, especially in elderly men. This may be of particular clinical relevance in the increasing burden of chronic wound healing in our aging population.

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The fatty liver as a pro-inflammatory environment

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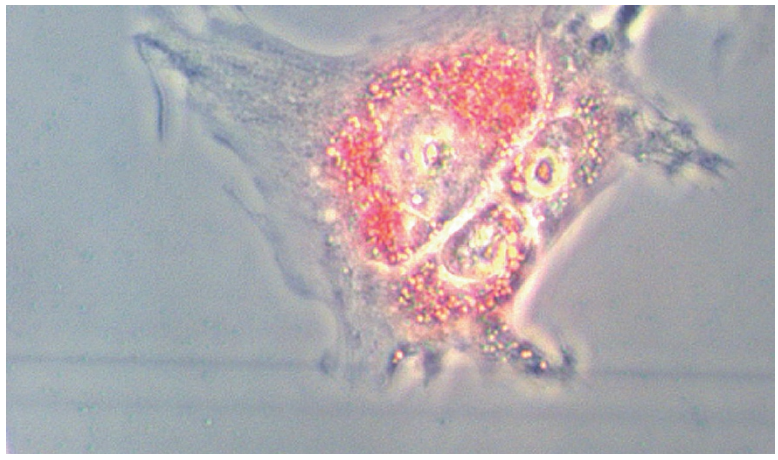
A key question to understanding the pathobiology of fatty liver disease associated with obesity and a 'metabolic syndrome' featuring insulin resistance is the cause of hepatic inflammation. Although the inciting events for so-called non-alcoholic steatohepatitis are poorly understood, attention must be given to the innate immune system within the liver. This consists of large resident populations of macrophages and various types of T lymphocytes, natural killer cells, and dendritic cells. Natural killer T (NKT) cells are particularly enriched in the liver, as opposed to being present at only trace levels in blood and other organs. The T-cell receptor (TCR) repertoire of NKT cells is limited to lipid antigens, with most NKT cells expressing a semi-invariant TCR (iNKT cells). Nearly all iNKT cells recognize the glycolipid α-galactosyl ceramide (αGalCer), presented in CD1d.

This intriguing biology of a restricted response to lipid antigens makes iNKT cells of considerable interest for the liver, especially since hepatocytes exhibit strong expression of CD1d on their surface membranes. CD1d traffics through intracellular endolysosomal compartments en route to the cell surface, and is presumably loaded with its lipid antigen αGalCer while in the endoplasmic reticulum (ER). The stage is thus set to examine the effect of hepatic steatosis and ensuant ER oxidative stress on both CD1d expression and hepatic NKT function.

In this issue, Yang *et al* demonstrate that cell-surface expression of CD1d is reduced in fatty hepatocytes and present evidence that an ER-stress-related mechanism is involved. Downregulation of CD1d expression in fatty hepatocytes is accompanied by functional consequences, including impaired activation of NKT cell hybridomas, reduced numbers of hepatic CD1d-αGalCer-reactive NKT cells, and Th-1 polarization of hepatic cytokine production (TNF-α and IFN-γ). These data suggest that ER stress may trigger self-reenforcing mechanisms that contribute to both hepatic steatosis and innate immune dysfunction, generating a pro-inflammatory bias in local immune responses. These findings complement and extend earlier evidence for NKT cell defects in fatty livers and have potential implications for the pathogenesis of diseases associated with



hepatic steatosis, including obesity, diabetes, and the metabolic syndrome.

Midkine, a new mediator of inflammation in diabetic nephropathy

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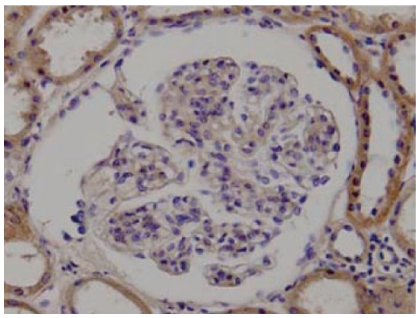

Midkine (MK) is a heparin-binding growth factor that has been implicated in a variety of biological processes, including cancer and inflammatory diseases. A recent study showed that MK deficiency protected mice from streptozotocin (STZ)-induced diabetic nephropathy. In cultured primary mesangial cells, MK accelerated glucose mediated signaling, including the production of TGF-β_1. In the present study by Kosugi *et al*, the same group now shows that MK is a key factor in the tubulo-interstitial inflammation that mediates pathogenesis in diabetic nephropathy. MK deficiency reduced numerous markers of tubulo-interstitial damage in mice treated with STZ, including expression of monocyte chemoattractant protein (MCP)-1 and subsequent macrophage infiltration.

In vitro studies showed a causal relationship among high glucose exposure, MK production, and MCP-1 secretion. Importantly, the authors showed MK expression in the renal glomeruli, tubular epithelium, and interstitium of patients with diabetic nephropathy. It has been recognized that MCP-1 expression and its consequent macrophage infiltrate were predictive of severe renal injury. This study identifies MK as a key mediator in this pathway, which should offer new venues for intervention and prevention of glucose-mediated inflammation.

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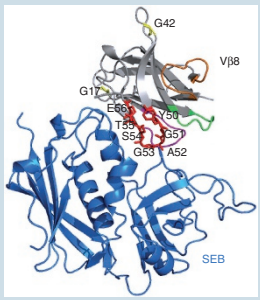
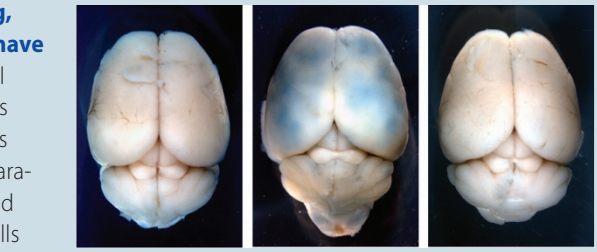
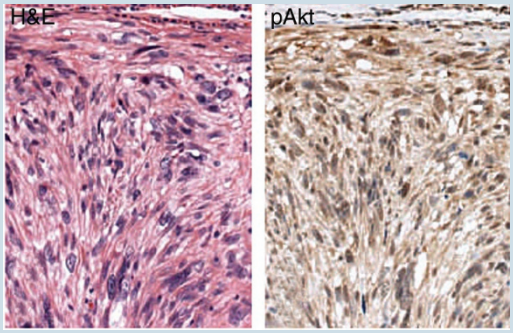
Shocking development Toxic shock syndrome is caused by staphylococcal enterotoxin B (SEB). Using directed evolution and yeast display, a soluble T-cell receptor (TCR) fragment that binds SEB with high affinity was engineered. Soluble TCR fragments inhibited SEB-mediated T-cell activation and neutralized the lethal activity of SEB *in vivo*. This is a potential treatment and, perhaps, broadly applicable approach to drug development.
Nature Medicine 2007;13:725–729; doi:10.1038/nm1584



An eye toward immune regulation Interleukin (IL)-17-expressing T_H17 T cells are involved in immune-mediated disease. A recent study evaluated T_H17 cells in uveitis and scleritis. Numbers of peripheral T_H17 cells and IL-17 expression were elevated in patients with active disease and in mice with experimental autoimmune uveoretinitis (EAU). EAU was ameliorated by IL-17 neutralization. These data suggest that T_H17/IL-17 antagonism may be a means of treating uveitis and also highlight the complexities of immune regulation.
Nature Medicine 2007; 13:711–718; doi:10.1038/nm1585

Despite global warming, carbon monoxide may have health benefits! Cerebral malaria (CM), which causes more than 1 million deaths annually, is triggered by parasite-induced hemolysis and free heme release. Host cells exposed to heme increase expression of heme oxygenase-1 (HO-1), which breaks down free heme. In a recent study, CM did not occur in Balb/c mice, which strongly upregulated HO-1 during infection, but did occur in ~80% of mice in which HO-1 was inhibited. Conversely, C57BL/6 mice, which induced HO-1 poorly, uniformly developed CM, but less than 10% developed CM when HO-1 was induced pharmacologically. Carbon monoxide, which binds hemoglobin and prevents heme release, also prevented CM. These data provide potential means of preventing CM and suggest that HO-1 induction variation may confer CM susceptibility.
Nature Medicine 2007;13:703–710; doi:10.1038/nm1586





Bad AKTors A group of pathologists recently used microarrays to show that PI3 kinase (PI3K), AKT, and other components of the PI3K-AKT survival pathway are activated in leiomyosarcomas; nearly 80% were immunohistochemically positive for active AKT. To test whether inactivation of PTEN, which inhibits PI3K-AKT signaling, could trigger leiomyosarcomagenesis, mice with smooth muscle–specific *Pten* knockout were created. These developed smooth muscle cell hyperplasia and abdominal leiomyosarcomas. The AKT effector mTOR was upregulated in leiomyosarcomas but not in benign hyperplasia, and pharmacological mTOR inhibition slowed tumor growth. These data suggest that additional events other than PTEN loss are necessary for progression to leiomyosarcoma and may open new therapeutic approaches.
Nature Medicine 2007;13:748–753; doi:10.1038/nm1560