By Elisa Westerhof

HOW DOES SMOKING INFLUENCE HEPATIC CANCER FROM A GENETIC PERSPECTIVE?

The liver is the largest internal organ. The organ is essential to help process and store many nutrients absorbed from the intestine and secretes bile into the intestine to help absorb nutrients. Furthermore, it synthesises clotting factors which are crucial to stop bleeding, as well as plays an important role in removing toxic wastes from the body. Men are twice as likely to develop liver cancer.

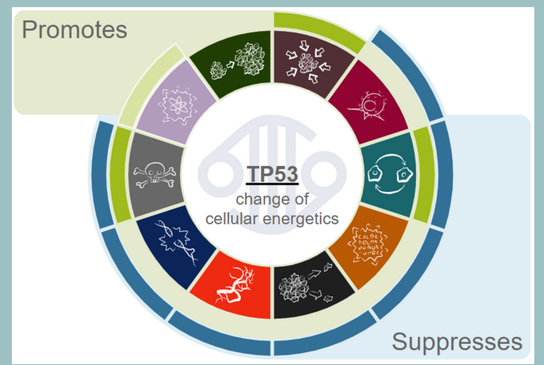

Figure 1 Displays the Catalogue of Effects caused by the TP53 gene. Can be found on: https://cancer.sanger.ac.uk/cosmic/census-page/TP53

IMPORTANT!

- Tar from cigarettes enters the blood, making it thicker, increasing the rate of clot formation, raising blood pressure and heart rate.
- Nicotine is transported into the lungs into the bloodstream through the alveoli, where cotinine undergoes hepatic metabolism.

1. INTRODUCTION

Hepatic cancer is characterised by the abnormal rapid growth of liver cells, causing a tumour due to mutations in their cells DNA. The liver is crucial in the process of metabolism (biotransformation of drugs and other harmful substances), immunity, digestion, detoxification, vitamin storage and more (1). Liver cancer begins in the liver cells, however cancer that spreads to the liver from other organs is more common (2). There are many types of liver cancer, where the most common type of (primary) liver cancer is hepatocellular carcinoma (HCC, main type of cells in the liver), while examples such as intrahepatic cholangiocarcinoma and hepatoblastoma are less common. The classification of diagnosis is split into stages 1-4, where the highest survival rate (4 years after diagnosis) is for stage 1 of over 45%, while stage 4 is almost 5%, less than nine times (3). 'Smoking a cigarette generates over 4000 chemicals', including chemicals which have oncogenic properties, raising the risk of hepatic cancer (4). Smoking may lead to uncontrolled cell proliferation, and suppress lymphocytes which then cannot induce apoptosis, decreasing the ability of the immune system to fight the cancer cells. Further risks include those suffering chronic Hepatitis C or B, those suffering existing liver conditions (such as cirrhosis, non-alcoholic fatty liver disease), certain inherited liver diseases, diabetes, exposure to aflatoxins (poisons produced by moulds growing on crops stored poorly) and excessive alcohol consumption. Some symptoms for hepatic cancer include: unintentional weight loss, loss of appetite, nausea and vomiting, weakness and fatigue, abdominal pain and swelling, jaundice and white, chalky stools.

2. OBJECTIVE

The objective of this research is to provide a comprehensive analysis of how smoking can instigate the influence of hepatic cancer and the genes involved. This research paper aims to analyse the mechanisms which smoking may cause cancer to evolve and how different drugs aim to stop this process.

3. METHODOLOGY

The majority of the research was conducted on PubMed, with the help of the Catalogue Of Somatic Mutations In Cancer (COSMIC) to identify the genetic mechanisms leading to the formation of the cancer and how drugs should be targeted towards hepatic cancer. Key words such as 'hepatic cancer', 'genetics', 'smoking', 'genetic mechanisms', 'HCC' were utilised to refine the search allowing to educate myself on this topic. Other useful websites included but not limited to Cancer Research UK and the American Cancer Society.

4. RESULTS

The exact cause of hepatic cancer is not known, nevertheless, chronic hepatitis B virus infection is the leading risk factor, while smoking may cause deleterious effects. Results from a study in Europe showed that 47.6% of HCC was associated with smoking (5). A study from China and Taiwan (2), found that in patients who are independent of the HBV status, the tumour suppressor gene p53, which is considered as the "genome guardian", has been linked in decreased gene expression due to tobacco smoking. Tar and nicotine suppress T-cell responses, meaning the immune system cannot examine tumour cells as effectively, preventing the initiation of apoptosis, allowing these tumour cells to grow. DNA disruption and gene mutations cause uncontrolled cell replication and suppress natural processes which would typically limit cell growth. The p53 gene directly binds and forms complexes with DNA containing mismatches providing a signal for DNA damage, resulting in genome instability and mutations (6). Furthermore, this gene suppresses angiogenesis inhibition, meaning the growth of blood vessels to the tumour is not blocked, thus increased blood supply allows it to grow more. With this information, angiogenesis inhibitors can be used to block the growth of blood vessels leading to the tumour, to stabilise the tumour growth and prevent further enlargement. Mutant p53 genes also allow for cell replicative immortality, thus it can continuously grow, escaping programmed cell death (apoptosis). The gene mutation can allow for increased metastasis as well as escape the immune response to cancer, as mentioned in the introduction, allowing the innate immune system to maintain tissue homeostasis as the cancer continues to grow. Another gene responsible for the cancerous growth is PD-L1 (7,8), which is a protein which when PD-1 binds to it, T cells are instructed to 'leave other cells alone', allowing it to 'hide' from the immune system. Some cancer cells have large amounts of PD-L1, allowing this binding process to happen more frequently, helping the cancerous cells hide from an immune attack. In light of this, scientists have developed PD-L1 inhibitors to decrease this binding process, allowing the immune cells to notice the presence of cancerous cells.

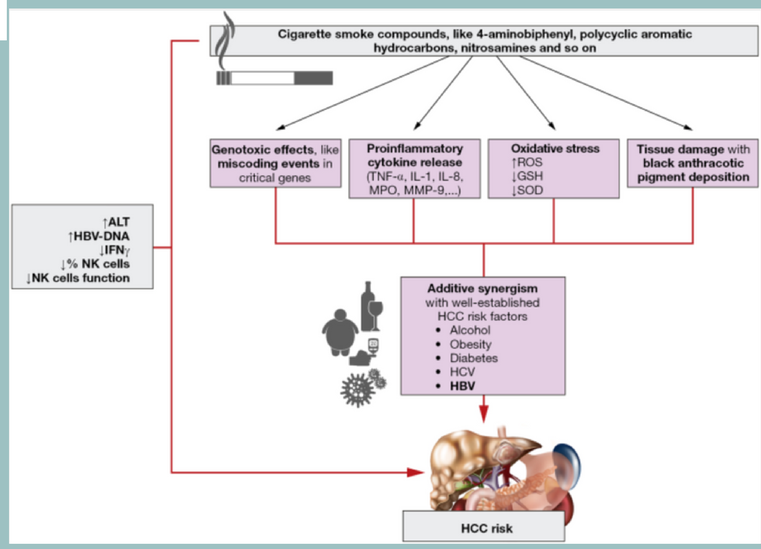

Figure 2 Displays the effects of smoking on increasing hepatocellular carcinoma cancer risk. Can be found on: https://atm.amegroups.org/article/view/25686/24578

5. DISCUSSION + CONCLUSION

Overall, the tumour suppressor gene p53 has been found to decrease gene expression in people who smoke and have no relation to a hepatitis infection. The culmination of the selected studies convey that smoking may have an influence on the development of hepatic cancer, however, the effects of smoking have a larger impact on the development of other cancers such as lung cancer. In the cases of a mutated p53 gene, this allows for the accumulation of the protein which lose their tumour suppressive activities and gain additional oncogenic functions that endow cancer growth due to survival advantages. Hepatocellular carcinoma has a relatively low survival rate, especially if it is detected in the late stages. Anti-PD-L1 directed combination therapies may be used (7) to allow the T cells to kill tumour cells, affecting the PD-1, PDL-1 mechanism. However, different genetic predispositions affect the efficacy of certain drugs and treatment plans which can be prescribed, therefore, 'histopathological examinations have been re-emphasised by current international clinical guidelines in addition to the standardised radiological diagnosis' (7), to improve patient care, increasing hope for positive results. In conclusion, smoking cannot be attributed as a cause of hepatic cancer, nonetheless is a significant risk factor (following HBV) which may cause certain mutations to occur influencing the development of hepatic cancer.

6. REFERENCES

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