

How Does Hepatitis Cause Liver Cancer?

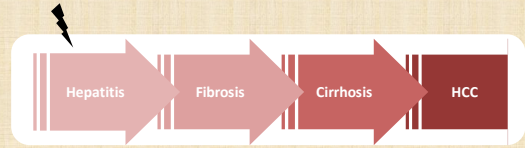


Dr Nadia Warner

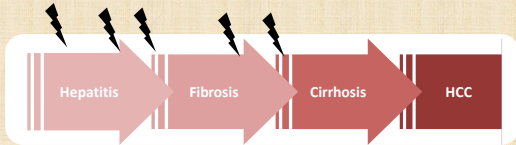
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Liver cancer (HCC) is caused by chronic liver injury



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Major causes of chronic liver injury associated with HCC:

Hepatitis B Virus
Hepatitis C Virus

} 80%

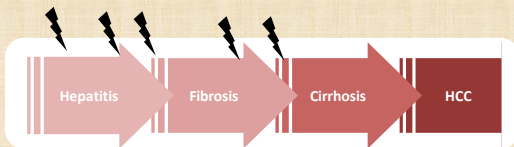
Alcohol

Aflatoxin B1

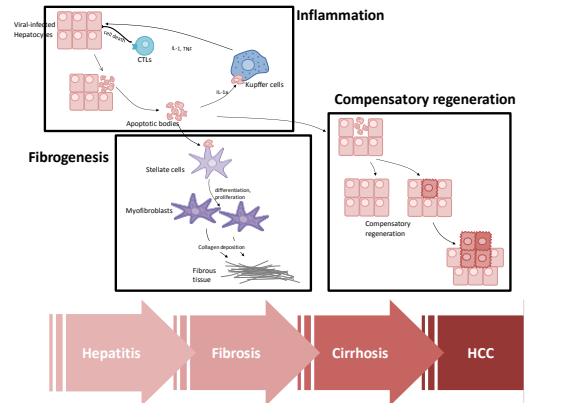
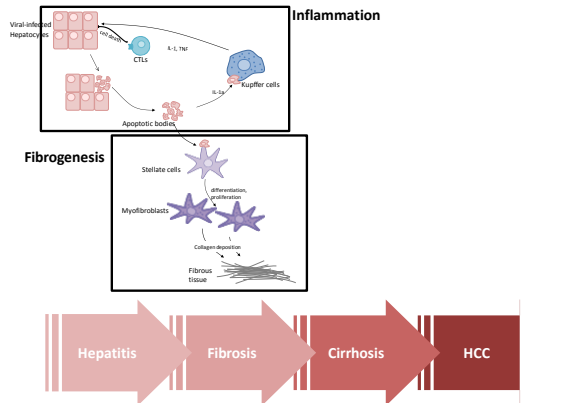
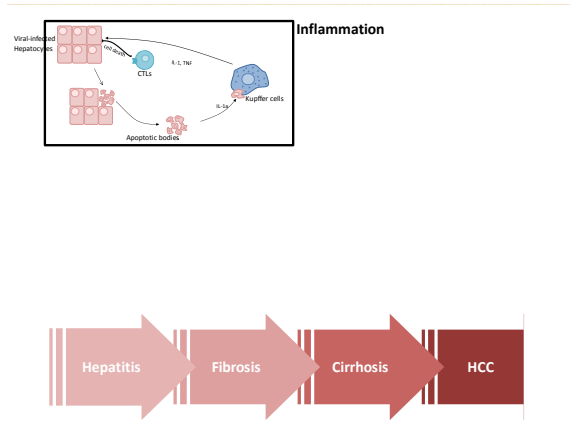
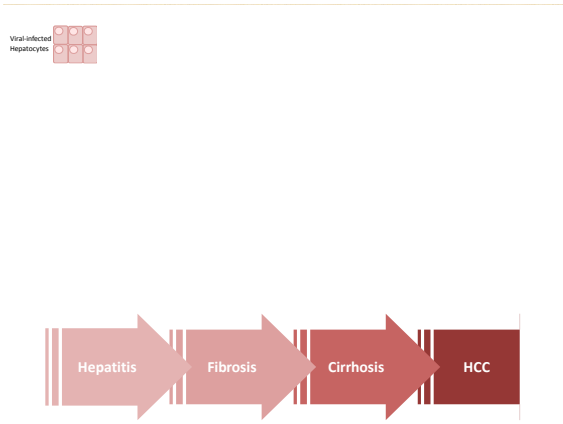
Two pathways to liver cancer in chronic viral hepatitis:

1: Immune response to the virus

2: Direct result of the virus



1: Most liver injury is caused by the *immune response* to viral infection

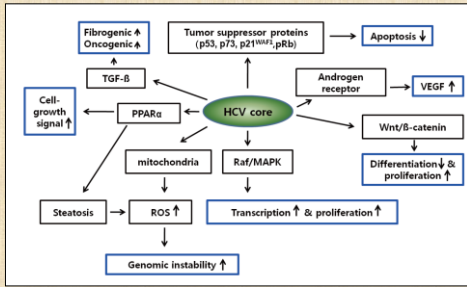


2: Hepatitis viruses can also directly alter the host cell

- HBV and HCV both encode proteins that can cause infected cells to become cancerous (transformation)
 - Survival and proliferation of infected cells
 - Resistance to apoptosis during immune attack

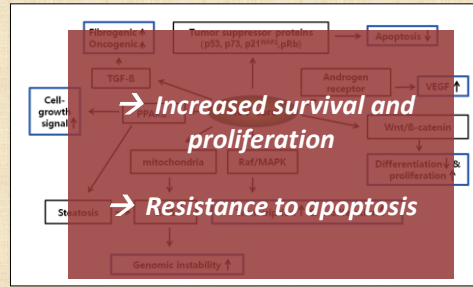
	HBV	HCV
Genome:	3.2kb DNA, 7 proteins	9.6kb RNA, 10 proteins
Lifecycle:	Nuclear and cytoplasmic components	Cytoplasm only
HCC mediators:	X, integration, mutations	Core, NS3, NS5a

HCV - Core protein



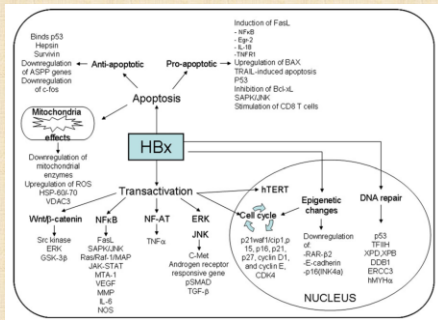
From: Jeong et al (2012) Clin Mol Hepatol 18:347-356

HCV - Core protein



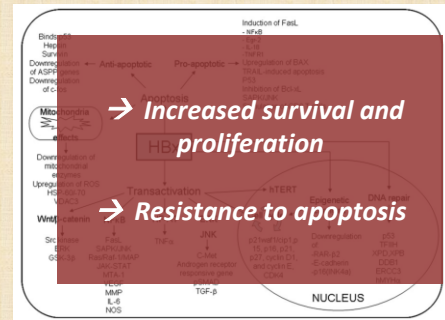
From: Jeong et al (2012) Clin Mol Hepatol 18:347-356

HBV - X protein



From: Ng and Lee (2011) Gastroenterol 46: 974-990

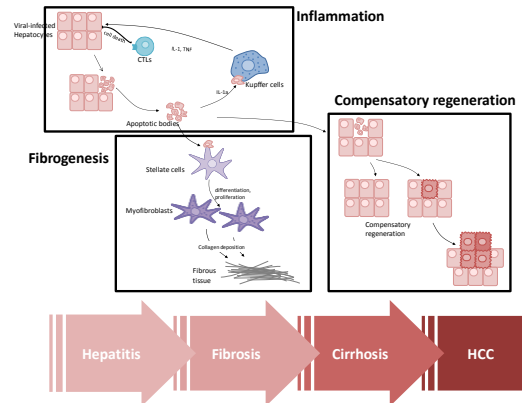
HBV - X protein

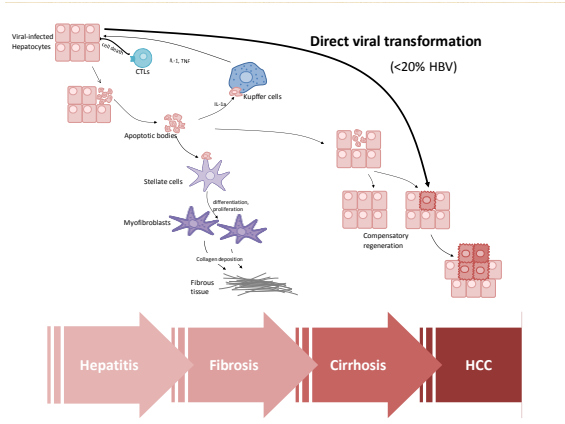


From: Ng and Lee (2011) Gastroenterol 46: 974-990

HBV - integration

- Integration is not required for HBV replication
- Integration of HBV DNA can occur, and is detected in both tumorous and non-tumorous tissue
- Integration is thought to be random
 - Insertional mutagenesis generates chromosomal instability
 - some studies suggest integration may be targeted genes involved in key HCC-associated pathways (eg. Human telomerase reverse transcriptase)
- Proteins expressed from integrated DNA may contribute to HCC
 - X
 - Truncated surface genes





Risk factors for HCC in HBV infection

	Hazard ratio (95% CI)	β coefficient	p-value	Robt score
Sex				
Female	0.99	0.00	-	0
Male	2.11 (1.4-3.0)	0.75(0.5)	0.0002	2
Age (years)				
20-24	0.64 (0.45-0.91)	-0.46(0.5)	<0.0001	5
25-29	-	-	-	0
30-34	-	-	-	0
35-39	-	-	-	0
40-44	-	-	-	0
45-49	-	-	-	0
50-54	-	-	-	0
55-59	-	-	-	0
60-64	-	-	-	0
≥65	-	-	-	0
AFP (ng/ml)				
<15	0.99	0.00	-	0
15-44	3.13 (1.9-5.0)	0.98(0.5)	0.0008	3
≥45	2.42 (1.4-4.2)	0.88(0.5)	0.0003	2
HBsAg				
Positive	2.08	0.81	-	0
Negative	2.13 (1.3-3.5)	0.75(0.5)	0.0005	2
HBV DNA level (copies per mL)				
<1000	0.99	0.00	-	0
1000-9999	1.19 (0.8-1.8)	0.17(0.4)	0.30(0.2)	0
10000-99999	1.17 (0.8-1.7)	0.16(0.4)	0.30(0.2)	0
100000-999999	0.71 (0.4-1.2)	-0.34(0.3)	<0.0001	5
≥1000000	0.11 (0.04-0.29)	-0.90(0.3)	<0.0001	6*

From: Yang et al (2011) Lancet Oncol 12:568-574

Summary

- There are multiple factors that contribute to the development of HCC over time
 - Immune response to the virus
 - Viral products
- Need to find better markers than AFP for earlier diagnosis
- Need to identify common pathways that can be targeted by chemotherapy

Thank you

HBV variants

- Some HBV genotypes are associated with higher rates of HCC
- Deletions within the PreS regions associated with HCC
 - ER stress, oxidative stress
- Truncated surface proteins
 - Transcriptional transactivation
- High viral loads (HBeAg, HBSP)
- Basal Core Promoter mutations