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Cirrhosis, von Willebrand Factor (vWF) and the Low Incidence of Metastatic Malignancy in Injured Liver

Hasarlı Karaciğerde Siroz, Von Willebrand Faktör (vWF) ve Düşük İnsidanslı Metastatik Malignite

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The work by Yilmaz et al. [1] in *The Eurasian Journal of Medicine* provides clinical evidence for the correlation between increased levels of von Willebrand factor (vWF) and the stage of cirrhosis. The authors observed significantly higher vWF antigen levels in cirrhotic patients compared to a control group, and also an increase with the increasing stages of cirrhosis according to the Child-Pugh score. These results indicate that vWF is produced as a reliable marker of endothelial dysfunction during hepatocellular failure in cirrhosis. Besides, in light of the results of Yilmaz et al. [1] another perspective regarding the low incidence of metastatic malignancy in cirrhotic patients and the potential role of vWF should be pointed out. The blood coagulation protein vWF is mainly secreted by endothelial cells into the subendothelial space and into the plasma, serving as an adhesive link between platelets and the vascular wall. It is known that liver sinusoidal endothelial cells are a prominent source of vWF, not only during haemostatic processes but also in tissue injury. Interestingly, many studies have implicated vWF as a key factor in resistance to metastasis. Terraube et al. [2] demonstrated that vWF plays a protective role against metastatic spread in a vWF-deficient mouse model. It appears that vWF can induce apoptosis of metastatic cells early after their arrest in the vasculature of the target organ. In the same line, Mochizuki et al. [3] found that aggressive cancer cells producing high levels of metalloproteinase ADAM28 are able to avoid vWF-induced apoptosis at micrometastatic sites. ADAM28 binds and degrades vWF, thus favouring the survival of metastatic cells in the target organ.

Metastases of colorectal cancers into injured livers, such as liver cirrhosis, are very infrequent. A recent meta-analysis by Augustin et al. [4] including 7 retrospective studies with a total of more than 4,000 patients showed a significant lower incidence of hepatic metastasis of primary colorectal cancer in the population with chronic liver injury. Although the contribution of other mechanisms in cirrhotic livers cannot be discarded–such as sensitization of cancer cells to Fas-mediated apoptosis by activated Kupffer cells or liver extracellular matrix remodelling and fibrosis–the probable anti-metastatic action of vWF suggests an attractive therapeutic strategy for hepatic metastatic disease in colorectal cancer. In this regard, an approach could raise the levels of vWF by a pharmacological intervention. We previously reported that intravenous administration of desmopressin (dDAVP), a synthetic peptide analogue of vasopressin, can inhibit the formation of metastasis in the experimental models of breast and colon cancer at clinically relevant doses [5]. The compound induces an abrupt release of vWF from endothelial cells through a specific agonistic action on V2 vasopressin receptors, with resulting haemostatic and antitumor effects. The perioperative and early postoperative period is an attractive window of opportunity to take advantage from this knowledge, aiming to combat the metastatic disease [5]. Since the release of vWF may favour the collapse of incipient metastatic foci, further evaluation of the dDAVP as well as other vasopressin analogues in clinical trials is warranted.

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