The Expression of IL-36 is Elevated in NSCLC and lung Cancer

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Abstract

Asthma and COPD are two respiratory disorders that have been linked to the IL-36 cytokines, a recently identified subset of the IL-1 family of cytokines. The purpose of this study was to look at the role of IL-36 cytokines in the pathogenesis of lung cancer in light of the shared aetiological ties between COPD and the emergence of lung cancer as well as the involvement of other IL-1 family members in the development of lung tumors. In this study, we show that lung cancer tissue expresses considerably higher levels of IL-36 cytokines and receptor mRNA and protein than does nearby non-tumor tissue. Two lung cancer cell lines, LLC murine lung cancer and SKMES-1 human squamous cell, were stimulated in in vitro tests. In all lung cancer cell lines, all IL-36 cytokines increased the expression of pro-inflammatory chemokines, and when cells were stimulated with IL-17, IL-22, and TNF, synergistic effects were observed. In addition, we reveal that the immune checkpoint inhibitor protein PD-L1 is expressed on lung cancer cells as a result of IL-36 cytokines. When considered as a whole, the data suggest that IL-36R signaling inhibition could be a beneficial targeted therapy for lung cancer patients with IL-36R+ cancer cells.

Keywords: IL-36 • IL-1 family • Tumorigenesis • Lung cancer

Introduction

Lung cancer has one of the lowest survival rates of any cancer type and is the most common cause of cancer-related mortality worldwide.The two main types of lung cancer are Small Cell Lung Cancer (SCLC), which makes up around 15% of cases, and Non-Small Cell Lung Cancer (NSCLC), which primarily consists of squamous cell carcinoma and adenocarcinoma. Despite recent developments in lung cancer therapy, particularly immune checkpoint inhibitors like PD-1/PD-L1 inhibitors, not all patients respond to the treatments currently available, necessitating the continued search for novel, effective treatment choices. The relationship between persistent inflammation and cancer is well known; lung cancer start, cellular proliferation, invasion, angiogenesis, and metastasis are all correlated with persistent inflammation. It is crucial to understand the components of the intricate Tumor Microenvironment (TME), where cytokines like interleukin-1 (IL-1) and their receptors are known to play a part in carcinogenesis. In fact, the incidence and death of lung cancer were considerably decreased by canukinumab, an inhibitory antibody that targets IL-1. Blocking IL-1 also improved the effectiveness of checkpoint inhibitor therapies indicating that focusing on IL-1 family members can alter the TME's pro-tumorigenic makeup and overcome immunotherapy resistance. A subset of the IL-1 superfamily of cytokines is the IL-36 family of cytokines.

The IL-36 receptor (IL-36R) and the IL-1 Receptor auxiliary protein make up the receptor complex that the three IL-36 agonistic members, IL-36, IL-36, and IL-36, all share (IL-1RAcP). The IL-36R antagonist, a pharmacological inhibitor of this complex, has also been discovered (IL-36Ra). The cytokine IL-38 has the potential to block signaling. Like other members of the IL-1 family, IL-36 cytokines play a significant role in activating both innate and adaptive immune responses. These cytokines have been demonstrated to be crucial in the pathogen clearance and tissue barrier maintenance processes, as well as in the development of respiratory, inflammatory bowel, and psoriatic illnesses. Research looking at the expression of IL-36 cytokines in cancer have found that reduction of these cytokines' expression is linked to poor clinical outcomes in melanoma, epithelial ovarian cancer, pancreatic adenocarcinoma, colon adenocarcinoma, and Hepatocellular Carcinoma (HCC).Moreover, in vitro research has demonstrated that cytokines like IL-36 can effectively activate effector cells like CD8+ T cells, NK cells, and T cells to generate an anti-tumorigenic phenotype. In addition, a number of in vivo animal models of HCC, fibrosarcoma, colon cancer, pancreatic cancer, melanoma, and breast cancer have shown that changes in the immune cell composition of tumors are the cause of IL-36 cytokines' capacity to lessen tumor burden. The development and maintenance of tertiary lymphoid tissues, which spread the Th1 immune response and encourage tumor rejection, may also be facilitated by IL-36 cytokines.With recent in vitro research demonstrating that IL-36 cytokines can directly contribute to cancer proliferation, migration, and invasion, expression studies have also revealed pro-tumorigenic connections for IL-36 signalling in colon and stomach cancer. Pre-clinical carcinogenesis models that focused on IL-36R signaling slowed the progression of breast, colon, stomach, and lung cancers. These in vitro and in vivo experiments show that IL-36 signaling has a dual role in the development of cancer. Using human tissue samples collected during cancer resection, we have shown in this study that the expression of IL-36 family members is elevated in lung cancer tissue compared to healthy tissue. We have also shown this association in two RNA-sequencing datasets. We find that several lung cancer cell lines express the IL-36 receptor and respond to IL-36 cytokines by increasing cellular proliferation and migration and inducing pro-inflammatory genes. Furthermore, we have demonstrated that IL-36-induced stimulation of cancer cells can boost the expression of the immunological checkpoint protein PD-L1. This work further implicates IL-36 cytokines as pro-tumorigenic cytokines that may be targeted as possible cancer therapeutics, which is consistent with recent studies examining the function of IL-36 signaling on cancer cells. The information presented here adds to the understanding of the intricacy of IL-36 cytokines in carcinogenesis. Early and ongoing research in the area of IL-36 in cancer showed how important it is for IL-36 to support the anti-tumor immune response, and these results sparked interest in examining IL-36 agonists as prospective cancer therapy alternatives. However, more recent research has emphasized the pro-tumorigenic effects of IL-36 cytokines in a variety of tumor types, and results from in vivo murine experiments have supported the idea that blocking the IL-36R could be an effective treatment strategy. Our results are consistent with the latter hypothesis, i.e., more research into the development of IL-36R-inhibiting treatments for NSCLC. The same group's second work, which found that IL-38 expression is an independent, unfavorable predictor of CD8+ TIL infiltration in lung cancer, confirmed this. Hence, these expression data clearly suggest that IL-36 signaling may play a protective role in the prevention and treatment of cancer by enhancing a prolonged type I response to specifically target cancer cells. The complexity of the role of IL-36 cytokines in tumorigenesis is highlighted by our data showing that IL-36 can directly increase checkpoint inhibitor protein expression. While IL-36 cytokines may promote an increase in anti-tumorigenic immune cell types into the TME, they can also increase PD-L1 expression in order to rate-limit the anti-tumor response.