Role of the IL-33/ST2 activation pathway in the development of the hepatic fibrosis induced by *Schistosoma mansoni* granulomas in mice

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Schistosoma mansoni eggs are often retained in the host's organs, mainly the liver, which induce the release of innate cytokines, and thereby contribute to the induction of Type-2 immune responses and granuloma formation. *Schistosoma*-induced granulomas not only restrain cytotoxic egg antigens, but also may lead to fibrosis. Although the IL-33/ST2 activation pathway has been shown to participate in models of inflammatory diseases and chemically induced fibrosis, its role in liver fibrosis in schistosomiasis remains unknown. Wild-type (WT) and IL-33 receptor knockout ($ST2^{-/-}$) BALB/c mice were infected with *S. mansoni*. The liver was used to assess granuloma formation and fibrosis. Histopathological analysis and immunohistochemistry for α-smooth muscle actin (α-SMA) were performed to evaluate inflammation and myofibroblast activation, respectively. Fibrosis was evaluated based on hydroxyproline content and collagen gene expression (*ColI, ColIII* and *Col VI*). Fibre organisation was analysed using Masson's trichrome, Picrosirius, and Gomori's ammoniacal silver staining. The data showed that the egg count and hydroxyproline content in the livers of infected mice were similar between different strains. However, extracellular matrix in granulomas from $ST2^{-/-}$ mice was loose and disorganised. During acute schistosomiasis, $ST2^{-/-}$ mice showed decreased expression of *α-SMA*, indicating lower myofibroblast differentiation; however, the mRNA expression of *vimentin* was higher in $ST2^{-/-}$ than in WT infected mice. Although *Col I* expression was increased in both strains, mRNA levels of *Col III* and *VI* and the presence of reticular fibres in granulomas were lower in $ST2^{-/-}$ mice. Therefore, IL-33/ST2 signalling is essential for myofibroblast activation during *S. mansoni* infection. Disruptions result in inappropriate granuloma organisation, partly due to the lower content of collagen types III and VI and reduced reticular fibre formation.

Keywords: *Schistosoma mansoni* infection, liver fibrosis, granuloma, collagen activation, reticular fibres, IL-33/ST2 activation pathway