Portal-systemic Collaterals and Angiogenesis

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Chronic liver diseases or liver injuries commonly result in increased intrahepatic resistance and subsequently lead to portal hypertension. Portal hypertension is associated with 2 distinct pathophysiologic features: hyperdynamic circulation and formation of portal-systemic collaterals.[1] Hyperdynamic circulation is characterized by increased splanchnic blood flow, cardiac output, decreased systemic arterial blood pressure and low peripheral vascular resistance. The formation of portal-systemic collaterals is manifested by the appearance of esophageal or gastric varices. These collateral vessels will shunt part of the portal blood flow bypassing the liver to systemic circulation. Shunting the portal blood flow through collateral vessels is an attempt to decompress the highly pressurized portal system. However, the formation of collateral vessels may lead to serious clinical events such as variceal rupture and bleeding, which carries a high risk of morbidity and mortality. Therefore, revealing the mechanism underlying the development of portal-systemic collaterals is an important issue and has been extensively investigated in recent years.

Both non-cirrhotic and cirrhotic models of portal hypertension have been extensively used in studies of the pathophysiology of portal hypertension and portal-systemic collaterals. The partial portal vein ligation (PVL) model has been widely used in the study of portal hypertension due to its reproducibility and being easy to perform. In the PVL model, portal-systemic collaterals can be detected as early as 2 days and develop fully after 1 week. The degree of shunting is very high and may approach 100%. The main drawback of the PVL model is that, contrary to the usual clinical situation, portal hypertension will gradually decrease after the establishment of portal-systemic collaterals. Thus, cirrhotic models of portal hypertension are closer to the real pathophysiology of cirrhotic patients in clinical practice. Cirrhotic models of portal hypertension are commonly induced by common bile duct ligation (CBDL), or liver toxins such as carbon tetrachloride and thioacetamide. In these models, the degrees of portal-systemic shunting developed gradually by time of liver injury and varied widely from less than 30% up to 60%, and were generally lower than in the PVL model.

Progress in understanding the pathophysiology and pharmacology of portal-systemic collaterals relies greatly on the technique of *in situ* perfusion of collateral circulation developed by Mosca et al in 1992.[2] They showed in PVL rats that several vasoactive substances produce direct vasodilatory or vasoconstrictory effects on collaterals. In addition, different types of receptors including α-receptor, β-receptor and 5-hydroxytryptamine receptors were expressed on the endothelium of collaterals vessels. Subsequently, using this technique, it has been demonstrated that arginine vasopressin and endothelin-1 (ET-1), as well as nitric oxide (NO) and prostaglandins, are able to modulate the vascular activity of portal-systemic collaterals.[3,4] Also, the non-vasoactive agents, somatostatin and octreotide, which are now widely used in the treatment of variceal bleeding, enhanced the vasoconstrictive effect of ET-1 on collateral vascular beds.[5] In 2004, this technique was modified and transferred successfully to CBDL rats to study the portal-systemic collaterals of cirrhotic rats. Similarly, as in PVL rats, there are many vasoactive factors involved in the regulation of collateral blood flow in cirrhotic rats even though there was less shunting. These results indicate that the portal-systemic collaterals are not simply a route to bypass the liver, but they are dynamic vascular beds that respond to many regulators.

The underlying mechanisms of the development of portal-systemic collaterals remain undetermined. On the one hand, it has been proposed that development of portal-systemic collaterals is a process of NO-mediated dilatation of pre-existing vessels.[1] NO is the main

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endothelial vasodilator. Chronic administration of L-NAME, a non-selective inhibitor of NO synthase, significantly decreased the degree of shunting, i.e. the formation of portal-systemic collaterals.[6] On the other hand, the development of portal-systemic collaterals in portal hypertension has been associated with the activation process of angiogenesis.[7] Several chemicals or cytokines which increased early in the portal hypertensive stage are reported to be factors involved in angiogenesis. These factors include NO, carbon monoxide and tumor necrosis factor-α. Growth factors such as basic fibroblast growth factor, vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) have also been shown to be important mediators of angiogenesis. Among them, VEGF and VEGF receptor-2 seem to be the major mediators in angiogenesis.[8]

An anti-angiogenic approach by targeting the VEGF or PDGF pathway is a new therapeutic strategy for the treatment of portal hypertension. Recently, researchers have performed several foresighted studies with exciting results. It has been demonstrated in portal hypertensive animals that chronic inhibition of VEGF and PDGF signaling significantly reduced the degree of shunting.[9] However, despite reducing the formation of portal-systemic collaterals, VEGF blockade will not always concomitantly reduce portal pressure. Similarly, in the study of Chang et al, chronic thalidomide treatment enhanced the collateral vasoconstrictive response to vasopressin without changing portal and systemic hemodynamics.[10] Thalidomide, known to be teratogenic and previously banned from use, is regaining much attention due to its anti-inflammatory, antiproliferative and anti-angiogenic effects, as well as its immunomodulatory activity. In recent years, thalidomide and its derivative have been vigorously investigated in anti-cancer therapy.[11] It is worth noting in Chang et al's study that thalidomide effectively reduced the plasma level of VEGF in cirrhotic rats. These findings may imply that the angiogenic process in portal-systemic collaterals of portal hypertension does not necessarily require the pressure-derived stimulus from portal tributary. Neovascularization of portal-systemic collaterals occurs continuously and anti-angiogenic therapy is possible even in the advanced stage.

There are other issues focusing on angiogenesis that deserve further investigation in portal-systemic collaterals. The initiation of vascular proliferation requires signal communication between endothelial cells and smooth muscle cells across the vessel wall. At present, the interactions between collateral endothelial cells, smooth muscle cells and the extracellular matrix remain unclear. How do the circulating VEGF and other growth factors or cytokine transmit the signals to initiate angiogenesis? Where and how are the signals processed and passed down to the effecter cells? Solving this complicated mechanism of cell–cell and cell–matrix interactions will help us better understand the pathophysiology of portal-systemic collaterals and develop more effective anti-angiogenic therapy for portal hypertension in the future.

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