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Osteopontin: a new player in regulating hepatic ductular reaction and hepatic progenitor cell responses during chronic liver injury

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In recent years, an increasing number of reports have shown the involvement of osteopontin (OPN), a pleiotropic cytokine and an important component of the extracellular matrix (ECM), in the pathogenesis of liver injury and the development of fibrosis.[12] OPN is also frequently overexpressed in hepatocellular carcinoma (HCC), where it modulates HCC growth, invasion and metastasis,[2] and in cholangiocarcinoma, where its expression bears prognostic significance. Previous studies[3] have shown that in injured livers OPN is expressed by hepatic stellate cells (HSC) and upregulates collagen I production. Interestingly, in HSC, OPN expression appears to be downstream of SOX9, a Hedgehog- and Notch-controlled transcription factor that is expressed also in biliary cells and hepatic progenitor cells (HPC)/hepatocytes committed to the biliary fate.[4–6] In this issue of *Gut*, two papers investigate the role of OPN in HPC-driven ductular reaction (DR) in relation to the progression of liver fibrosis.[78]

DR, a histological lesion present in most chronic liver diseases, is a dynamic, multicellular complex characterised by the presence of ‘reactive’ ductular epithelial cells, arranged in irregular strings along the margins of the portal tract in close contact with mesenchymal, inflammatory and endothelial cells. Reactive ductular cells acquire novel functions including the secretion of cytokines, chemokines, growth factors and angiogenic factors, enabling them to establish intense paracrine communications with a variety of cells and to orchestrate the repair of the epithelial wound. DR cells acquire also limited mesenchymal properties that endow them with increased motility and the ability to detach from the epithelial layer. Ductular reaction is driven by the activation of the HPC compartment, a compensatory mechanism of liver repair triggered when proliferative ability of mature hepatocytes or cholangiocytes is compromised[9] such as in most human liver diseases.

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Several studies indicate that the extent of DR closely correlates with the amount of collagen deposition, ultimately leading to tissue scarring and lobular architectural distortion.[10] This process depends upon a complex interplay between paracrine signals released by HPC/DR able to activate a fibrogenic programme and promote changes in the ECM.[10] In this context, OPN is a molecule of particular interest, being able to act as an ECM protein directing cell motility and adhesion as well as a cytokine regulating T-lymphocyte and macrophage responses in inflammation.[1] The two studies published in this issue of *Gut* further expand the role of OPN in HPC activation and DR as a critical mechanism responsible for the progression of liver fibrosis across different experimental models of chronic liver injury.[78]

In particular, the two papers show that OPN produced by HPC contributes to DR by stimulating HPC proliferation and migration, while concomitantly it reduces hepatocyte proliferative capability.[78] Furthermore, they demonstrate that OPN plays an important role in regulating the interaction between HPC and HSC, and in modulating myofibroblast activation and collagen production synergistically with transforming growth factor-β (TGF-β).[78] In turn, TGF-β influences OPN signalling in cultured HPC cell lines.[7] In line with these observations, OPN deficiency or OPN inactivation with OPN-specific aptamers or neutralising antibodies reduces DR, HPC response and fibrogenesis in different experimental models of chronic liver disease (figure 1). Altogether, the two studies nicely complement each other in addressing the importance of OPN in driving HPC expansion and DR.

Although these two reports make an important contribution in elucidating the complex role of OPN in chronic liver diseases, a number of issues remain unsolved. Two forms of OPN are known: an intracellular form (iOPN) involved in regulating cell migration and inflammatory signalling in lymphocytes and dendritic cells, and a secreted form (sOPN) with cytokine and ECM protein properties.[1] The data of Coombes *et al*[8] using OPN-specific aptamers or neutralising antibodies suggest that sOPN has an important role in fibrogenesis. However, further studies are required to fully understand the role of iOPN. The second question that remains lingering is the cellular origin of OPN in liver diseases. Several cells, including hepatocytes, macrophages, cholangiocytes, T-lymphocytes, natural killer T-cells and HSC, contribute to hepatic OPN production,[2] making it difficult to dissect the specific contribution of each cell type to the overall effects. Using immunohistochemistry and morphometry, Wang and coworkers[7] studied the relative contribution of different hepatic cell populations to OPN production in control and thioacetamide (TAA)-treated mice. They show that, while in control mice hepatocytes and cholangiocytes are the main sources of OPN in injured livers, HPC and HSC appreciably contribute to OPN production.[7] However, even in these conditions more than 90% of OPN staining involves hepatocytes.[7] Further studies using animals with selective inactivation of the *OPN* gene in specific hepatic cell populations are required to better elucidate the origin of OPN that drives DR. Finally, a third question involves the difficulty in discriminating among the pleiotropic actions of OPN. It remains unclear to what extent the capacity of OPN to stimulate HPC response and fibrogenesis depends on its activity as a pro-inflammatory cytokine or by its ability to stimulate HSC activation and collagen production.[23] Dissecting the pro-inflammatory

activity of OPN is important in characterising its role in DR as this response implies a significant contribution of inflammatory cells.[9]

Altogether, the results presented by Wang *et al*[7] and Coombes *et al*[8] along with previous data suggest OPN as a possible therapeutic target for liver fibrosis. Furthermore, the results of the inhibition studies in these manuscripts represent a further strong piece of evidence that the 'Holy Grail' of chronic liver disease progression lies buried in the crosstalk between epithelial and mesenchymal/inflammatory cells,[10][11] and whoever follows just one lead will never find it.

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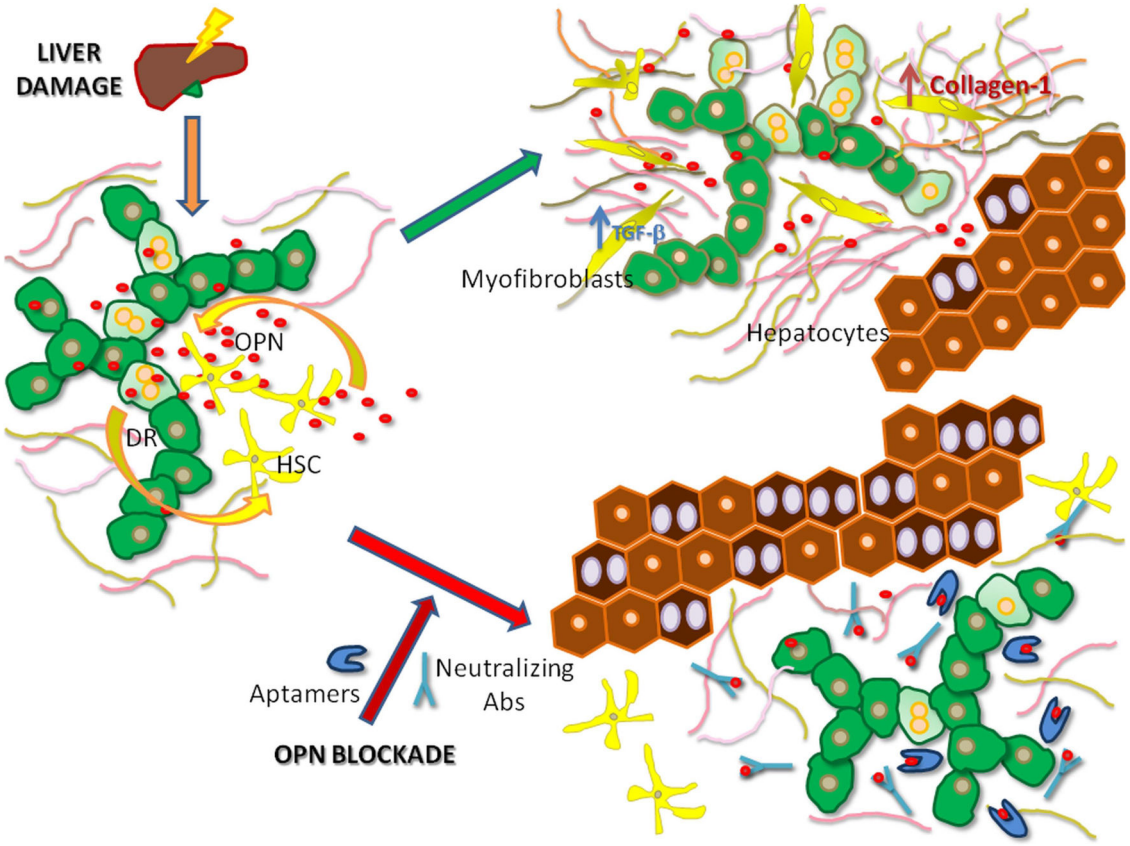

Figure 1.

Osteopontin (OPN) is an important regulator of the interaction between ductular reaction (DR) cells and hepatic stellate cells (HSC): it may represent a molecular target for therapeutic interference. Following chronic liver injury, OPN produced by DR cells, including hepatic progenitor cell (HPC), stimulates HSC recruitment and activation into myofibroblasts, where it induces transforming growth factor-β signalling and increased collagen deposition; on the parenchymal side, OPN simulates HPC proliferation and migration, while concomitantly downregulating hepatocyte proliferation (green arrow). OPN blockade by specific aptamers or neutralising antibodies halts the crosstalk between DR cells and HSC, thereby hampering myofibroblast activation and reducing matrix production, while turning up hepatocyte proliferation (red arrow).