What inherited genetic mechanisms underlie familial non-small cell lung cancer?

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Abstract

Lung cancer is the leading cause of cancer deaths worldwide for both men and women. Oftentimes, this can occur through the inheritance of gene mutations. When these are frequently found in families, these cases are called familial cancer syndromes. One example of a cancer with possible genetic influence is non-small cell lung cancer (NSCLC). Our goal is to identify what inherited genetic mechanisms underlie familial non-small cell lung cancer. This paper will begin by looking at the epidemiology of NSCLC and then identifying the specific genes that are associated with it in families. In particular, we will look into mutations of the genes EGFR, ALK, HER2, KRAS, and p53 because of their occurrence in NSCLC cases as well as research done using genome wide association studies. We examined these genes in order to understand the specific genetic mechanisms that cause NSCLC. We did this by reviewing and interpreting the data from primary research articles. In the end, we were able to identify how EGFR, ALK, HER2, KRAS are tumor promoters, while p53 is a tumor suppressor. We also examined specific inhibitors that are available to cancer patients who are afflicted with these mutations. Using this data, we hope to inform afflicted patients and their families about their mutations, as well as potential treatment options.

Introduction

Currently, lung cancer is the leading cause of cancer death in the world, with deaths from lung cancer accounting for 1 out of 5 cases [1]. It is the second most common case in men after prostate cancer, as well as the second most common cancer in women, after breast cancer. Unsurprisingly, lung cancer is most common in places where the smoking rate is higher. Lung cancer is the most common cancer for men in 37 countries, including Russia, China, most of Eastern Europe, the Middle East, and Southeast Asia. Meanwhile, for women, lung cancer is the most common cancer in North Korea [2]. Despite this, some good news can be seen: compared to 1992, lung cancer cases in 2020 have fallen lower because of a lull in smokers [3].

Mortality rates in lung cancer are extremely high. In 2018, lung cancer was considered the leading cause of death for men in 93 countries, including the US, China, and Russia. Meanwhile, for women, it was the leading cause of death in 28 countries, including the US and China [4]. Unlike men, the lung cancer susceptibility rate had increased for women. In 2017, lung cancer passed breast cancer as the leading cause of cancer death in Europe.

One type of lung cancer is non-small cell cancer, or NSCLC. It can affect both smokers and non-smokers. It has three subgroups: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [5]. Adenocarcinoma lung cancer is the most common, especially for non-smokers, and it is typically seen along the outer lungs. Meanwhile, squamous cell carcinoma usually begins in the middle of the lungs. Lastly, large cell carcinoma begins anywhere in the lungs [6]. No matter the type, lung cancer and other cancers in general are extremely impactful on our population, and many studies have been done in order to combat this disease. One of these aspects is studying one's genetics.

One question that comes up when researching cancer, and lung cancer specifically, is its possible genetic impact or cause. Genes like EGFR, ALK, HER2, and KRAS are all responsible

for cell growth [7]. When mutated, these genes can cause lung cancer and cancerous cells to spread more quickly because of the disruptions caused in a cell's mechanisms. Another gene that is frequently mutated in cancer is p53, which stops the formation of tumors [8]. Other non-genetic factors that impact cancer formation can include one's environment and habits. For example, smoking can increase one's risk for lung cancer substantially [9]. By looking at the effects of one's environment and lifestyle, called epidemiology, we will be able to increase understanding of the *why* behind lung cancer, making the research into its specific factors much easier.

It is important to understand the mechanisms that impact the development of NSCLC in order to be able to create treatments that effectively target it. This paper will examine specific cases of NSCLC development and data from clinical trials regarding specific genes in order to highlight the most important factors that impact NSCLC development.

Epidemiology

One of the largest factors in lung cancer is one's environment, and more specially, smoking. Cancer develops as a result of the abnormal spread of cells, which often occurs due to changes in sections of one's DNA, or genes. The chemicals that are produced by smoking are often toxic, and once they travel to one's lungs, they damage sections of our DNA. As a result, many of the remaining cells are unable to repair this damage, which can cause cancer cells to form [10]. Besides smoking, the impact of breathing it in and being exposed to it can also play an important role. This process, called second-hand smoke, can also cause lung cancer, since people breathe in some of these harmful chemicals. One's environment can also play a role in contributing to lung cancer risk. Air pollution and climate change have been increasing problems in this century, and because of this, people are breathing in much more harmful air. And while some believe this to be a problem of other sources, like gas emissions, it is actually shown that smoking cigarettes plays a vital role in climate change as well [11].

Another aspect in one's daily life that can affect lung cancer is one's consumption habits. When one consumes foods rich in Vitamins C and E, they are shown to have positive effects [12]. On the other hand, cured meats and alcohol have been shown to be harmful and detrimental because they contain chemicals that can damage cells [13].

However, there can be other factors that contribute to lung cancer that are not limited to one's environment or habits. Familial lung cancer susceptibility genes have been indicated as risk factors. For example, patterns for familial lung cancer were seen in the gene TP53, and those who carried this gene and smoked were increasingly more likely to develop cancer than those who abstained from smoking and carried the gene. So, while those with cancerous genetics are shown to be more susceptible to cancer, outside factors also have an impact, and together, the combination of these components contribute to cancer [14].

Despite the severity of lung cancer, survival rates are increasing. This could be due to a variety of different reasons, such as earlier detection thanks to new technology, improvements in treatment and targets, and the lull in smoking [15].

This evidence helps us understand the background of lung cancer, and it is time to focus on NSCLC. There are many genes that play specific functions in our cells, and because of mutations, these cells can go awry and cause lots of damage and possibly cancer. We have examined several GWAS experiments, which are Genome Wide Association Studies. By looking at these cases, we can identify specific genes that we want to focus on. EGFR, ALK, HER2, KRAS, and p53 all have specific roles in the function of our cells, and we will examine these genes on a closer level in order to determine possible genetic factors at play when being diagnosed with lung cancer [16].

Genetic Factors that Contribute to Lung Cancer Development

Even despite the environmental factors, another huge impact on lung cancer can be seen on the molecular level. The human body's cells are constantly carrying out mechanisms for one's body, and without them, our bodily functions would not be able to occur. This is why the impact of mutations in a cell is so dire. Once a cell mutates, it can divide uncontrollably and oftentimes, this process can cause cancer. We will examine several genes that control the dividing processes of the cells, including EGFR, ALK, HER2, and KRAS, before focusing on a gene that deals with the stop of the dividing process, p53.

EGFR

The gene EGFR is also known as Epidermal Growth Factor Receptor. In cells, growth factors are molecules that control division and migration of cells. The epidermal growth factor (EGF), controls epithelial cells, which come before carcinomas. Epithelial cells are one of the most common cells in one's body, and they are crucial in controlling the human life cycle [17]. Carcinomas are cancers that begin in one's skin or tissues that line our internal organs [18]. Carcinoma's receptor, EGFR, can cause cancer through amplification of cells, and many mutated forms of EGFR can be found in brain, lung, and other cancers. In lung cancer, point mutations (a single nucleotide base) and insertion mutations are frequently seen as mutations of this gene. Because of this, EGFR and its partner gene, HER2, are often targeted in lung cancer treatments [19].

Mouse Models and Doxycycline

EGFR is one of the most frequently mutated genes in cancer and is associated with many other genes in the same subgroup, including HER2, which will be discussed later. As seen in a study done in 2021, common EGFR mutations include deletions in exons 2-7, as well as deletions in exon 19, and T-G base substitutions in exon 21 [19]. EGFR is commonly overexpressed in many cancers, including lung and breast. Gliomas and lung cancers especially are seen to have high levels of EGFR. Patients with both of these cancers are often female, nonsmokers, and Asian. Moreover, other mutations within this subgroup are known to have sensitivities towards several tyrosine kinase inhibitors (TKIs), which are developed by researchers that are used to target certain cancerous mutations. Some EGFR TKIS include gefitinib and erlotinib [19]. However, there is still uncertainty behind the connection between responses to TKIs and cancer survival rate.

To understand the connection between TKI responses and cancer survival rates, researchers tested these specific mutations in mice. They examined gene expression after these genes were transferred, using doxycycline, which is used to induce gene expression of mutations as well as

prevent infections. The usage of it didn't appear to affect their results. They compared the results of this experiment by administering doxycycline to some mice, while withholding it from others. In order to display their results, researchers used an antibody that identified both human and mouse EGFR. In order to depict these results more clearly, more doxycycline was injected. They concluded that this type of cell growth seen in these mice was BAC, or bronchioloalveolar carcinoma. [19].

Overall, this experiment consists of many studies done on genetically engineered mouse models. Using this new specimen, scientists were able to model many types of lung cancer and specific mutations in EGFR. Additionally, by using doxycycline on some mice and withholding it from others, they were able to observe many differing results. This study provided important information for researchers to understand how specific EGFR mutations impact function and how they might be resolved. The usage of doxycycline can be used in the future for other studies, and overall, we are now able to understand the processes of mouse models and the injection of cancerous cells more clearly [19].

ALK

ALK stands for anaplastic lymphoma kinase, and its gene rearrangements have been seen in a few NSCLC cases. ALK is essential for cell signaling and making sure proteins are made. These gene rearrangements affect downstream cell signaling, which when mutated, can have many harmful effects on a person's DNA [20]. An embryo contains the ALK gene in its body, and its purpose is to help the gut and nervous system develop. Once the child is out of the womb, this gene gets turned off. However, for some people, ALK turns back on and fuses with another gene, causing ALK fusion/ALK rearrangement. In turn these mutations can cause lung cancer. The gene that ALK fuses with most often is EML4, which has many subtypes of its own [21]. Despite this, when a patient is ALK-positive, it can affect them in many different ways, often causing one's immune system to become weaker [22].

ALK Rearrangements

In this study, researchers wanted to find better methods to identify the presence of ALK rearrangements in NSCLC. They planned to do this by testing two DNA/RNA based methods, next-generation sequencing (NGS) and Ventana immunohistochemistry (IHC), in order to determine the effects of TKIs, or tyrosine kinase inhibitors [20].

14, 894 patients with NSCLC were collected. 12,533 of these samples were analyzed and extracted using DNA-based NGS, while 2,361 were analyzed using RNA-based NGS. In comparison, all these samples were analyzed using Ventana IHC. [20].

Out of the 12,533 patients who were detected with DNA-based NGS, 3.5% of them were found to have ALK-rearrangements. To add on, the majority of these cases were found to be EML4 rearrangements, while the rest were KIF5B, KLC1, and GCC2, which are other types of rearrangements that are found in a cell. Meanwhile, for the RNA-based NGS, 2.2% out of the 2,361 subjects tested were found to be ALK-positive. The majority of rearrangements were EML4, while the others that were also seen included KIFB5 and KLC1. Lastly, for Ventana IHC, 3.63% of the ones that were analyzed using DNA-based NGS. Out of these 16 samples, there

were 15 atypical positive results and 1 atypical negative result. Meanwhile, in comparison to RNA-based NGS, 2.63% were found to be positive by Ventana IHC, and all results were typical. In total, 103 patients who were analyzed with NGS and Ventana IHC were found to have ALK rearrangements, and were able to receive crizotinib treatment. The overall response rate to this treatmentwas 71.84%. For the patients who received inconsistent responses, they received ALK-TKI treatment [20].

Overall, this study was done in order to identify ALK rearrangements using DNA and RNA-based NGS, as well as Ventana IHC in patients with NSCLC. The study provided important insight into researchers' ability to successfully detect ALK rearrangements through a combination of novel methods.

HER2

HER2 is another gene frequently mutated in lung cancer. Similarly to EGFR, it regulates cell signaling. Once mutated, it can create a cancerous cell, which is a result of over-expression and gene amplification. However, one difference is that HER2 doesn't bind to any molecules, while EGFR does. Despite this, their functions are very similar. Most often, a HER2 mutation can be found in an individual who has NSCLC and with little to no smoking history. The most significant mutation in HER2 is called an exon 20 insertion [23].

Exon 20 Mutations

While there are many TKIs that affect EGFR and HER2 mutants in NSCLC, patients with mutations in exon 20 do not appear to respond to any available therapies. To explore possible treatments for patients with these mutations, researchers tested a variety of inhibitors. About 10-15% of those with NSCLC have "classical" sensitizing mutations in the exon 19 region. These mutations can be targeted through gefitinib and erlotinib. 70% of the patients treated with these TKIs have received good responses. On the other hand, 10-12% of these tumors have mutations in exon 20 insertions. These insertions are resistant to any of the TKIs mentioned above, which poses a problem. This is especially relevant for those who have HER2 mutations, since 90% of HER2 mutations in NSCLC are exon 20, and 3% of patients with NSCLC have HER2 mutations. Overall, EGFR and HER2 exon 20 mutations are found in 4% of all patients with NSCLC [24].

As a result of this, researchers examined patients with exon 20 mutations and their responses to erlotinib, gefitinib, and afatinib. For these treatments, patients with regular EGFR mutations had a median of 14 months, compared to the 2 months of those with exon 20 mutations. Knowing these results, scientists resolved to find out the reason behind the resistance to EGFR TKIs. By using 3D modeled crystal structures, it was concluded that these mutations have an increased affinity to ATP, which therefore causes a lack of binding for inhibitors. Because of the aforementioned experiment, researchers wanted to change and develop the binding factors of exon 20, which would then help TKI's become more effective. They figured out that the TKI poziotinib would be most effective, and since it successfully bound and prohibited EGFR and HER2 kinases. It was also able to stop cell death in their mutated NSCLC cell lines [24].

Additionally, to test its usage even further, scientists used mouse models in order to compare poziotinib to afatinib. Once cancer cells were injected into mice and clear tumors were shown, a

portion of these test subjects received poziotinib treatments, while another portion received afatinib. These tests turned out to be more successful with poziotinib treatment, since it reduced tumors by more than 85% in eight out of nine mice [24].

This study points towards the effectiveness of poziotinib. Before, the exon 20 mutations that afflicted NSCLC patients were not able to successfully receive any treatment from any TKI. Because of this study, scientists and doctors are now about to use poziotinib in order to target these mutations [24].

KRAS

KRAS is responsible for cell growth. It provides instructions for making a protein called K-Ras, which is located in the RAS/MAPK pathway. This pathway is important because it communicates cell signals from the outside of a cell to a cell's nucleus. These signals are useful because they are in charge of instructions for a cell to grow/divide (proliferation) or mature and perform special functions (differentiate). This protein is called a GTPase, which converts a molecule called GTP into another called GDP. In order to transmit signals, the K-Ras protein must be bound to a molecule of GTP. When it is converting GTP to GDP, it is "turned off", and when it's bound to GDP, it cannot transmit signals to a cell. For lung cancer, mutations in the amino acid glycine cause the K-Ras protein to be "always on". Cancer is the uncontrollable division of cells, and K-Ras protein "on" stage is especially dire, since it causes cells to proliferate beyond their normal rate. These mutations are more common in smokers with lung cancer [25].

In order to further determine the actions of these genes and how they act in a cell, this next study will examine KRAS in a cancer cell and how it reacts towards treatment and therefore survival rate.

KRAS and Cell Signaling

In this experiment, scientists aimed to test KRAS and determine its purposes in NSCLC mutations. Specifically, they wanted to observe the substitutions in mutated KRAS amino acids. They were able to use 215 patient tissues and tested them with various TKIs, including erlotinib, vandetanib, bexarotene, and sorafenib. Scientists observed these subjects for eight weeks, before eventually extracting RNA for further study [26].

Overall, this trial, called the BATTLE trial, determined that these KRAS mutations as a whole did not play a part in any survival rates. When examining these mutations separately, researchers determined that out of the 268 patient samples, 48 had KRAS mutations. They were also able to analyze the amino acid data and how it related to KRAS and patient survival [26].

They were also able to analyze the effect of KRAS mutations on downstream cell signaling, and every test came to the same result. The mutated KRAS gene did not have any effect on any survival rate. However, this study was also able to find the connections between amino acid substitutions and survival rates. Overall, with these findings, researchers delved deeper into the connections between KRAS mutations, survival rates, and connections to downstream cell signaling pathways and amino acids. With the results above, we can determine the relationship between mutated KRAS, and with this new evidence, researchers can look into gene mutations

and how they affect proteins and cell signaling. This can be especially relevant to further studies. Despite not much knowledge about this specific study, researchers are hopeful and aim to conduct more studies on this subject [26].

P53

P53 is the gene that stops cells from dividing, which stops the formation of tumors. Unlike the other genes, which controlled the “start” amount of cell division, p53 controls the “stop”. It is found inside the nucleus, and mutations will cause cells to divide uncontrollably, which therefore causes cancer [27]. Oftentimes, it is also called the tumor protein suppressor p53. Normally, it functions in the nucleus of the cell, where it binds to DNA. When DNA gets damaged, for example by UV rays, the purpose of p53 is to determine whether the DNA will be repaired or will self-destruct. If it can be repaired, p53 alerts other genes to fix it. If it cannot, then p53 will signal for the cell to self-destruct. Since p53 stops mutated and damaged cells from diving, it therefore prevents tumors. So, p53 mutations are especially relevant because they have the power to completely change all the functions of a cell and create irreversible damage. If the p53 gene is mutated, cell division will continue uncontrollably, which can lead to the formation of a tumor [28].

DNA and Cell Growth Regulation

Because of the important role of p53 in controlling cell growth, researchers sought to understand how specifically it was able to do so. They were able to use bacterial strains, plasmids, and antibodies in order to collect their data. In order to model it, they used western blots. First, they started by cloning p53 in order to more closely observe both its wild type and mutated type. Using western blots, they mapped out the DNA binding of both respective cases [29].

In this study, they found that wild type p53 is linked towards a DNA binding domain in the C-terminus of a molecule. This area is very secluded and is central for DNA binding and regulation. They determined that DNA binding and transcription is monitored by p53 as well. Overall, these results can be used to determine the important function of p53 in a cell and how its mutated version can have extreme effects when applied to cancer [29].

Overall, despite the differing mechanism of p53 when compared to the other genes discussed, it is still very relevant to the study of genetics in cancer today. Scientists must observe all possible TKIs and treatment options, and in order to do so, they must examine every gene. Because of this study, researchers are now able to use this information in order to gain more knowledge about this particular gene, and utilize it towards more studies in the future [29].

Conclusion

While the growing prevalence of lung cancer is becoming increasingly more significant, as the world continues to progress and develop, there is much more new technology that can help combat this disease. By examining specific genes and their mutations, a connection can be linked from genetic mechanisms and the inheritance of lung cancer, and specifically, NSCLC. Beside the genes EGFR, ALK, HER2, KRAS, and p53, there are many more genes and possible genetic applications that scientists can discover. With the usage of tyrosine kinase inhibitors, researchers and doctors hope to target these mutated genetics and further research for a cure to cancer.

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