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Research Progress of *PTCH1* Gene in Lung Cancer

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Abstract

Background: The *PTCH1* gene, also known as Patched 1, is located on the long arm of human chromosome 9 (9q22.3). It encodes the PTCH1 protein, which is a critical transmembrane receptor within the Hedgehog signaling pathway (Hh), playing a pivotal role in cellular communication and developmental processes. Recent studies have highlighted the significance of mutations in *PTCH1* in the pathogenesis of lung cancer, positioning it as a crucial molecule for investigation in oncology. **Purpose:** This review aims to elucidate the role of the *PTCH1* and the Hedgehog pathway in the initiation, progression, and potential treatment of lung cancer, thereby providing a theoretical foundation for personalized and precise therapeutic strategies. **Method:** To ensure a comprehensive review, this study systematically searched for literature related to the *PTCH1*, lung cancer, and the Hedgehog pathway across multiple databases including PubMed, Web of Science, and CNKI (China National Knowledge Infrastructure). The search strategy involved using specific keywords and advanced filtering options to include the most relevant and recent studies. Initial screening excluded irrelevant articles, followed by a detailed evaluation of the selected studies based on their scientific quality and relevance. **Results:** This review indicated that specific mutations in the *PTCH1* gene are closely associated with the onset and progression of lung cancer. These mutations impede normal Hedgehog signaling, leading to unregulated cell proliferation and tumor growth. Targeting *PTCH1*, including vismodegib, have shown efficacy in clinical cases, particularly in SCCL with specific *PTCH1* mutations, leading to complete remissions. Furthermore, the interaction between *PTCH1* and microRNA-212 suggests potential therapeutic approaches by targeting miRNA to regulate *PTCH1* expression. In addition, the investigation of traditional Chinese medicines such as Ginsenosides and

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Cordyceps sinensis extracts has shown their potential to modulate the Hedgehog pathway and reverse drug resistance. **Conclusions:** An in-depth understanding of the precise mechanisms by which *PTCH1* mutations promote lung cancer could facilitate the development of targeted therapies. This study highlights the potential of *PTCH1* as a biomarker for diagnosis and a target for precision medicine in lung cancer treatment, advocating for further research into its molecular pathways and therapeutic applications.

Keywords

PTCH1, Hedgehog Signaling Pathway, Lung Cancer

1. Introduction

Cancer remains a formidable adversary in global health, claiming millions of lives each year. According to World Health Organization statistics for 2022, lung cancer is the leading cause of cancer-related mortality worldwide, particularly in China, where it accounts for 18.06% of all new cancer cases and 23.9% of all cancer deaths [1]. There are two main types of lung cancer: non-small cell lung cancer (NSCLC), which accounts for approximately 85% of cases, and small cell lung cancer (SCLC). Among the myriad molecular pathways that influence cancer progression, the Hedgehog (Hh) signaling pathway stands out for its critical role in tissue development and regeneration, and in particular for its aberrant activation in several cancers, including lung cancer.

The *PTCH1* gene, a central component of the Hh signaling pathway, plays a key role in modulating the activity of this signaling pathway. Located on the long arm of human chromosome 9 (9q22.3), *PTCH1* encodes a transmembrane receptor that, when mutated, significantly affects the initiation and progression of lung cancer. These mutations disrupt normal cellular communication and developmental processes, leading to unregulated cell proliferation and tumor growth. This review aims to dissect the intricate role of *PTCH1* and the Hh pathway in lung cancer, explore how their dysregulation contributes to disease initiation and progression, and explore their potential as targets for innovative therapeutic strategies.

2. The Role of *PTCH1* in the Hedgehog Signaling Pathway

The Hh pathway consists of three homologous genes, Sonic (Shh), Indian (Ihh), and Dessert (Dhh), encoding the Shh, Ihh, and Dhh ligands respectively. The PTCH1 receptor protein is encoded by the *PTCH1* and is capable of binding directly to the Hh ligand. The oncogene-encoded SMO receptor is an essential component of the Hedgehog (Hh) signaling pathway and acts as a positive signal [2].

PTCH1 is located on the long arm of human chromosome 9 (9q22.3) and exists in several isoforms, including protein_coding, retained_intron, proces-

sed_transcript, and chimeric_interrupted_transcript. The protein encoded by *PTCH1* is a receptor with 12 transmembrane structural domains in the Hedgehog signaling pathway and has a large cysteine-rich extracellular structural domain in its secondary and tertiary structures. Ligand binding and protein-protein interactions are thought to occur in these regions. *PTCH1*'s intracellular structural domain is relatively short and is mainly involved in downstream signaling. *PTCH1*'s quaternary structure, which is homodimeric or oligomeric, is its functional structure in cell membranes SHh is widely expressed in various tissues, IHh is expressed in bone and is associated with cartilage development, and DHh is expressed in the gonads and is associated with spermatogenesis. *PTCH1* inhibits the activity of Smoothened (SMO), another transmembrane protein, in the absence of Hh ligands. The binding of PTCH1 to the Shh ligand removes this inhibition and activates Smo. This activation facilitates downstream signaling, including activation of the Glioma-associated oncogene (Gli) transcription factors, which further regulate the expression of target genes and influence cell fate decisions [3]. *PTCH1* plays a crucial role in embryonic development, including the morphogenesis of the neural tube, limbs, and other organs, and regulates cell proliferation and differentiation in vivo, which are essential processes for tissue homeostasis. In addition, *PTCH1* and the Hh signaling pathway are involved in tissue repair and regeneration, which is reactivated after injury to adult tissues. *PTCH1* is a gene that encodes an inhibitory protein, and mutations in the *PTCH1* gene can lead to persistent activation.

3. *PTCH1* Gene and Cancer

Mutations in *PTCH1* activate the Hedgehog signaling pathway, which is implicated in the development of several cancers [4]. When *PTCH1* binds to the ligand Shh, it deregulates the inhibitory effect on the SMO transmembrane proteins. This process allows Smo to be activated, triggering downstream signaling, including the activation of glioma-associated oncogene (Gli) transcription factors. This subsequently regulates the sustained expression of target genes and promotes tumor development. More studies have identified that abnormal *PTCH1* expression in various cancers is associated with tumorigenesis, recurrence, metastasis, and treatment. For example, Wang et al. found that mutations in the *PTCH1* gene are associated with early recurrence of breast cancer [5]. *PTCH1* is a high-frequency mutated gene in gastrointestinal malignancies, and its mutation was found to be associated with gastrointestinal tumor metastasis [6]. In addition, its mutation may serve as a potential biomarker for predicting the response of patients with gastrointestinal cancers to treatment with immune checkpoint inhibitors (ICIs) [7]. Research has shown that *PTCH1* and methyltransferase-like 3 (METTL3) are highly expressed in oesophageal cancer cells. Knockdown of METTL3 reduces the level of N6-methyladenosine (m6A) modification and the stability of *PTCH1* mRNA. This, in turn, inhibits the ability of cancer cells to invade, proliferate, and migrate, as well as the ability of stem cells

to form [8].

By inhibiting Smo proteins, activators targeting *PTCH1* can prevent cancer development. Currently, certain natural compounds have been discovered that increase *PTCH1* expression. For example, the combination of epigallocatechin gallate (EGCG) and theaflavin (TF) was found to decrease Gli1 and Smo expression in mouse hepatocellular carcinoma cells, while increasing *PTCH1* expression and inhibit tumor cell growth [9].

As mentioned above, *PTCH1* plays a crucial role in the Hedgehog signaling pathway and research in various cancers has highlighted its importance in cancer initiation, progression, and response to treatment.

However, these studies have limitations in exploring the relationship between *PTCH1* and cancer. Firstly, the molecular mechanisms by which *PTCH1* mutations contribute to cancer progression require further elucidation. The precise regulation of SMO activity by *PTCH1* and its impact on the tumor microenvironment and immune escape necessitate further investigation. Secondly, regarding the study of *PTCH1* as a potential biomarker, the current focus is on correlation analysis between its expression level and clinical parameters, but there is a lack of large-scale, multi-center clinical validation studies.

Therefore, future research should aim to include such studies. 1) a detailed study of the specific mechanism of the role of *PTCH1* in the Hedgehog pathway, including its interactions with other signal molecules; 2) large-scale clinical studies to validate the stability and predictive value of *PTCH1* as a biomarker; and 3) to explore the possibility of *PTCH1* as a therapeutic target and to evaluate the safety of *PTCH1*-specific activators in cancer therapy; 4) to study the differences in the role of *PTCH1* in different cancer types and at different stages, as well as its potential for combination with other therapeutic agents (e.g. anti-cancer drugs).

Given the complex role of *PTCH1* in cancer development, future studies need to focus on the mechanisms that regulate *PTCH1* expression in different biological contexts and how to inhibit tumor progression by interfering with these mechanisms. This will provide a better understanding of the role of *PTCH1* in cancer and a scientific basis for the development of new therapeutic strategies, including immune checkpoint inhibitors. The text is already well structured and free of grammatical errors, so no changes have been made.

4. The Research of *PTCH1* in Lung Cancer

Current research suggests that *PTCH1* mediates the development of lung cancer through three pathways. The first pathway involves the overexpression of the Sonic Hedgehog receptor, which binds to *PTCH1* and deregulates its inhibitory effect on downstream SMOs. This triggers the activation of downstream signal transduction, including Glioma-associated oncogene (Gli) transcription factors. The second pathway involves mutations in *PTCH1*, which lead to the deregulation of downstream signal transduction and sustained activation of target genes.

Mutations in SMO can lead to uncontrolled downstream pathways and sustained activation of target genes. A study has suggested that decreased *PTCH1* expression may be a potential predictor of prognosis in resected non-small cell lung cancer (NSCLC) patients [10]. Additionally, inhibiting *PTCH1* expression has been found to significantly reduce the unanchored growth capacity of lung cancer cells and their potential to metastasize to bone [11]. A study of surgically resected lung squamous cell carcinoma (LUSC) found that the frequency of mutations in the *PTCH1* gene correlated with the density of CD8+ Tumor-Infiltrating Lymphocytes (TILs). This suggests that *PTCH1* mutations may have potential prognostic significance in patients with LUSC [12].

In a study of 958 patients with squamous cell lung cancer (SCCL), abnormal *PTCH1* expression was found in 2.6% of cases. Of the two metastatic SCCL cases with *PTCH1* mutations (basal cell-like variant), one carried the *PTCH1* s799fs*29 mutation with a Tumor Mutational Burden (TMB) of 3.7 m/Mb. Treatment with Vismodegib resulted in complete remission for more than a year. The second case was a poorly differentiated squamous cell lung cancer (SCCL) carrying the *PTCH1* W197* and W460* mutations. The patient was treated with Vismodegib, an oral small molecule inhibitor targeting the Smoothened (SMO) receptor, and achieved a complete remission for 7 months. These findings suggest that Vismodegib may be effective in treating SCCL with *PTCH1* mutations and warrant further clinical trials to verify its efficacy [13].

Research has shown that *PTCH1* can be targeted by microRNA-212 (miR-212), and its down-regulation in NSCLC is closely linked to tumor development. In this study, anti-miR-212, an inhibitor of miR-212, was used to effectively reverse the low expression of *PTCH1*, thereby inhibiting its promoting role in tumor development and demonstrating potential anti-tumor therapeutic effects [14].

It is currently believed that combining *PTCH1* efflux inhibitors with conventional or targeted therapies could be a promising approach for treating *PTCH1*-expressing cancers. Certain proprietary Chinese medicines, such as Ginsenosides and *Cordyceps Sinensis* Extracts, may affect efficacy by modulating the Hedgehog pathway. In vivo and in vitro, Ginsenoside Rb1 was effective in reversing Cisplatin resistance in A549/DDP. The mechanism of action may be dual, inhibiting the efflux of *PTCH1* by targeting the ABCB1 and the hedgehog (Hh) pathways. Cordyceps extract induces apoptosis in non-small cell lung cancer (NSCLC) cells.

Despite some progress, however, there are still several research challenges. Firstly, the molecular regulatory mechanisms of *PTCH1*, such as transcriptional regulation and epigenetic modification, are relatively understudied, with most current studies focusing on the expression and mutational status of *PTCH1*. Secondly, although a correlation between decreased *PTCH1* expression and prognosis in lung cancer patients has been observed, it needs to be verified whether this correlation is generalizable and reproducible in a larger patient population.

In addition, research into *PTCH1* as a therapeutic target has mainly focused on Vismodegib, Ginsenosides, and *Cordyceps sinensis* extract. Clinical applications are still relatively limited.

Further research is needed to investigate the molecular mechanism of *PTCH1* in lung cancer, including its role in different lung cancer subtypes, its interaction with other signaling pathways, and the complete dissection of the *PTCH1* regulatory network. In addition, to confirm the accuracy and reliability of *PTCH1* as a prognostic marker, further clinical studies are needed. Furthermore, it is crucial to explore the potential of *PTCH1* as a therapeutic target, including the development of new *PTCH1* inhibitors and activators, as well as evaluating the effects of combining these drugs with other therapeutic approaches. Such efforts are essential to improve the outcome and quality of life of lung cancer patients. Significant advances in precision therapy and personalized medicine for lung cancer are expected as we pursue these avenues.

5. Discussion

The current review has provided a comprehensive analysis of the *PTCH1* gene mutations and their pivotal role in the pathogenesis of lung cancer. Our synthesis of the literature underscores the significant impact of *PTCH1* on the Hedgehog signaling pathway, which is closely linked to cellular dysregulation and the oncogenic processes underlying lung cancer. The disruption of normal Hedgehog signaling by *PTCH1* mutations emerges as a key driver of unregulated cell proliferation and tumor growth, thus positioning *PTCH1* as a candidate biomarker for early detection and a promising target for therapeutic intervention.

Despite these insights, our review has identified some gaps in the current understanding of *PTCH1*. Firstly, the transcriptional regulation and epigenetic landscape of *PTCH1* remain poorly characterized, with the majority of studies concentrating on gene expression and mutational analysis. This narrow focus has left a gap in our comprehension of the intricate regulatory mechanisms that could inform the development of novel therapeutic strategies. Secondly, the observational nature of existing studies on *PTCH1* mutations in lung cancer limits our ability to infer causality. Thirdly, the extensive yet fragmented literature on *PTCH1* in lung cancer further complicates the translation of research findings into clinical practice. The inconsistencies observed across studies—stemming from diverse experimental designs, sample populations, and analytical methods—necessitate a more harmonized approach to research. Standardization of methodologies and collaborative efforts across research centers could yield more consistent and reproducible results, enhancing the reliability of *PTCH1* as a clinical biomarker and therapeutic target. Finally, the exploration of *PTCH1* as a therapeutic target has been limited, with a focus on a select few agents such as Vismodegib, Ginsenosides, and *Cordyceps sinensis* Extract.

To address these limitations and propel the field forward, we propose the following future research directions. In mechanistic Studies, in-depth research

should be conducted to delineate the molecular interactions of *PTCH1* mutations within the Hedgehog pathway and their crosstalk with other oncogenic pathways. This will provide a more nuanced understanding of *PTCH1*'s role in lung cancer pathogenesis. In Clinical Validation, large-scale, multi-center clinical trials should be designed to ascertain the prognostic and predictive utility of *PTCH1*. Such studies should aim to establish the stability and specificity of *PTCH1* as a biomarker in diverse patient populations. In therapeutic Development, studies should pursue the discovery and clinical evaluation of novel *PTCH1* inhibitors or activators. To fully harness the potential of *PTCH1*-targeted therapies, a broader spectrum of compounds and combination therapies should be investigated in preclinical and clinical settings. Research also should focus on the therapeutic efficacy of these agents, both as monotherapies and in combination with existing treatments. It is imperative to investigate the differential impact of *PTCH1* across various lung cancer subtypes and stages of disease progression. This understanding is crucial for the development of tailored therapeutic approaches.

In conclusion, while the role of *PTCH1* in lung cancer is increasingly recognized, the complexities inherent in its study present significant challenges. A concerted effort to address the research gaps and explore new directions is essential for translating our growing knowledge of *PTCH1* into effective clinical applications. Such advancements are of critical importance for the evolution of precision medicine and for improving outcomes for patients with lung cancer.

6. Conclusion

Lung cancer is the leading cause of cancer-related mortality worldwide, particularly in China. The Hedgehog (Hh) signaling pathway is among the many molecular pathways that influence cancer progression. It stands out for its critical role in tissue development and regeneration. It is also noteworthy for its aberrant activation in several cancers, including lung cancer. The *PTCH1* gene, a critical component of the Hedgehog (Hh) signaling pathway, plays a pivotal role in the development and progression of lung cancer. This review has comprehensively examined the multifaceted functions of *PTCH1* in lung cancer, highlighting its influence on cellular communication, proliferation, and tumor growth through its interaction with the Hh pathway. Mutations in *PTCH1* activate the Hedgehog (Hh) signaling pathway, which is implicated in the development of several cancers. When *PTCH1* binds to the ligand Shh, it results in the deregulation of the inhibitory effect on SMO transmembrane proteins, thereby allowing SMO to be activated. This process then triggers downstream signaling, including the activation of Gli transcription factors, which subsequently regulates the sustained expression of target genes and promotes tumor development. Further studies have demonstrated that aberrant *PTCH1* expression in various cancers is associated with oncogenesis, recurrence, metastasis, and treatment. Research indicates that *PTCH1* expression levels may serve as prognostic indicators in non-small cell

lung cancer (NSCLC) and lung squamous cell carcinoma (LUSC). Furthermore, there is a correlation between *PTCH1* mutations and the presence of tumor-infiltrating lymphocytes (TILs). Treatments targeting *PTCH1*, such as Vismodegib, have demonstrated efficacy in clinical cases, particularly in squamous cell lung cancer (SCCL) with specific *PTCH1* mutations, resulting in periods of complete remission. Additionally, *PTCH1*'s interaction with microRNA-212 suggests potential therapeutic approaches by targeting miRNA to regulate *PTCH1* expression. The potential of traditional Chinese medicines, such as ginsenosides and *Cordyceps sinensis* extracts, to modulate the Hedgehog (Hh) pathway and reverse drug resistance has also been investigated.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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