

The Correlation Between Idiopathic Pulmonary Fibrosis and Lung Cancer

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Abstract. The prevalent chronic lung condition known as idiopathic pulmonary fibrosis (IPF) is defined with the repeated scarring of pulmonary tissues. About 3 million individuals are impacted globally, and that figure is only increasing. There are no effective treatments available right now to help IPF sufferers with their symptoms. The lungs, one of the essential organs in charge of exchanging oxygen, are affected by lung cancer, a terrible condition that can be fatal. It affects both men and women of all ages and is the main reason for cancer-related deaths globally. This research focuses on the correlation between similar risk factors and related causes of these two diseases. By discussing the transforming growth factor β (TGF- β) and telomeres, it would be able to see how the two diseases are related. In addition, targets for the vaccination will also be analyzed, and the current stages of clinical therapeutic methods will be discussed.

Keywords: lung cancer; idiopathic pulmonary fibrosis; relationship.

1. Introduction

Cancer remains one of the most significant public health challenges worldwide. It is not uncommon for people to become anxious at mentioning a tumor growing in them despite substantial advancements in medical science. The complex nature of the disease has a simple causation with the mutation of just 2 to 3 genes within the genome of a cell, which may result in substantial effects: the growth pattern of the cell may be disrupted while there is also an underlying risk of the spread of cancer cells. It necessitates continuous exploration for more effective and targeted therapeutic strategies. While the hotspot of cancer may not cool down for another decade, some of the works in therapeutic vaccine treatment for cancer show promising results and may change how cancer could be treated.

Traditional ways of treating tumors, such as chemotherapy and radiation therapy, are still valid, but they significantly damage the patient's body. Chemotherapy's mechanisms differ by the types of chemical substances used during the treatment. At the same time, they present positive results of eradicating the tumor. It is also unavoidable for them to decrease the patient's immune system. Conversely, radiation causes severe destruction to the cancer cells and the normal cells, bringing the patients plentiful distress. Hence, in the early 1990s, anti-cancer vaccines were developed to identify tumor-associated antigens.

Like all vaccines, cancer vaccines come in two types: prophylactic vaccines and therapeutic vaccines. Over the past decade, cancer vaccines in treatment for human papillomavirus (HPV), Hepatitis B, and Hepatitis C have already been approved by the Food and Drug Administration (FDA). They have few side effects compared to conventional cancer treatment methods, making themselves hot on the market. Though numerous vaccinations are undergoing various stages of clinical trials, research and development into cancer vaccines are still in their relative infancy. To examine preventive and therapeutic vaccinations, the scientific theories supporting their application, and the advancements made thus far in this field, this research will address the present research in cancer vaccines. It will also examine how well they work based on information from clinical trials, actual uses, and difficulties encountered during development. The goal is to present a thorough grasp of the possibilities and challenges in cancer vaccine development, opening the door for debates on potential

future directions and oncology breakthroughs. And this research will discuss the therapeutic targets that could be mediated in developing a vaccine against lung cancer. It will look at the correlation between idiopathic pulmonary fibrosis (IPF) and lung cancer. In contrast, they are discovering similarities in their pathophysiology and how their correlation may bring susceptible targets to vaccination.

2. IPF and Lung Cancer

IPF is becoming increasingly common in contemporary culture. Coughing, weariness, shortness of breath, and rounded and swollen fingers are among the symptoms. The manifestation of these symptoms in patients' daily lives will be less active, producing complications in everyday activities. The condition can be fatal, and the average survival time following diagnosis is roughly 2-3 years. Furthermore, if medical costs rise, families' financial strain may grow. Because there is no viable cure for IPF yet, current treatment is limited to relieving patients' symptoms. Two new drugs, pirfenidone and nintedanib, have been developed to help people with IPF, but the results have been unsatisfactory. IPF can be caused by hereditary or environmental factors such as smoking, illness, and dust. The risk also rises with age [1]. Though the pathogenesis of IPF remains unknown, it is identified that the transforming growth factor (TGF)- β plays a crucial role in the proliferation of fibroblasts. For example, it can be found 324 individuals with lung cancer among 3178 IPF patients (prevalence=10.2%) and recorded them in ten years. By the end of the study, it was recognized that lung cancer patients had increased to 26.6 percent. Evidence of a correlation is present. In a retrospective survey, the research conducted computed tomography scans of 917 patients with primary pulmonary cancer. They classified them as to whether they had pulmonary scarring or not. The results show that one in three patients had pulmonary scarring, further evidence of a correlation.

3. Pathogenesis Similarity Between Essential Risk Factors

3.1. TGF- β Pathway Correlation

TGF- β is an essential cytokine that needs to be considered in both IPF and lung cancer [2]. An essential mediator governing apoptosis is this growth factor its role includes but not limited to the development of organs, the immune system, cancer metastasis, and progression are all cardinal to the human body. TGF- β signaling pathways can promote cellular growth in cancer cells but restrain cellular growth in benign cells. Such a strange characteristic is named the "TGF- β " paradox [3]. Such a paradox remains a mystery, but it could be partially explained: extracellular signal-regulated kinase (ERK) is an enzyme that enables signals to be passed to the nucleus. It was previously thought that when prevalent in cancer cells, TGF- β promotes the inactivation of ERK. However, such activation or inactivation relates to the concentration of TGF- β . In cells that shows benign symptoms, TGF- β with a low concentration may activate ERK and cell proliferation while creating an auto-introduction of TGF- β . Thus, the concentration of TGF- β rises, leading to growth arrest and creating negative feedback. However, ERK would be activated in cancer cells no matter the dosage. The master regulator of tumor development and metastasis is the activated ERK. Additionally, it will produce additional TGF on its own, resulting in a positive feedback loop of TGF-signaling in tumor development. TGF- β promotes cell proliferation, inducing angiogenesis, hence creating an environment suitable for tumor growth. While on an innate immunity level, TGF- β stimulates regulatory T cell proliferation, which counteracts effector T cell activity that controls the activation of macrophages. Hence, innate immunity and adaptive immunity are both mitigated, creating an environment suitable for tumor growth.

The role of TGF- β within IPF is simple; this cytokine has already been classified as the most decisive profibrotic factor [1]. Through SMAD protein pathways, in the initial stages of TGF- activation, TGF-ligand be able to bind to a heteromeric complex. The receptor-activated SMADs (R-SMADs), SMAD2 and SMAD3, are phosphorylated and activated. R-SMAD activation and proper signaling transmission are blocked by SMAD7's competition with R-SMADs for interactions with type I

receptors. Variety I receptors are split apart by activated r-SMADs to form a complex. The trimeric complex moves into the nucleus where it interacts with chromatin remodeling proteins (CR) and high-affinity DNA binding transcription factors (TF), which can be used to control the transcription of the target gene.

3.2. Telomere Correlation

To maintain the integrity of the chromosomes, “cap structures” are formed by repetitive nucleotide sequences known as telomeres. Their association with human diseases such as IPF and other germline or degenerative somatic disorders has long been understood. As we now understand, telomeres protect the chromosomes from losing genetic information. After each replication, they lose parts of their genetic sequence and get shortened. To prevent telomere attrition, telomerase is manufactured by germline cells and somatic cells, an enzyme that catalyzes DNA synthesis to keep telomere length constant. To synthesize DNA content to maintain telomeres' length, Telomerase reverse transcriptase (TERT) molds off the telomerase RNA component (TERC). In a study conducted by Armanios et al., they examined 73 families known to have familial idiopathic pulmonary fibrosis [4]. Among these, 6 families tested positive for a TERT and TERC genetic mutation, proving the relevance of such genetic mutations to IPF over other causes. Their modification was also proved common in patients of IPF with no family history [5]. It is also understood that telomere shortening causes dysfunctional chromosomes, which triggers genomic instability, a cancer mark. Interestingly, similar to the TGF- β paradox, it has been examined that even patients with long telomere mutations are more susceptible to cancer than those with medium length.

3.3. What is the Correlation Between TGF- β and Telomeres about Tumorigenesis?

In cancer, telomeres and TGF- β have a complex interplay. TGF- β signaling can cause telomere shortening by suppressing telomerase expression or activating telomere-shortening pathways. Reducing cell proliferation and encouraging senescence may support TGF- β 's tumor-suppressive actions. On the other hand, advanced-stage cancers frequently have aberrant TGF- β signaling, which encourages tumor growth. TGF- β may occasionally promote telomerase expression, preventing telomere shortening and promoting unabated cell growth. TGF- β signaling can also interact with another telomere maintenance-related molecular pathways, such as the p53 pathway, resulting in complicated interactions and possibly affecting carcinogenesis.

Telomeres and telomerase were shown to control TGF- β 's effects on cell senescence and cell proliferation, two processes known to be influenced by TGF- β . It was recently discovered that TGF- β increased the histone methyltransferase expression, hence regulating telomere length. The shortening of telomeres thus can be used to increase the vulnerability of the cellular genome, making unstable genes and creating an environment that would only be friendly to cancer development. As shown in the above paragraphs perhaps TGF- β would be the susceptible target for vaccination. Due to its complexity however, it must be carefully examined on whether it could really be muted or knocked out.

3.4. How does the Correlation between IPF and Lung Cancer Bring Susceptible Targets to Vaccination?

As mentioned in the above text, correlations between the pathology of IPF and lung cancer present susceptible targets. The identified cytokine of vaccination would be TGF- β . Current measures could be taken to exemplify genetic silencing methods of reducing the number of TGF- β receptors, especially T β RII.

Recent advancements in therapeutic methods in treating both cancer and fibrosis have shown promising results by targeting TGF- β [6-10]. Therapeutic trials are still in their early stages, but viable methods that may inhibit TGF- β pathways are already prevalent [6]. The most recent research showed that sorafenib inhibits TGF-signaling by directing TRII into a route driven by lipid rafts and caveolae and ultimately into specific locations for destruction. Though it must be mentioned, through

experiments, it is already proven that a total knockout of TGF- β would do more harm than good. And, the TGF- β should be activated, as shown in Fig. 1. Hence, the level of inhibition would be another factor to consider.

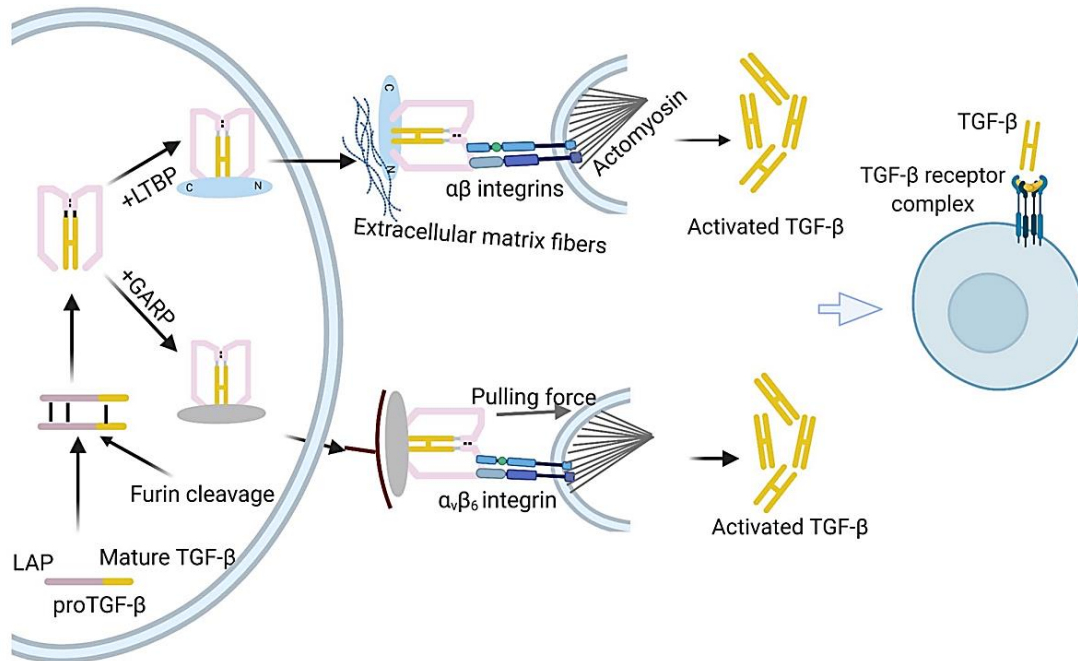


Figure 1. A schematic illustration for the TGF- β activation [7].

Furthermore, though sometimes it is reasonable to have a systemic reaction in response to the vaccines developed, it should consider whether it does better than bad or the other way around. Questions that it should consider while developing this vaccine is that are able to control the reaction in a way that it can only be local. Some experiments use monoclonal antibodies as their missile for therapy, but the targeted receptor is currently only found in mice. Improvements are needed to discover a similar receptor in the human body.

4. Conclusion

In scattered pieces, it is able to see a correlation between IPF and cancer. Through future analysis of similar risk factors between both diseases, it would be believed that there will eventually be a way to eradicate these diseases. TGF- β is only one of the millions of cytokines with essential roles within our immune system. It cannot be sure whether inhibition of such a cytokine would lead to unwanted results or successful trials. Current therapeutic methods are still novel, and it must have the patience to wait for a breakthrough. Teams are already working on promising methodologies for delivering vaccination vehicles. Missile therapies may be the future as a therapeutic target receptor is already known. Another notable experiment using antisense oligonucleotide in LNA-Gapmer design proves the safe and effective inhibition of TGFBR2 is possible.

It is very much possible that years are to come before a possible drug can be invented. In the meantime, traditional methods of chemotherapy would still be the most effective way of treating cancer. Individuals with IPF or any other chronic lung illness should take the necessary steps to safeguard their respiratory health. In order to avoid respiratory infections, which can increase lung damage and perhaps worsen the condition of those who already have lung disorders, this may entail taking the required immunizations.

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