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INFECTION

Activation of Hedgehog pathway promotes fibrogenesis and vascular remodelling in human schistosomiasis

Infection with *Schistosoma mansoni* can cause portal fibrosis and portal hypertension, but the exact mechanisms that underlie these processes are unclear. New research published in *Liver International* now indicates that schistosome egg antigens (SEAs) stimulate macrophages in the liver to produce Hedgehog (Hh) ligands that, in turn, promote fibrogenesis and vascular remodelling in human schistosomiasis.

"The parasite eggs lodge in tiny blood vessels within the liver. Over time, egg-derived factors trigger immune responses that can lead to progressive liver scarring and blood flow abnormalities, which can be life-threatening," explains author Anna Mae Diehl. The researchers investigated whether the Hh pathway regulates this disease course in humans.

Immunohistochemical analysis of liver biopsy samples from 28 patients with varying levels of schistosomiasis

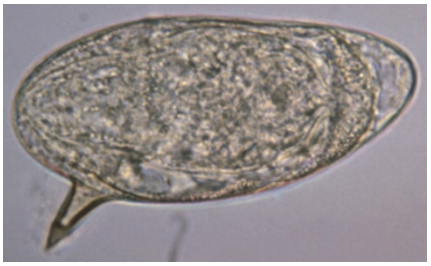

Image courtesy of CDC

fibrosis revealed that, in contrast with healthy individuals, patients infected with *S. mansoni* expressed high levels of Hh pathway ligands (SHH and IHH) and targets (PTCH1 and GLI2) in macrophages. Furthermore, the severity of liver scarring and vascular abnormalities matched the level of Hh ligand production and pathway activation.

In vitro studies confirmed that SEAs stimulated macrophages to express Hh ligands, which led to alternative activation of macrophages (M2 phenotype), and promotion of fibrogenesis and the development of vascular abnormalities; these processes could be blocked *in vitro* by treatment with Hh inhibitors.

Looking to the future, the authors are already investigating whether Hh pathway inhibition can reverse fibrosis and vascular remodelling in experimental models. They say: "If we indeed demonstrate that … pharmacological inhibitors of Hh pathway could constrain, or even ameliorate, pathological tissue remodelling, this could benefit patients with fibrovascular complications of hepatic schistosomiasis and may be a nonsurgical intervention."

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Original article Pereira, T. A. Macrophage-derived Hedgehog ligands promotes fibrogenic and angiogenic responses in human schistosomiasis mansoni. *Liver Int.* doi:10.1111/liv.12016