Role of Angiogenesis in Portal Hypertension

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Increased splanchnic angiogenesis in portal hypertensive mice

Fernandez et al., Gastroenterology 2004
Increased splanchnic angiogenesis in portal hypertensive rats

Fernandez et al., Journal of Hepatology 2005
Does the increased angiogenesis contribute to the formation of portosystemic collateral vessels in portal hypertension?

Opening of pre-existing blood vessels

Growth of new blood vessels (angiogenesis)
Anti-angiogenic strategy: Monoclonal antibody against VEGFR-2 (DC101)
DC101 decreases portosystemic collateralization and splanchnic neovascularization in portal hypertensive mice

Fernandez et al., Gastroenterology 2004
Does the increased angiogenesis contribute to increase splanchnic blood flow in portal hypertension?

↑ splanchnic arteriolar vasodilatation

↑ splanchnic neovascularization
Anti-angiogenic strategy: Inhibitor of tyrosine kinase domain of VEGFR-2 (SU5416)
SU5416 decreases splanchnic blood flow, portosystemic collateralization and neovascularization in portal hypertensive rats

Fernandez et al., Journal of Hepatology 2005

52% inhibition

Vehicle
SU5416
Anti-angiogenic strategy: Inhibitor of VEGF mRNA translation (Rapamycin)
Rapamycin decreases splanchnic blood flow and portosystemic collateralization in portal hypertensive rats

**Graphs:**
- **Portal pressure (mm Hg):**
  - SO Rats: 5 (Vehicle) vs. 16 (RAPA)
  - PPVL Rats: 15 (Vehicle) vs. 16 (RAPA)
- **Superior mesenteric artery blood flow (ml/min/100 g bw):**
  - SO Rats: 6 (Vehicle) vs. 8 (RAPA) (24%)
  - PPVL Rats: 6 (Vehicle) vs. 8 (RAPA) (24%)
- **Superior mesenteric artery resistance (mm Hg/ml/min/100 g bw):**
  - SO Rats: 20 (Vehicle) vs. 15 (RAPA) (66%)
  - PPVL Rats: 20 (Vehicle) vs. 15 (RAPA) (66%)
- **Extent of portosystemic collateral vessels (%):**
  - SO Rats: 10 (Vehicle) vs. 10 (RAPA) (67%)
  - PPVL Rats: 10 (Vehicle) vs. 10 (RAPA) (67%)
Rapamycin decreases splanchnic neovascularization in portal hypertensive rats

Fernandez et al., Hepatology 2007
Portal hypertension

↑ VEGF expression

↑ Angiogenesis

DC101
SU5416
Rapamycin

Prevention

✓ Formation of portosystemic collaterals

✓ Development of hyperdynamic splanchnic circulation
Oxidative stress modulates angiogenesis in portal hypertension

↑ Heme oxygenase

↑ VEGF

Portal hypertension → Increased oxidative stress → VEGF signaling pathway → Angiogenesis

Angermayr et al., J Hepatol 2006
Angermayr et al., Gut 2007
PROPHYLACTIC STUDIES

- Anti-angiogenic treatment is performed when portal hypertension is ACTIVELY DEVELOPING.

Induction of portal hypertension (PPVL) + Start of anti-angiogenic treatment

1 week

Studies

- Does inhibition of angiogenesis PREVENT the development of circulatory abnormalities associated with portal hypertension?
THERAPEUTIC STUDIES

- Anti-angiogenic treatment is performed when portal hypertension is COMPLETELY ESTABLISHED.

Induction of portal hypertension (PPVL)

1 week

Start of anti-angiogenic treatment
(Portal hypertension is fully developed)

2 weeks

Studies

Does inhibition of angiogenesis REVERT the circulatory abnormalities associated with portal hypertension once these are fully developed?
Endothelial cell activation and proliferation

Angiogenic factor production

Endothelial cell migration and assembly

Pericyte recruitment and vessel stabilization and maturation

Tube formation

VEGF

PDGF
Simultaneous targeting of VEGF/endothelium and PDGF/pericytes

Rapamycin

Gleevec

Stable

Destabilized

Regression
Progressive overexpression of VEGF and PDGF over the evolution of portal hypertension in rats

Fernandez et al., Hepatology 2007
A combination of Rapamycin and Gleevec decreases splanchnic neovascularization and the pericyte coverage of neovessels when portal hypertension is completely established in rats.

Fernandez et al., Hepatology 2007
A combination of Rapamycin and Gleevec decreases portal pressure, splanchnic blood flow and portosystemic collateralization when portal hypertension is completely established in rats.
Portal hypertension

↑ VEGF and PDGF expression

Angiogenesis & neovessel maturation

Rapamycin + Gleevec

Reversal

✓ Maintenance of portal hypertension, hyperdynamic splanchnic circulation, and portosystemic collateralization
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