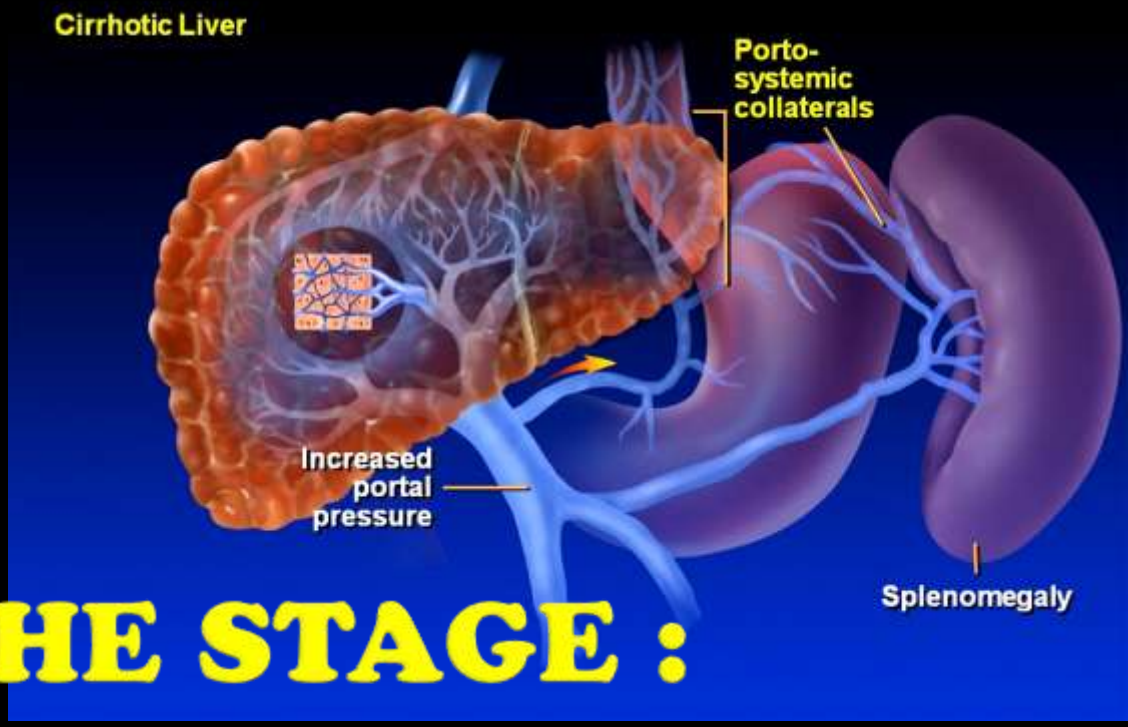

SETTING THE STAGE :

Understanding the pathogenesis of hepatic fibrosis and portal hypertension

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National Kidney and Transplant Institute

General Principles on Hepatic Fibrosis

1. It is a wound-healing response in which extracellular matrix (ECM), or "scar" is accumulated.

2. Myofibroblast-like cells produce hepatic fibrosis regardless of underlying cause.

3. It follows a chronic, not self-limited injury.

4. It occurs earliest in regions where injury is most severe.

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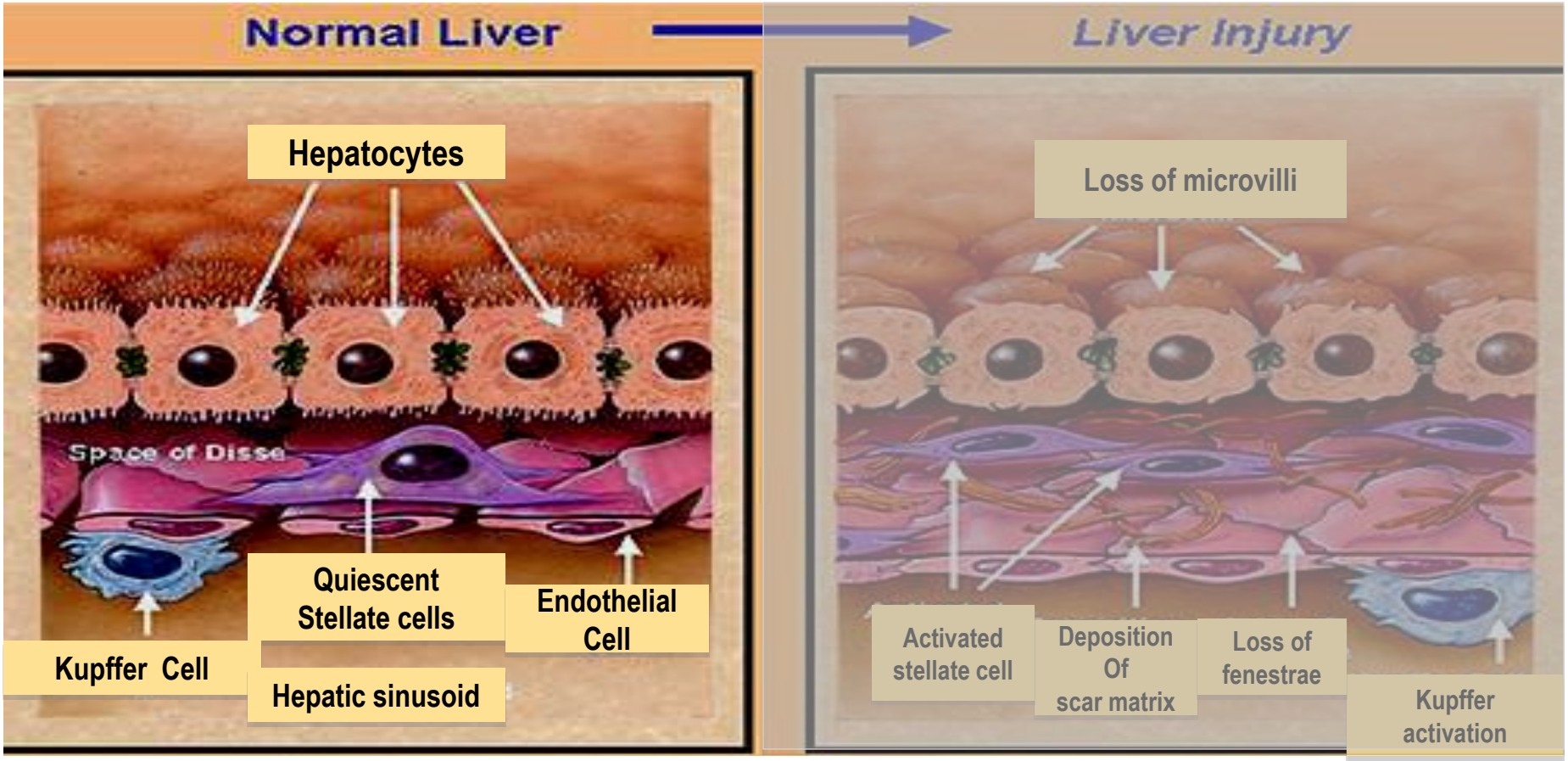
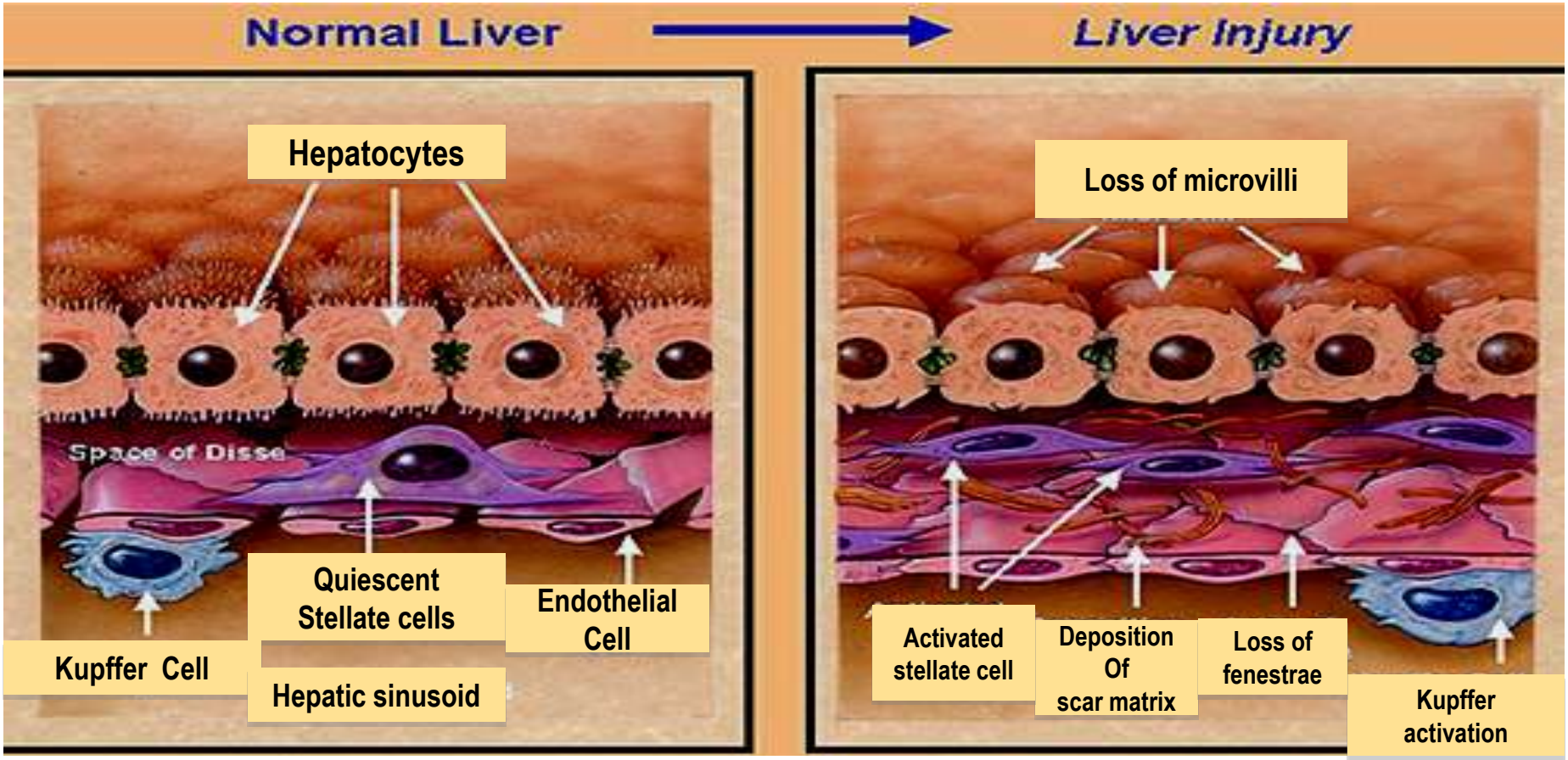
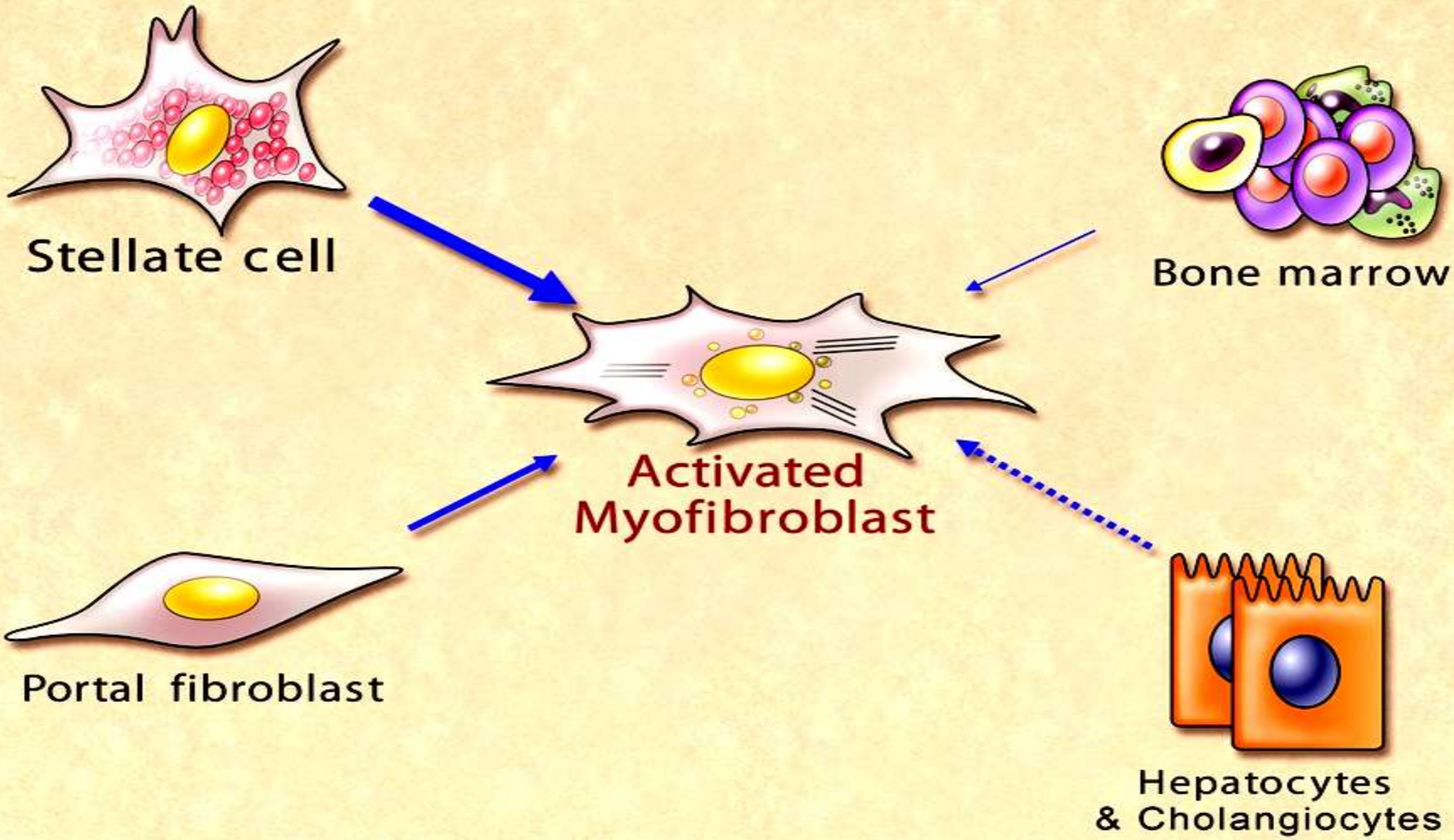
Matrix and cellular alterations



Matrix and cellular alterations

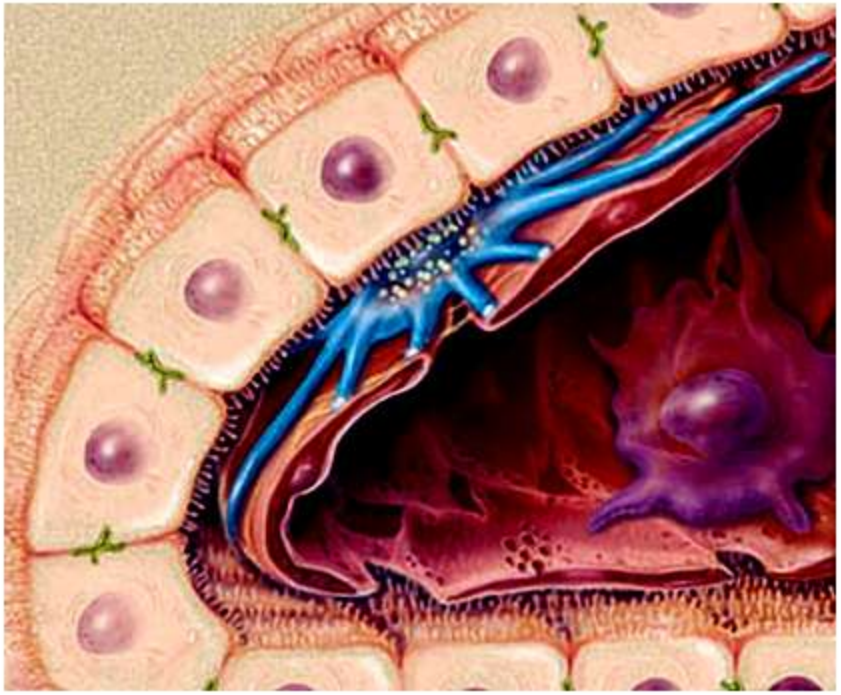


Cellular sources of ECM

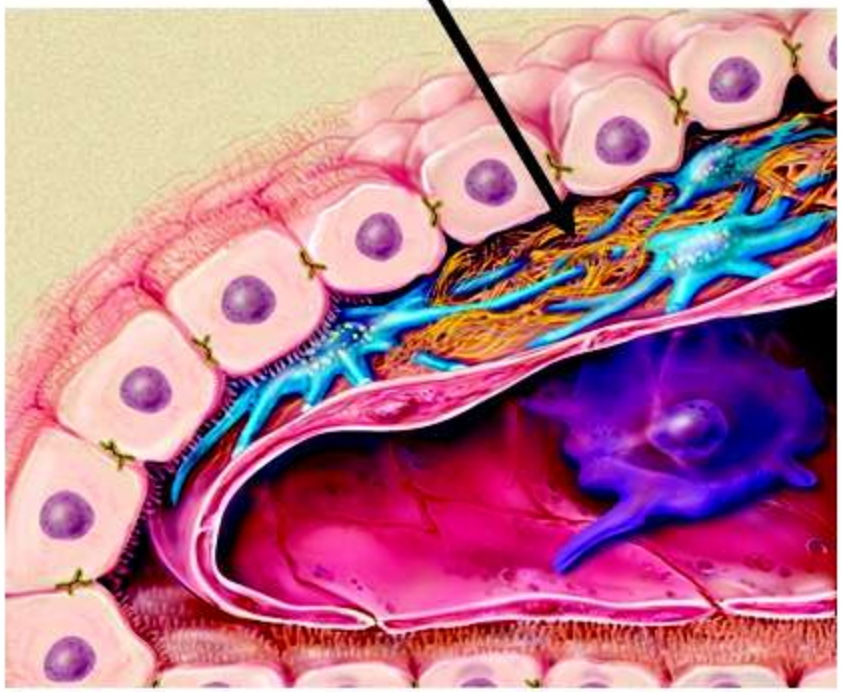


Stellate Cell Activation: Central event in Hepatic Fibrosis

Normal Liver



Activated HSC with Fibrosis

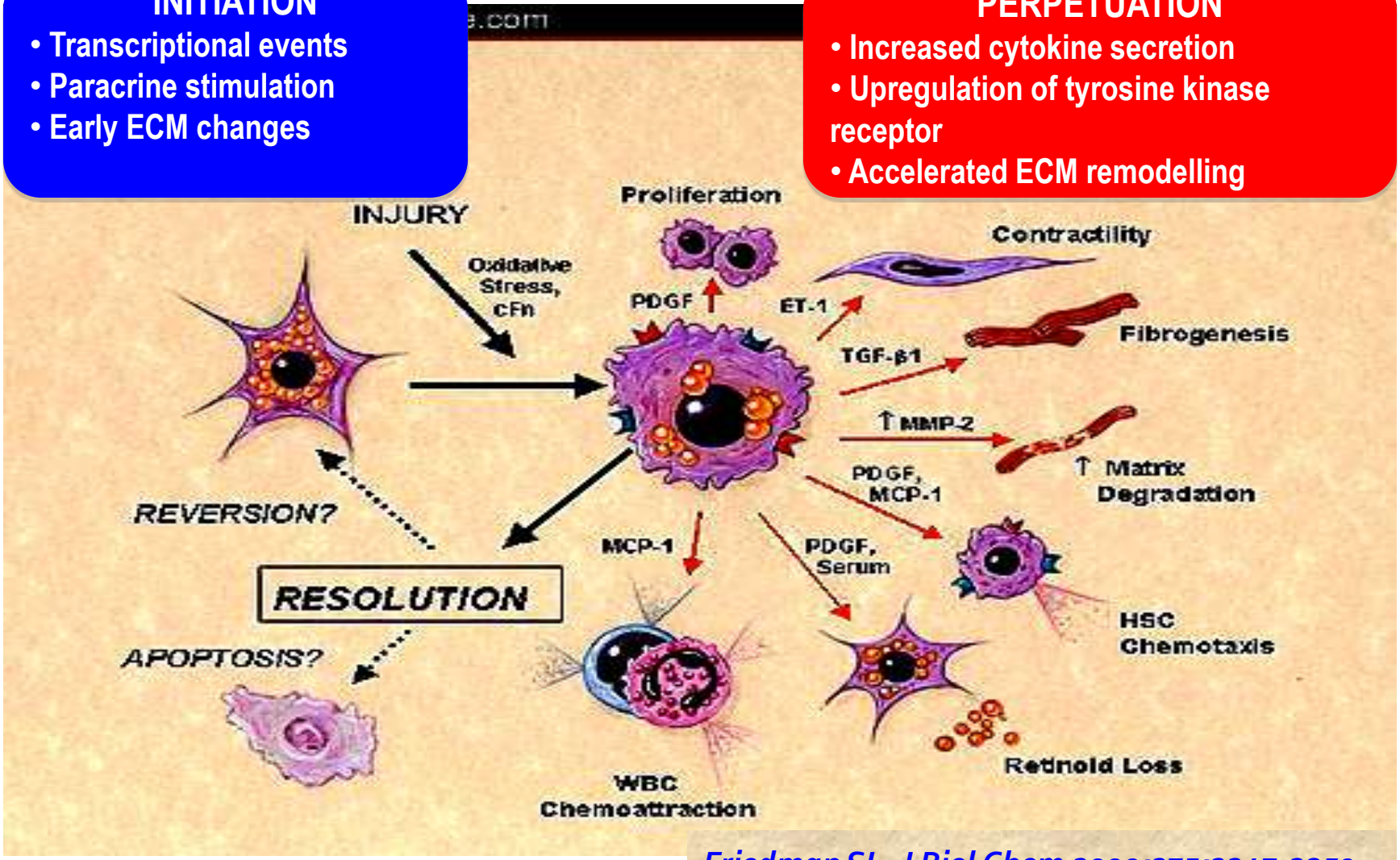


Friedman SL and Arthur, *Science and Medicine*, 2002

Phases of stellate cell activation

INITIATION
- Transcriptional events
- Paracrine stimulation
- Early ECM changes

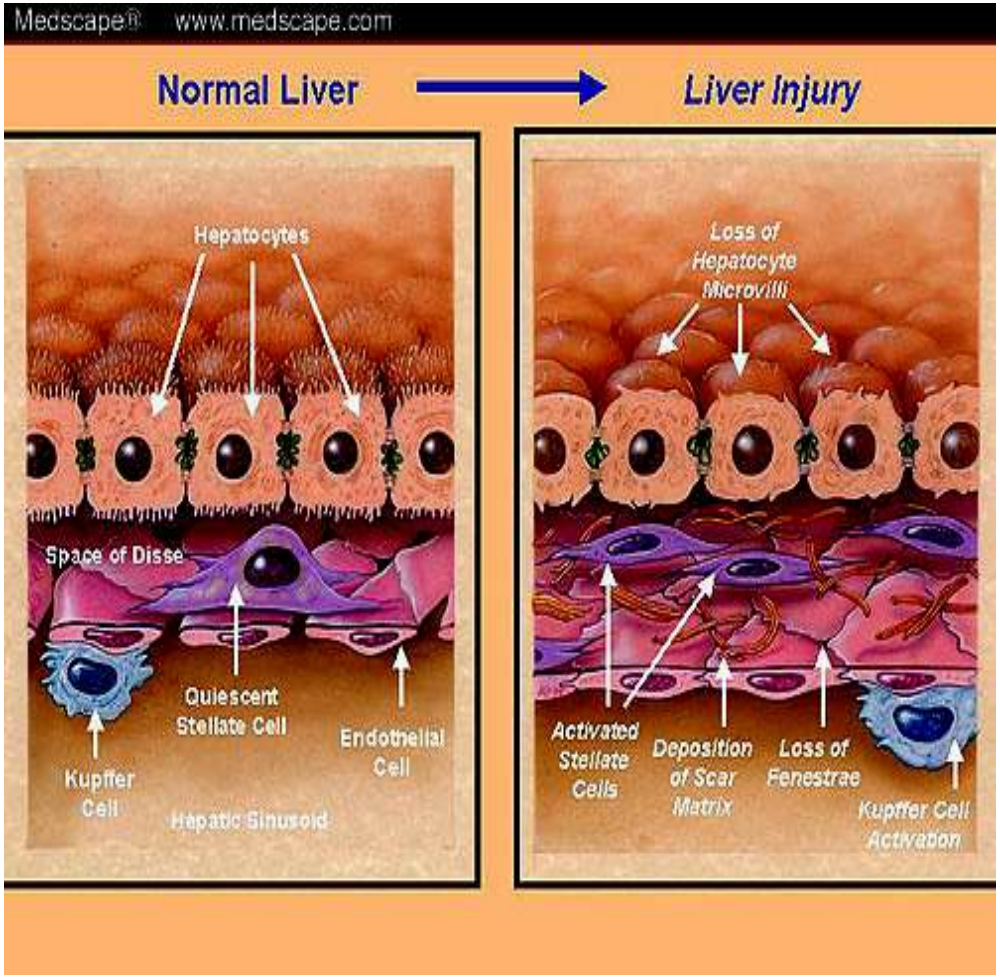
PERPETUATION
- Increased cytokine secretion
- Upregulation of tyrosine kinase receptor
- Accelerated ECM remodelling



Friedman SL. J Biol Chem 2000;275:2247-2250

Initiation of stellate cell activation

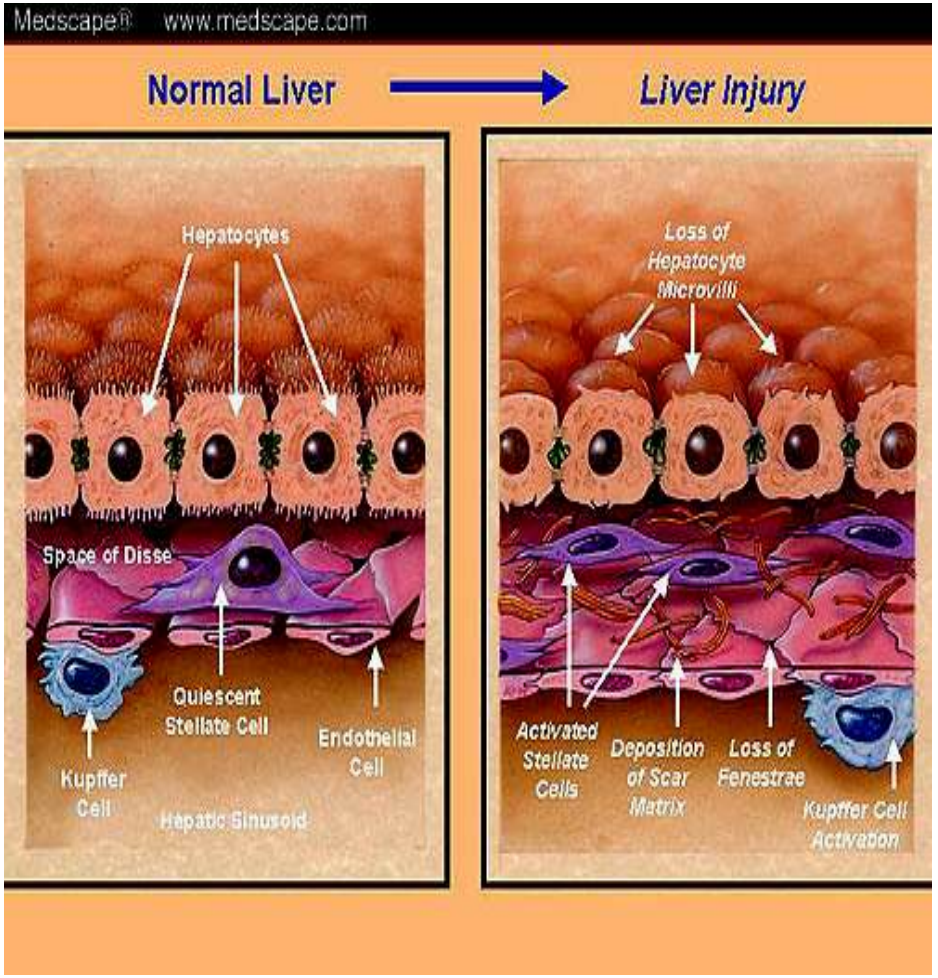
- Earliest changes from paracrine stimulation (i.e. sinusoidal epithelium, Kupffer cells, hepatocytes and platelets) (1)
- Endothelial cells
  - Loss of fenestrations (2,3)
  - Production of cellular fibronectin (1)
  - Conversion of TGF-B to profibrogenic form (2,3)
  - Express proinflammatory molecules (e.g. VEGF, adhesion molecules intercellular adhesion molecule 1) (2,3)



1. Olaso et al. Hepatology 2003;37:674-685
2. LeCoute J, et al. Science2003;299:890-893

Initiation of Stellate cell activation

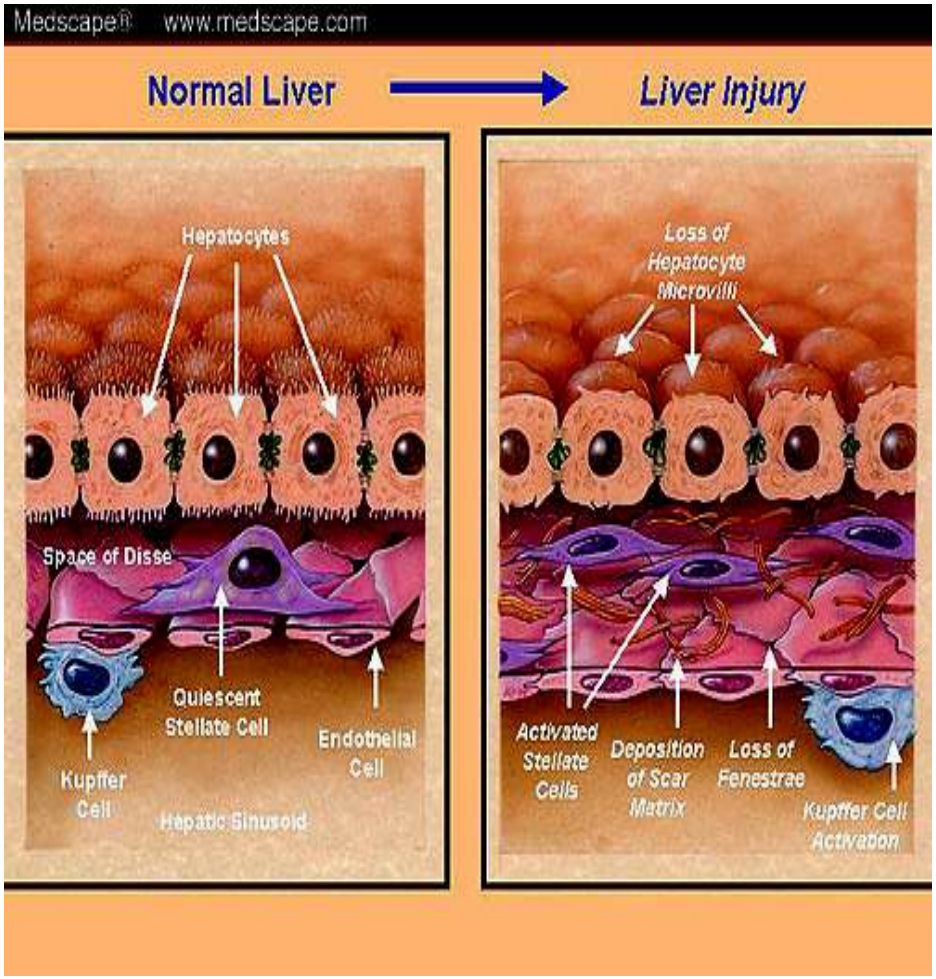
- Kupffer cells
  - Influx [1]
  - Matrix synthesis, cell proliferation, release of retinoids (mediators: TGF-B1, reactive O2 intermediates/lipid peroxides)[1]
- Hepatocytes
  - Potent source of fibrogenic lipid peroxides [2,3]



1. Friedman SL. J Clin Invest 2005;115:29-32
2. Paradis V, et al. J Clin Pathol 1997;50:401-406
3. Nieto N, et al. Hepatology 2002;35:62-73

Initiation of Stellate cell activation

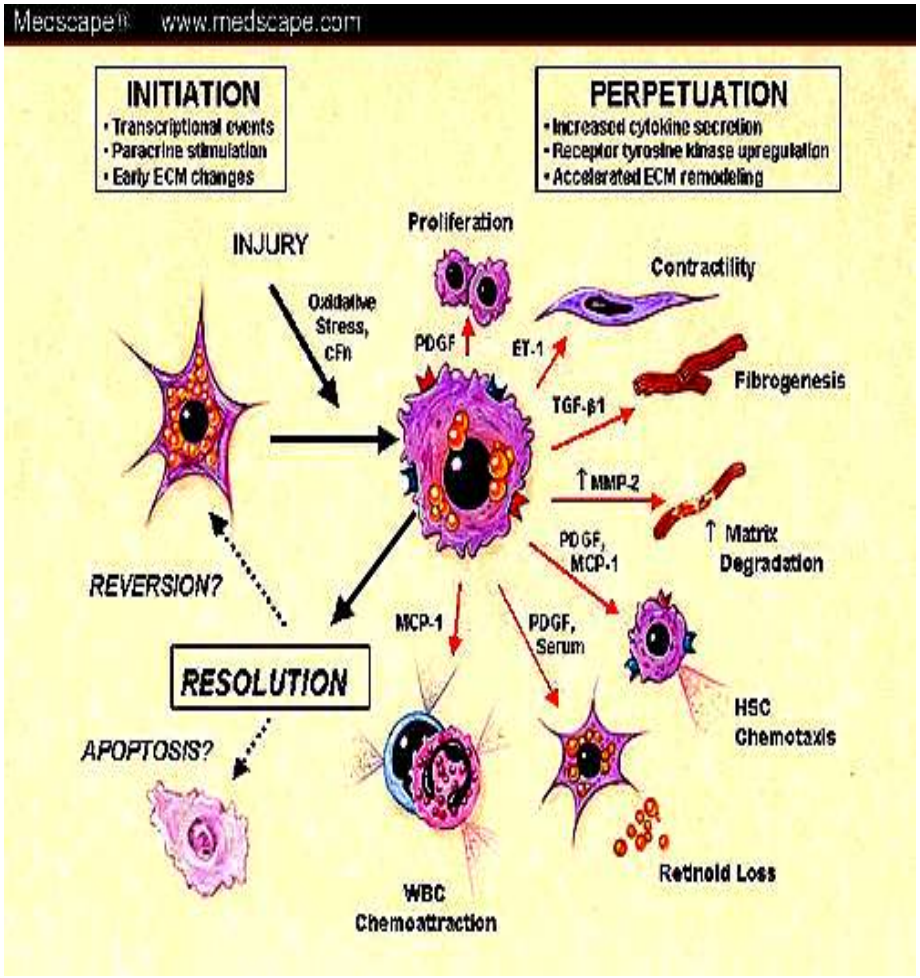
- Platelets
  - Potent source of growth factors [1]
  - Mediators: PDGF, TGF-B1, epidermal growth factor (EGF)[1]



1. Bachem MG, et al. Jclin Chem Clin Biochem 1989;27:555-565

Perpetuation of stellate cell activation

- *Net effect:* increase in the accumulation of ECM
- Proliferation and chemotaxis
  - Increase in the numbers of collagen-producing cells
  - More matrix production per cell
- Cytokine release
  - Amplify the inflammatory and fibrogenic responses
  - Matrix proteases hasten production scar



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Perpetuation of stellate cell activation

Changes in stellate cell behavior	Mediator/s	Key Events
1. Proliferation	PDGF	Induction of PDGF receptors
2. Chemotaxis	PDGF, MCP1	Migration of stellate cells toward cytokine chemoattractants
3. Fibrogenesis	TGF-B1	Increased matrix production (Collagen type 1); production of other matrix components (fibronectin, proteoglycans)
4. Contractility	ET-1, Angiotensin II	Increased expression of cytoskeletal protein; decreased portal blood flow

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Perpetuation of stellate cell activation

Changes in stellate cell behavior	Mediator	Events
5. Matrix degradation	MMP-2	Quantitative and qualitative changes in matrix protease activity
6. Retinoid loss	PDGF	Loss of perinuclear retinoid (vitamin A) droplets and acquire a more fibroblastic appearance
7. WBC chemoattractant and Cytokine release	MCP-1	Amplification of inflammatory response by inducing mononuclear and PMN infiltration; production of chemokines (i.e. MCP-1, RANTES, CCR- ... expression of toll-like rece...

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Summary

- Hepatic fibrosis is a wound-healing response characterized by accumulation of ECM.
- Hepatic fibrosis follows a chronic, but not self-limited, liver disease.
- Activation of hepatic stellate cells is the central event in hepatic fibrosis.
- Hepatic stellate cells and related myofibroblasts from intra and extrahepatic sources orchestrate an array of changes including degradation of normal ECM, deposition of scar molecules, vascular and organ contraction , and release of cytokines.

Portal Hypertension (PHT): Definition

- Pathologic increase in portal pressure, in which the pressure gradient between the portal vein and inferior vena cava (portal pressure gradient, PPG) is increased above 5 mm Hg [1-4]

- Clinically significant when PPG increases above 10 mm Hg (e.g. formation of varices) or 12mm Hg (e.g. variceal bleeding, ascites)[1-4]

- Subclinical portal hypertension : PPG between 6 to 10 mm Hg [1-4]

1. Casado M, et al. Gastroenterology 1998;114(6): 1296-1303
2. Rigau J, et al. Gastroenterology 1989;96(3):873-880
3. Viallet A, et al. Gastroenterology 1975;69(6):1297-1300
4. Garcia-Tsao, et al. Hepatology 1985;5(3):419-424

Mechanisms of PHT

- PPG (P) results from interaction between the portal blood flow (F) and resistance to flow (R)

$$P = F \times R$$

- PHT can result from:
  1. Increase in vascular resistance (cirrhosis)
  2. Increase in portal blood flow
  3. Combination of both

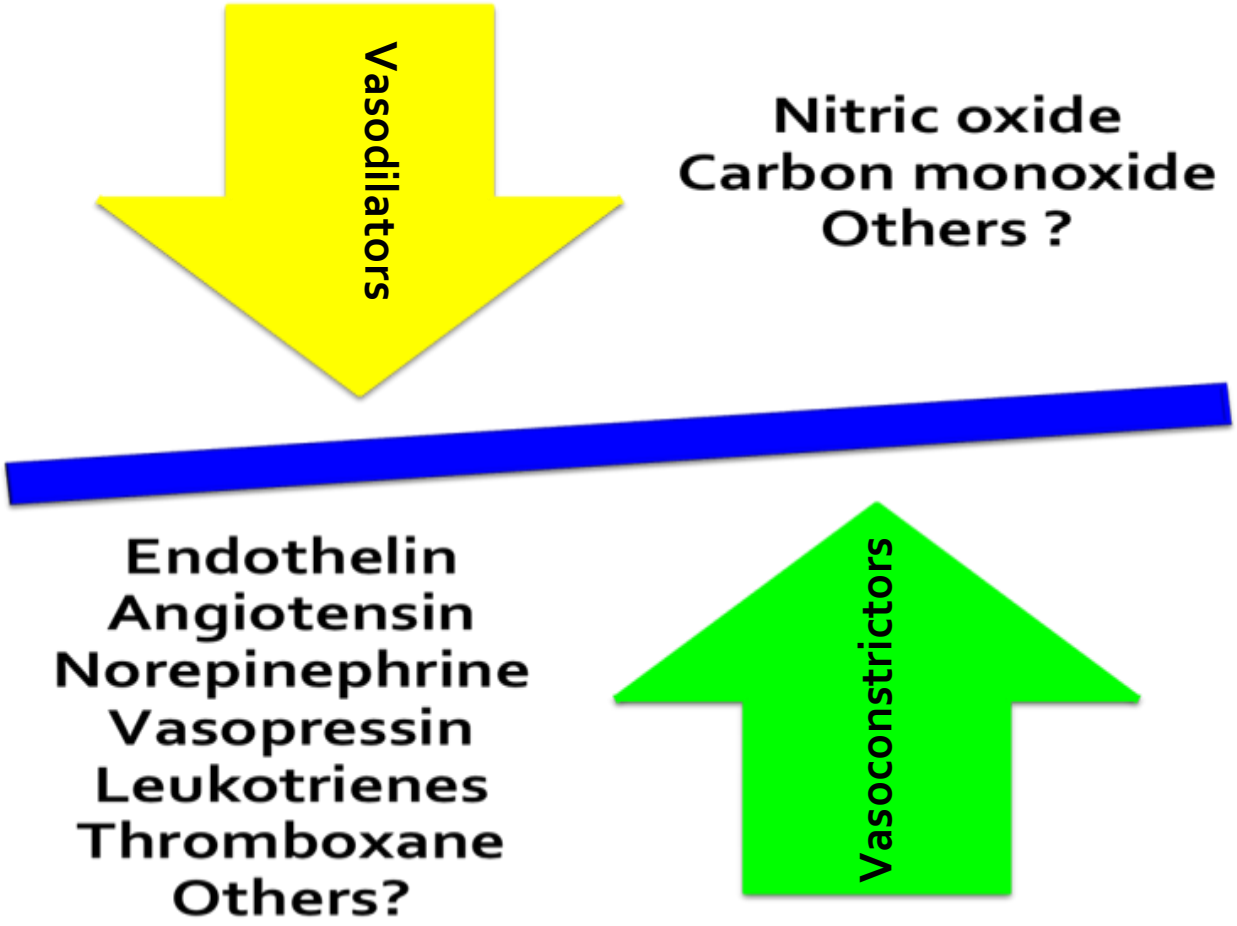
Bosch J, et al. Gastenterol Clin North Am 1992;21(1): 1-14.

Increase intrahepatic vascular resistance (architectural disturbances)

- Consequence of architectural distortion of hepatic circulation by fibrosis (fixed and mechanical)[1]
- Thrombosis of medium and large portal and hepatic veins [1]
- Active contraction of contractile elements (i.e. smooth muscles, stellate cells and hepatic myofibroblasts) of the liver (dynamic) [2]

1. *Wanless IR, et al. Hepatology 1995;21(5):1238-1247*
2. *Bathal PS, et al. J Hepatol 1985;1:325-329*

Increase intrahepatic vascular resistance (functional alterations)



Other functional alterations

- Endothelial dysfunction of the hepatic vascular bed [1]
  - Abrupt post-prandial increase in portal pressure [2]
  - Impaired response to endothelium-derived vasodilator, acetylcholine [3]
- Overactivation of COX-1 pathway with an increased production of vasoconstictor-derived compounds (i.e. TXA2) [4]

1.Gupta TK, et al. Hepatol 1998; 28(4):926-931
2. Bellis L et al. Hepatol 2003;37(2): 378-384
3. Graupera M, et al. J Hepatol 2003; 39(4): 515-521
4. Aleixandre de Artinano M, et al. Pharmacol Res 1999; 40(2):113-114

Increase portal blood flow

- Observed in the advanced stages of PHT
- Result from the marked arteriolar dilatation in the splanchnic organs draining into the portal vein (SPLANCHNIC VASODILATION)

Splanchnic vasodilation

MECHANISMS

- Neurogenic
- Humoral
  - Increased levels of vasodilators
- Local

CANDIDATE VASODILATORS

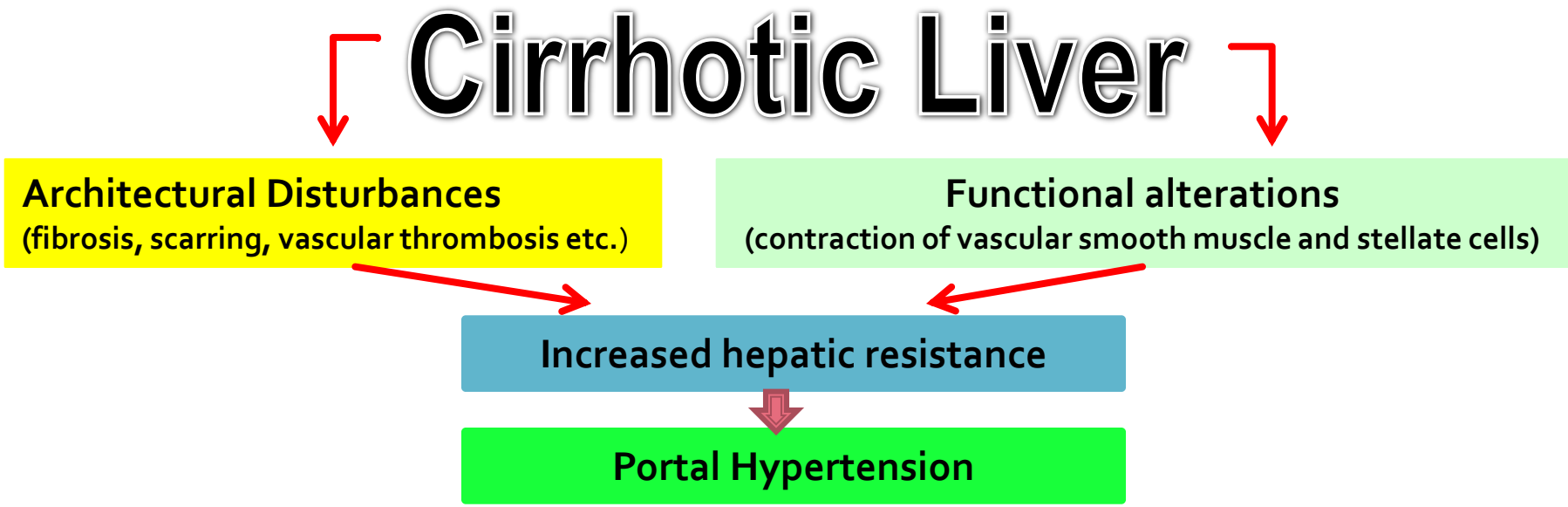
1. Glucagon
   - most evidence
2. Endocannabinoids
3. Nitric oxide
4. Prostaglandins
5. Carbon monoxide

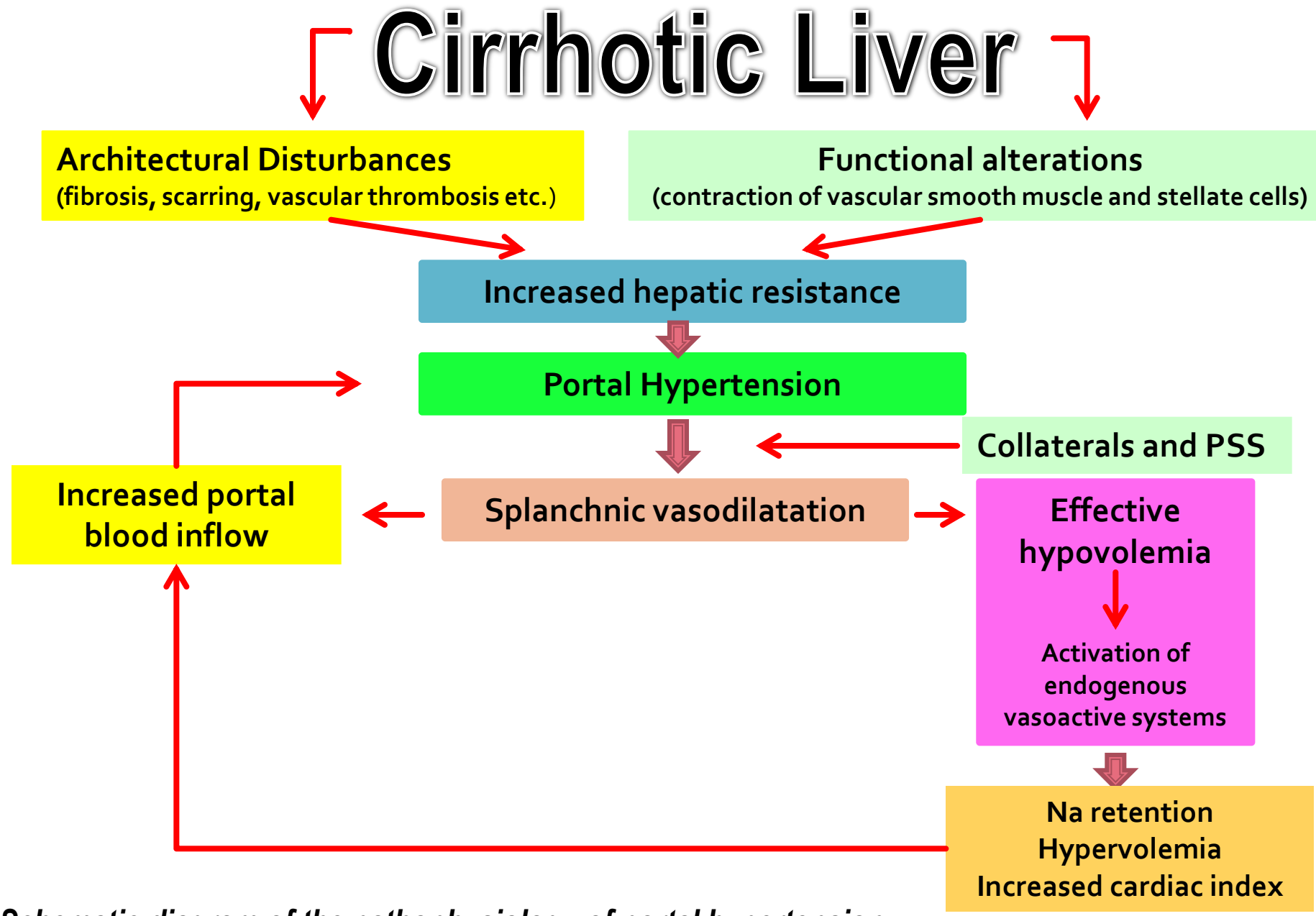
Splanchnic vasodilation: Candidate vasodilators

Vasodilator	Mechanism/s of action
1. Glucagon	vascular smooth muscle relaxation and decreasing its sensitivity to endogenous vasoconstrictors i.e. norepinephrine, angiotensin II and vasopressin. (SOMATOSTATIN and ITS ANALOGUES)
2. Endocannabinoids	Increase NO production by activation of endothelial CB_1 receptor
3. Nitric oxide	
4. Prostaglandins	Vascular smooth muscle relaxation by activating adenylate cyclase and augmenting intracellular level of cyclic adenosine monophosphate (CAMP)
5. Carbon monoxide	

Splanchnic vasodilation

- Portosystemic collateral circulation
- Peripheral vasodilation and hyperkinetic circulation
  - Characterized by reduced arterial pressure and peripheral resistance, and increased plasma volume and cardiac output (CO)
  - Activation of neurohumoral systems that cause Na retention, increases plasma volume and cardiac index
- Expansion of plasma volume
  - Necessary to maintain an increased CO


Cirrhotic Liver
Architectural Disturbances
(fibrosis, scarring, vascular thrombosis etc.)
Functional alterations
(contraction of vascular smooth muscle and stellate cells)
Increased hepatic resistance
Portal Hypertension



Schematic diagram of the pathophysiology of portal hypertension

Summary

- Portal pressure gradient is determined by the product of blood flow and vascular resistance within the portal venous system.
- PHT is initiated by an increased resistance to portal blood flow and aggravated by an increased portal venous inflow.
- Increased resistance in cirrhosis is due not only to disruption of vascular architecture but also a dynamic component from active contraction of endothelial SM, myofibroblasts and hepatic stellate cells.

Summary

- Portal inflow is increased by sphlanchnic vasodilation, which is caused by an increase secretion of local endothelial factors and humoral vasodilators.


Thank you for your kind attention !!!