**How Does Hepatitis Cause Liver Cancer?**

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**Liver cancer (HCC) is caused by chronic liver injury**

- **Hepatitis**
- **Fibrosis**
- **Cirrhosis**
- **HCC**

**Major causes of chronic liver injury associated with HCC:**

- **Hepatitis B Virus**
- **Hepatitis C Virus**
- **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: Hepatitisviruses 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**

- Increased survival and proliferation
- Resistance to apoptosis

**HBV - X protein**

- Increased survival and proliferation
- Resistance to apoptosis

**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 (e.g., Human telomerase reverse transcriptase)
- Proteins expressed from integrated DNA may contribute to HCC
  - X
  - Truncated surface genes

**Inflammation**

- Fibrosis
- Compensatory regeneration

**Hepatitis**

- Fibrosis
- Cirrhosis
- HCC
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

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

Risk factors for HCC in HBV infection

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

Thank you