How Does Hepatitis Cause Liver Cancer?

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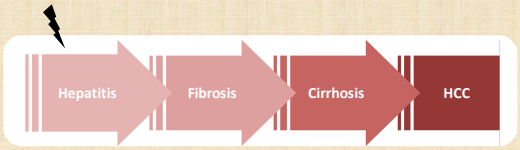
Liver cancer (HCC) is caused by chronic liver injury



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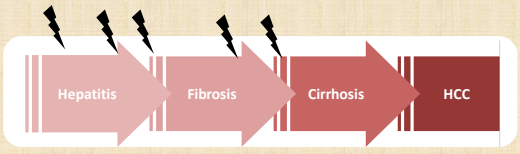


Major causes of chronic liver injury associated with HCC:

Hepatitis B Virus
Hepatitis C Virus } 80%

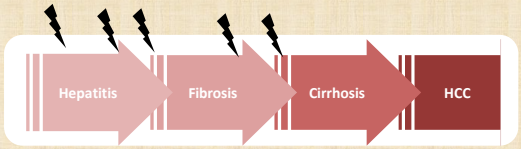
Alcohol

Aflatoxin B1

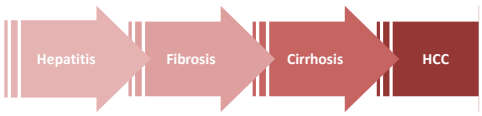
Two pathways to liver cancer in chronic viral hepatitis:

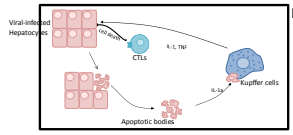
1: Immune response to the virus

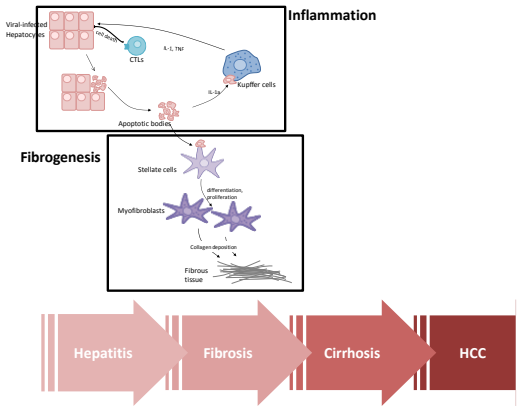
2: Direct result of the virus

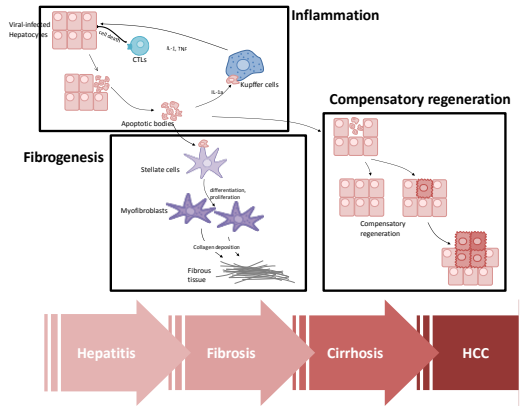


1: Most liver injury is caused by the *immune response* to viral infection



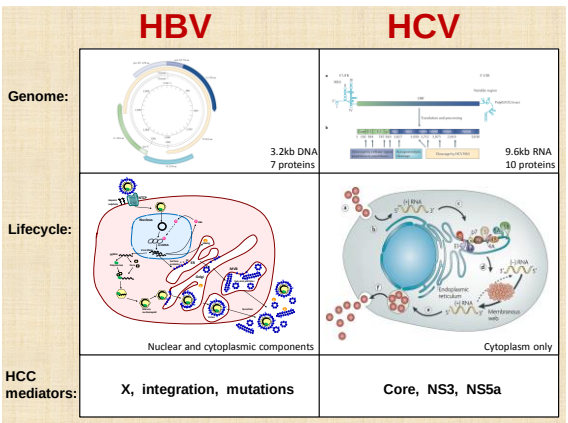




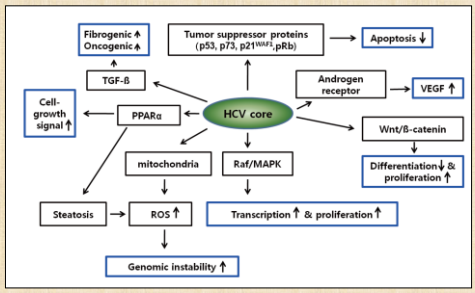


2: Hepatitis viruses can also directly alter the host cell

- 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

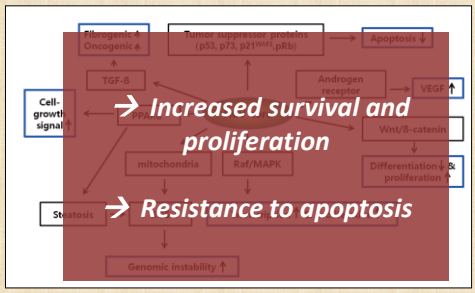


HCV - Core protein



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

HCV - Core protein



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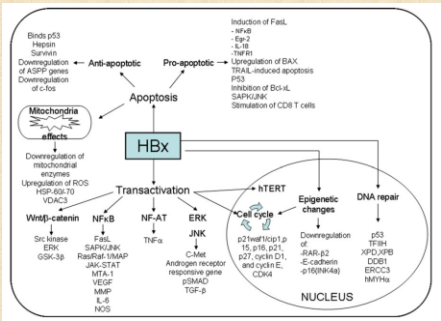
HBV - X protein



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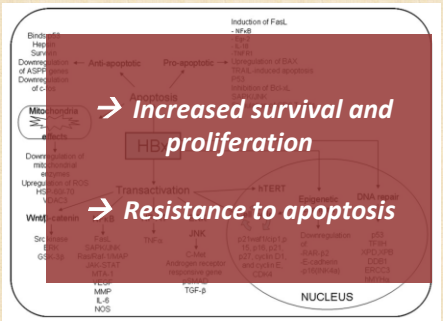

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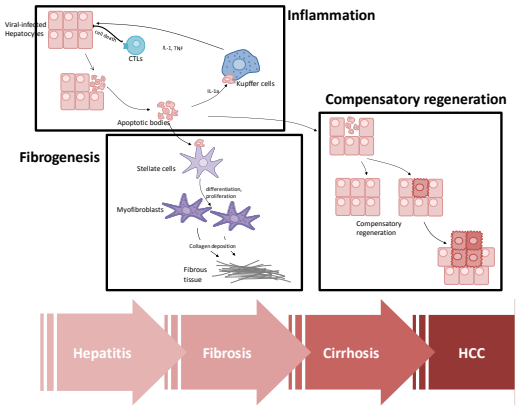
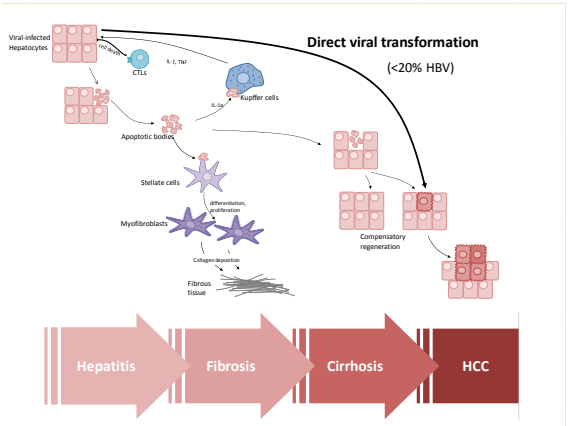
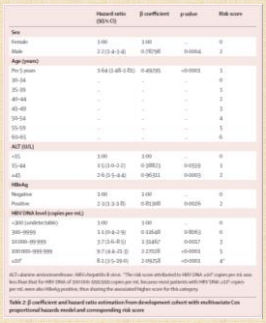
HBV - integration

- Integration is not required for HBV replication
- Integration of HBV DNA can occur, and is detected in both tumourous and non-tumourous 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



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