The Wnt and Hippo Signaling Pathway on Lung Cancer Treatment: A Descriptive Research

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ABSTRACT

Wnt signaling pathway and Hippo signaling pathway are two pathways in cancer treatment research. Many essays have discussed the signal initiators and inhibitors that influence the pathways used for cancer treatment. In this article, there are two elements that each pathway use in cancer treatment research. The circRNAs and matrine are inhibitor processes in the Wnt signaling pathway. In research, people use them to decrease the growth rate of cancer and limit cancer migration. And then, for Hippo signaling pathway, one of the YAP inhibitors in the pathway is Claudin, which controls the overexpression of YAP protein, thus causing the progression and migration of cancer. Also, the plumbagin and cisplatin synergistically inhibit LAST1 and YAP, which can inhibit cancer.

KEYWORDS

Wnt signaling pathway; Hippo signaling pathway; CircRNAs; Matrine; Claudin; Plumbagin; Cisplatin

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1 Introduction

Lung cancer is one of the most common cancers in the world, with the highest death toll. Lung cancer is classified into small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) according to the biological cell structure. Most lung cancer are NSCLCs, accounting for about 80-85%, but NSCLC is more difficult to cure than SCLC. Recently, the signaling pathway has become popular in cancer treatment research, but it is still a new method that people use. In several articles that research the signaling pathway, people figure out the significant relationship between those pathways and several cancers, but it is not generally used in clinical treatment. Also, it has been found that many different pathways can influence cell growth, replication, and reproduction, and each signal pathway may interact with the others. Most of the papers focus on explaining the relationship between pathways and cancers or chemical works on the pathway, it is rare that show clinical experiments and data that prove the function of the signaling pathway, which is essential that be more convincing to the reader to understand. Right now, the research about signaling pathways working on Lung cancer is in been initial stage, many more areas require people to search and conduct intensive studies.

Thus, in the course of cancer treatment research, it is hard but necessary to know several pathways, one needs to consider many elements and resources that may help kill cancer cells or limit the reproduction of cancer cells. This article is an introduction and summary of two signaling pathways related to cell therapy, to understand the promotion or restriction of lung cancer-related signaling pathways to limit and kill NSCLC cells, and to figure out the relationship between the two signaling pathways that may work together. Cell signaling pathways are not commonly used in medical or chemical therapy. Introducing these two signaling pathways may help people understand and study

the signaling pathways with cell cancer therapy. First, the Wnt signaling pathway is found in rat cells and is associated with the production of cancer stem cells. Wnt proteins bind to the Frizzled (FZD) family proteins and bind to the axin protein group, which phosphorylates the β-catenin and degrades it when the Wnt signal is turned off. Then the free β-catenin interacts with DNA in the nucleus with TCF/LEF to transcribe and produce Wnt response genes that contribute to cell cancer. Then, the Hippo signaling pathway is found in the Drosophila cell, which is activated at the beginning of cell and organ growth. In mammal cells, the Hippo protein is released by Mst1/2 protein, but both can be activited by Mer and Exp proteins. When Mst1/2 protein is active, it phosphorylates Lats1/2, which phosphorylates the YAP/TAZ protein, leading to YAP/TAZ decomposition. If Hippo signaling is turned off, YAP/TAZ will interact with TEAD, a transcription factor that increases the production of many oncogenic genes.

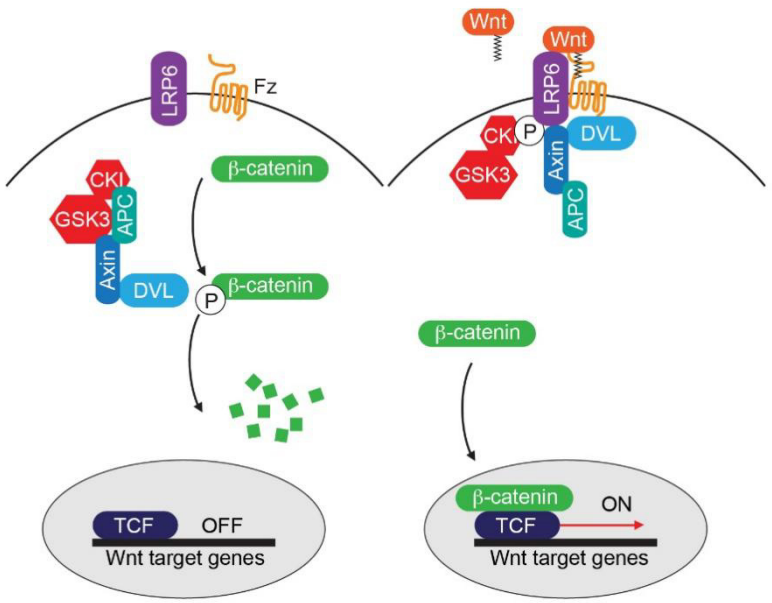

Figure 1. Wnt signaling pathway

Second, regarding the signaling pathways relevant to cancer treatment, inhibitors are the most common treatment methods that limit cancer growth and migration. About the Wnt signaling pathway, studies on circRNAs and matrine have found that these are related to Wnt/β-catenin and contribute to lung cancer cell treatment. At first, circRNAs have been used in cancer treatment, and researchers have demonstrated that many circRNAs may be related to the development of lung cancer and can be used as targeted therapy [1]. In the article, circRNAs help greatly in the treatment planning and early diagnosis of lung cancer therapy. Still, people lack cognition about the circRNAs' religion and function, and people are not able to control and create it. Then, many studies have talked about the effects of matrine on several cancers like liver cancer and colon cancer. Some studies have found that it also works on NSCLC, and some clinical trial results have shown that matrine can limit the proliferation of several kinds of lung cancer cells and make them disappear [2]. Through the experiment and clinical application shown in the article, matrines play an important role in A549 cancer cell limitations and degradation. They also suggest that try to use matrines to prevent cancer recurrence and metastasis, as there are good results in cancer treatment.

Third, the Hippo signaling pathway is usually an inhibitor of YAP/TAZ and Lats1/2 proteins, rather than Mst1/2. Because there are many other factors that can influence YAP/TAZ phosphorylation, the most important factor in the Hippo signaling pathway is YAP/TAZ. Claudin, plumbagin, and cisplatin

are inhibitors of YAP/TAZ proteins. Claudin is famous for its targeted treatment and has already been found in about 27 different members of the claudin protein family. Claudin-3 has been found to be overexpressed in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) relative to several signal pathways. Claudin-3 protein helps to detect the recovery and survival rate of patients after the surgery [3]. Also, the overexpression of claudin-7 can break down cells through cell connections, leading to the inability of cancer to grow and migrate, which is relative to many kinds of cancers [4]. About the plumbagin, it restrains NL9980 cells, or NSCLC, which are dependant on the concentration of plumbagin [5]. Finally, cisplatin has already been used in cancer treatment for a long time. People have found that cancer cells are resistant to cisplatin, so they try to use other things in combination with therapy, and claudin is one of them.

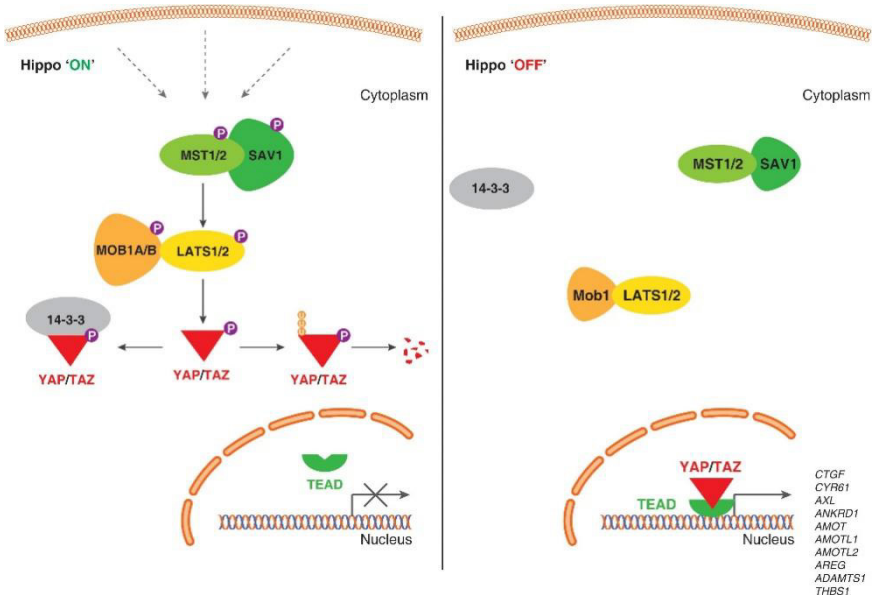

Figure 2. Hippo signal pathway

2 Research Analysis

CircRNAs have a huge family, with several signaling pathways associated with circRNAs' family. One essay talks about the expression of circRNAs will influence Wnt/β-catenin activation, promote or limit the growth and migration of lung cancer cells. The data show that circ-SOX4 has high expression of Wnt/β-catenin and can activate and promote overgrowth, migration, EMT, and anti-apoptosis of cancer cells. Then, another circRNA, circ-ITCH has low expression of Wnt/β-catenin and can inhibit or contribute to the growth of cancer cell growth. According to Lingxia Wang, the use of circRNAs in cancer research is a new area and has been proven to involve the triggering, migration, invasion, and progression of lung cancer. CircRNAs interact with Wnt/β-catenin in cancer, which will become a new therapeutic target for cancer treatment [6]. Also, there is another paper discussing the circRNAs and Wnt/β-catenin in cancer therapy. Jinyou Li and his group published their research on the circCCT3 and miR-107 regulating the Wnt signaling pathway in NSCLC. At first, the research showed that circCCT3 regulated cancer cell A549 with decreased size and cell numbers, and then exposed the circCCT3 to opposite Wnt3a and miR-107, to show its expression. This demonstrates that the circCCT3 interacts with miR-107 and then with the Wnt pathway, which triggers the protein of the Fibroblast Growth Factor 7 (FGF7) gene to encode cancer genes and influence the NSCLC. Jinyou said that through this

research, they figured out the mechanism by which circCCT3 interacts with miR-107 through the Wnt pathway to NSCLC [7]. The article introduces the circCCT3 mechanism about the interact with Wnt pathway to FGF7 factor, that relative with EMT and targeted therapy.

The second type is matrine, which is rarely dicussed from the Wnt pathway. Li Xiuwei and his group wanted to figure out the function of matrine on lung cancer. At first, they found out that matrine worked on A549 lung cancer cells, which became smaller than usual. Research also showed that matrine, combined with the radiotherapy, enhanced the influence of A549 on the formation rate and tumor size. Then, the data show that matrine after radiotherapy can influence several proteins with pathway, one of which is β-catenin, which decreases as the number of phosphorate radicals decreases, and c-myc downregulated by the Wnt pathway gene also shows a lower number. Li can increase the sensitivity of lung cancer cells to radiotherapy through matrine, which may be related to the Wnt/β-catenin pathway , and then regulate cell growth and migration [8].

Furthermore, regarding the Hippo signaling pathway, claudin (Cldn) plays a significant role in cancer treatment, and it is variable, containing many proteins in members of the Cldn family. The essay "The correlation between YAP and claudin and lung cancer stem cells" wanted to figure out the interaction between claudin and YAP transcriptional regulatory proteins. They mentioned the lung cancer stem cell (LCSC) hypothesis related to tumor triggering, processes, and drug resistance associated with YAP expression. The Hippo signaling pathway triggered the activation of YAP expression, while the Cldn group contributed to regulating YAP activity. According to their study, silent Cldn-3 could decrease the activity of YAP protein, and Cldn-6 was related to another Cldn expression. In addition, Cldn-7 was considered to be the end-point factor in the pathway. Cldn-18 with high expression would increase cancer growth and migration, but overexpression of Cldn-18 would decrease the activity of YAP protein through transcription. Thus, Zhou Chan believed that the Cldn family played an important role in the Hippo signaling pathway of YAP protein, and it was necessary to have more research on it [9]. Also, there is an article about the discussion of Cldn-18 relative to the YAP regulator lung stem, which explains in detail about the effect of Cldn-18 expression level on lung cancer cells. Beiyun Zhou concluded that Cldn-18 restricted the YAP activity with the growth and migration of cancer cells [10].

Then, here is an essay that talks about the synergistic regulation of lung cancer cells through Hippo signaling pathway by plumbagin and cisplatin. In the experiment, plumbagin was used to compare the inhibition of A549 cancer cells with different volumes. The more plumbagin there was, the more A549 cells were restricted. Also, there is a sample shows that plumbagin and cisplatin limit lung cancer cell form and numbers, respectively, that they interact better when used in combination than when used alone, and that the combination works well at an apoptosis rate of about A549 cells. Related to YAP and Last1, processes in the Hippo signaling pathway combined with plumbagin and cisplatin influence the expression of YAP and Last1 proteins and inhibit the expression of A549. The research results of Li Yan's group indicated that compared with the control group, the combination of plumbagin and cisplatin interacts with A549, and the single element group has a high proliferation inhibition and apoptosis-inducing function, which is closely related to the Hippo signaling pathway [11]. The research helps to find the relationship between the plumbagin group and the Hippo signaling pathway and wants to further experiment to prove or found the ingredients that process and anticancer ability, and then relative to traditional Chinese medicine working on cancer therapy.

3 Conclusion

The Hippo signaling pathway and Wnt signaling pathway contain a large number of studies related to lung cancer regulation, mainly focusing on specific proteins or genes interacting with transcription to limit the anti-cancer factors to process the restriction of tumor growth and migration. However, most of the research has tried to find out the relationship between cancer and the material, and then figure out the pathway, rather than using the pathway to discover new kinds of substances that can be used to treat cancer. One of the reasons for this is that the signaling pathway is a new idea, so there are not enough experiments or studies on inhibitors or enhancers associated with it, and it takes time and lots of experiments to figure out possible uses for cancer therapy through this pathway. Second, researchers prefer to use known drugs that are already used in cancer therapy to prove that the signaling pathway is an important factor, which is much easier to study experimentally. Third, the signaling pathway is complicated. For example, the Wnt signaling pathway is surrounded by many proteins and protein families. When interacting with one of them, the pathway will change. Also, Hippo and Wnt are relative, one of the ends of transcription of the Wnt pathway can participate in Hippo pathway expression. The signaling pathway looks like a web, it is complicated to figure out and can influence each other. However, some achievements have been made in the research of the signaling pathway. There is a serious problem in cancer therapy, namely, drug resistance. The signaling pathway is a great direction for finding elements on the same pathway and combining them for treatment. As several articles focus on the combination of therapy and it increases the expression, which is better than separate, it is a good solution to drug-resistant problems. Combined medication is a common way of cancer therapy, especially targeted treatment or chemotherapy. When working with radiotherapy, it can also increase drug reactions, which may be related to the signaling pathway.

About the Author

Changhao Shen is an undergraduate of Arizona State University, and his research field is tumor immunotherapy and immune escape.

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