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Hepatic DNA deposition drives drug-induced liver injury and inflammation

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Drug-induced liver injury (DILI) is an important medical problem worldwide, but with limited therapeutic options. During DILI, hepatic necrosis with concomitant release of intracellular content induces liver inflammation and injury. Amongst these intracellular molecules, DNA has been widely shown to trigger inflammatory and autoimmune diseases. However, the mechanisms involved in DNA release and accumulation into the necrotic liver, and the impact of its recognition by the immune system remains elusive. Here we showed that treatment with different hepatotoxic compounds (acetaminophen and thioacetamide) caused DNA release to the hepatocyte cytoplasm, which occurred in parallel with cell death *in vitro*. Administration of these toxins *in vivo* caused massive DNA deposition within liver necrotic areas, together with a widespread intravascular DNA coating. Using confocal intravital microscopy, we showed that liver injury led to a directional migration of neutrophils to DNA-rich areas, where they exhibited an active patrolling behavior. Interestingly, DNA deposits were negative for neutrophil elastase, suggesting it was not derived from neutrophil extracellular traps. DNA removal by intravenous DNASE1 injection or blockage of TLR9-mediated sensing significantly reduced systemic inflammation, liver neutrophil recruitment and hepatotoxicity. Flow cytometry of liver leukocytes revealed that emigrated neutrophils upregulated TLR9 expression in the plasma membrane during liver necrosis, and these cells sensed and reacted to extracellular DNA by up-regulating NF-κB and CXCR2 expression. Likewise, adoptive transfer of wild-type neutrophils to TLR9-/- mice reversed the hepatoprotective phenotype otherwise observed in TLR9 absence. We concluded that hepatic DNA accumulation is a novel feature of DILI pathogenesis and blockage of DNA recognition by the innate immune system may consist in a promising therapeutic venue for DILI.

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Risk assessment of the fungal metabolite, Fumonisin B1 in humans: A hepatotoxic and –carcinogenic contaminant in corn

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When considering the carcinogenic properties of the fumonisins, a fungal metabolite produced by *Fusarium verticillioides* in corn different hepatotoxic and -carciogenic scenarios need to be considered. Although the fumonisins lack direct DNA reactivity in various *in vitro* genotoxicity assays, cancer development in the liver closely mimics genotoxic carcinogens and occur via a chronic toxic hepatitis. *In vitro* genotoxicity assays indicated that FB1 induced clastogenic effects, presumably via the disruption of cellular oxidative pathways. Major emphasis on fumonisin-induced hepato-carcinogenesis is placed on the cancer promoting properties which, with respect to risk assessment, is considered to follow a typical threshold approach. However, the fumonisins cause a wide spectrum of cellular effects and disrupt a several signal transduction pathways associated with cell proliferation and apoptosisin the liver which may act separately, additively and/or synergistically with different dietary factors and/or carcinogenic principles. As these so-called epigenetic and synergistic events complicate a strict threshold type of approach aspects regarding specific risk models to be utilized for the fumonisins in humans will be critically assessed.

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