

Review

CARD9 as a potential therapeutic target in lung cancer

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1. Abstract

Caspase recruitment domain-containing protein 9 (CARD9) is highly expressed in myeloid cells and has been identified as a central regulator of innate immunity. Increasingly, studies demonstrate that CARD9 also plays a critical role in the development of lung cancer. This review focuses on the clinical significance and potential molecular mechanisms that CARD9 plays in lung cancer.

2. Introduction

Lung cancer remains a challenging disease largely due to its high mortality and morbidity. Data gathered in the USA indicate that in 2018 approximately 230,000 new cases of lung cancer were diagnosed and that this accounted for approximately 13% of all cancer cases [1–3]. Despite great advances in effective prevention, early diagnostic detection, and more effective therapeutics, many patients still experience disease recurrence without significant improvements in survival. The current therapeutic options for lung cancer include radiation, chemotherapy, and surgery. Each of these approaches has limitations, and patient prognosis remains dismal. Specifically, the 5-year survival rate for lung cancer is estimated at 18%, and lung cancer is responsible for approximately 25% of all cancer-related deaths,

more than breast, colorectal, and prostate cancer [4, 5]. Therefore, it is critical to further explore molecular mechanisms that could improve diagnosis and therapy for lung cancer patients.

Emerging studies have emphasized the critical role of the tumor microenvironment (TME) in tumor progression. Myeloid-derived suppressor cells (MDSCs), a heterogeneous group of immune cells derived from myeloid lineage, attenuate host immune responses through production of suppressive components within the TME [6–8]. In the context of the tumor, MDSCs can facilitate tumor escape, abnormally activate tumor cells, and suppress T cell function by increasing levels of reactive oxygen species, arginase, and nitric oxide synthase production [6, 8]. Additionally, MDSCs contribute to tumor angiogenesis, tumor cell invasion, and premetastatic niche formation through activation of non-immunologic mechanisms [9, 10].

It is clear that understanding MDSC biology is critical for improving clinical prognosis and improved treatment strategies in lung cancer patients [11]. Interestingly, CARD9 is highly expressed in MDSCs and exhibits a central role in regulating innate immunity [1]. Recently, it was reported that CARD9 function in MDSCs might drive a novel mechanism of lung cancer development [1, 12, 13]. This review focuses on our current understanding of

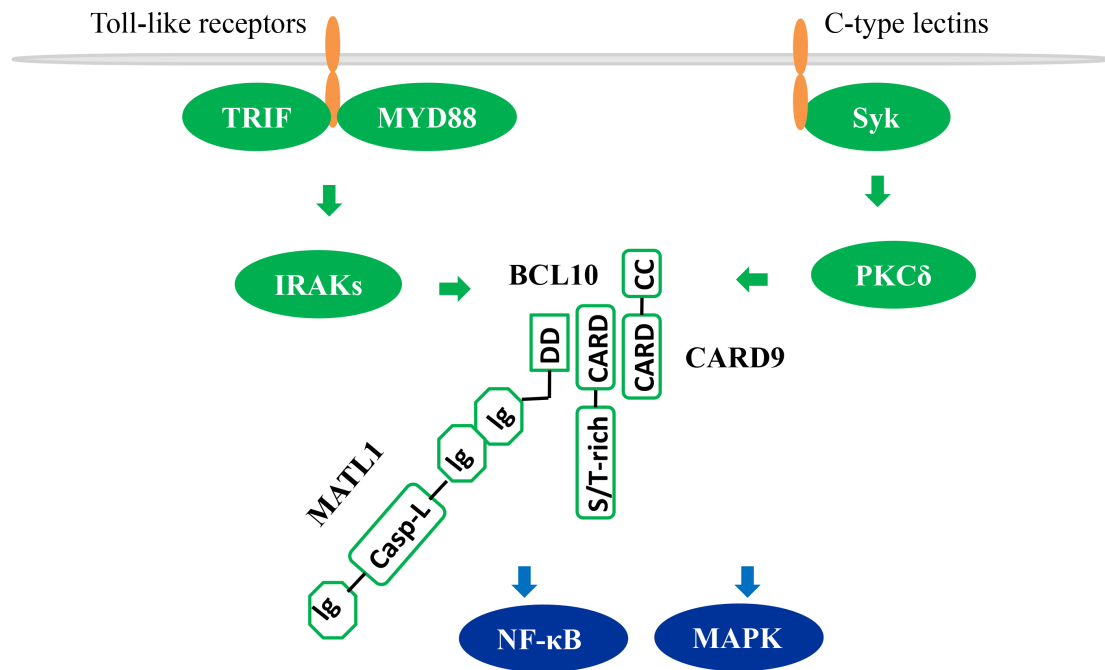


Fig. 1. CARD9-dependent NF- κ B and p38 activation in myeloid cells.

CARD9 function in lung cancer and discusses CARD9 clinical significance, its molecular mechanism of action, as well as its potential as a therapeutic target.

3. CARD9 as a central integrator of immune response

CARD9 is highly expressed in myeloid cells especially macrophages, dendritic cells, and MDSCs [14–16]. CARD9 is known as the downstream effector molecule of the pattern recognition receptors including Toll-like receptors and C-type Lectins. Upon activation of these receptors, CARD9 triggers activation NF- κ B and/or mitogen-activated protein kinases (MAPK) signaling in myeloid cells (Fig. 1). This leads to activation of an inflammatory cytokine cascade that defends against microbial invasion, especially in fungal infection [14–16]. These findings have resulted in a consensus view that CARD9 functions as a central integrator of innate and adaptive immunity.

Through its myeloid cell functions, CARD9 has emerged as an essential player in tumor initiation and progression. We previously summarized the clinical significance of CARD9 in a variety of tumor types (Table 1) including hepatocellular carcinoma, intestinal carcinoma, gastric carcinoma, kidney carcinoma, and malignant pleural effusion [16, 17]. These studies suggest that high CARD9 expression is associated with tumor progression and poor survival rate [18–22]. However, preclinical studies in tumor-prone mouse models indicate that CARD9 plays a dual role in the carcinogenic process as it exhibits both a pro-tumor and/or anti-tumor activity [23–26]. Specifi-

cally, CARD9 promoted tumor progression in kidney and intestinal cancer by activating NF- κ B and STAT3 signaling [23, 24]. Conversely, CARD9 inhibited tumor progression in leucocythemia and melanoma by both promoting tumor antigen-specific CD8⁺ cytotoxic T lymphocyte (CTL) cross-presentation and induction of cancer cell apoptosis [25, 26]. This paradox may account for the cellular distribution of CARD9, as CARD9 expression in tumor tissues was found in tumor-infiltrating macrophages, but not tumor cells themselves [16, 17].

Macrophages are a prominent constituent of the tumor microenvironment where they can either promote, or suppress, tumor growth and metastasis depending on their biological state [27–29]. Further, CARD9-induced tumorigenesis was reported in a small cohort of patients, but exact evaluation in a large patient cohort is likely needed to confirm these findings.

4. Clinical significance of CARD9 in lung cancer

A recent study conducted by Qu *et al.* [1] studied 31 patients diagnosed with lung cancer. To address the relationship between CARD9 and MDSCs in these patients, CARD9 expression level and types of cells expressing CARD9 in lung tissues were examined. Compared with normal tissues, expression of CARD9 was significantly unregulated in both tumor and paracancerous tissues. The study documented that CARD9 was principally expressed in myeloid cells resident within the tumor tissue, but not tumor cells themselves. Furthermore, an increased popu-

Table 1. The preclinical studies of CARD9 in tumor.

Gene	Tumor	Function	Mechanisms
CARD9	Intestine	Pro-tumor	IL-1 β , IL-17A, IL-22, STAT3
CARD9	Intestine	Pro-tumor	IL6, G-CSF, RANTES, T-cell, macrophage
CARD9	Intestine	Pro-tumor	IL-12, IL-10, IL-1 α , TGF- β , NF- κ B, M2 macrophage
CARD9	Kidney	Pro-tumor	Card9 linked pVHL to NF- κ B biology
CARD9	Kidney	Pro-tumor	Card9-induced JNK hyper-activation
CARD9	Melanoma	Anti-tumor	Dectin-1-mediated cross-priming of CD8 ⁺ CTLs
CARD9	Leucocythemia	Anti-tumor	leukemic cell apoptosis

lation of MDSCs was observed in larger tumors and this was closely associated with higher expression of CARD9. Moreover, clinical pathology data indicated that CARD9 expression was positively correlated with tumor size [1]. In sum, this study provides a framework for understanding the contribution of CARD9 to lung cancer development in humans.

Miwa and colleagues reported that CARD9 served as a prognostic marker of poor outcome in lung cancer patients [13]. In this investigation, a total of 74 lung cancer patients diagnosed with adenocarcinoma were enrolled. Of these, 24 patients harbored CARD9-low expression, and the remaining 50 cases were characterized as CARD9-high expression. Clinicopathologic analysis demonstrated that CARD9 expression was positively associated with poor overall survival, but not vascular and lymphatic invasion. This implicates CARD9 expression as an independent prognostic factor in lung cancer patients. Of note, in contrast to other studies that documented CARD9 expression uniquely in MDSCs [1], CARD9 was found to be expressed in adenocarcinoma cells in this study.

Pan and co-workers also identified CARD9 as a potential prognostic indicator in lung cancer [30]. Contrary to previous findings [1, 13], CARD9 expression was reduced in lung cancer and exhibited anti-tumor activity in this study. A total of 94 cases diagnosed with non-small cell lung cancer were studied in this report and CARD9 expression, at both protein and mRNA levels, indicated a clear decrease in cancer tissue in comparison with adjacent normal tissues. Clinicopathologic analysis indicated that CARD9 was negatively correlated with lymph node metastasis, T category, histological differentiation, tumor node metastasis (TNM) stage, and remote metastasis. Low CARD9 expression was associated with poor overall survival and progression-free survival of patients. Additionally, CARD9 in clinical specimens was found to be expressed in both tumor cells and macrophages.

5. Preclinical studies of CARD9 in lung cancer

Two studies reported that CARD9 regulated lung cancer through the control of MDSCs activation and in-

doleamine 2, 3-dioxygenase (IDO) production [1, 12]. In the Lewis lung cancer mouse model, CARD9 deletion induced tumor cell proliferation, increased tumor size and weight, and aggravated splenomegaly. The expression level of MDSCs-related functional genes in tumor tissues of CARD9-deficient mice, such as iNOS-2, Arg-1, S100A8/A9, GP91phox and IDO, was significantly increased compared with that of wildtype mice. This result suggested that CARD9-deficiency in the TME may impair anti-tumor immune response through the activation and accumulation of immunosuppressive MDSCs. MDSCs are identified as the main obstacle in anticancer immunity and immunotherapy [31–33]. To test the pro-tumor function of MDSCs in CARD9-deficient mice, anti-Gr-1 monoclonal antibody, which effectively removes MDSCs, was injected into mice. As expected, this antibody decreased the number of MDSCs and coordinately increased the number of tumor-associated CD8⁺ CTLs within the tumor of CARD9-deficient mice. Additionally, CARD9 deficiency promoted MDSCs differentiation and enhanced the inhibitory effect of MDSCs on T cells. Importantly, depleting MDSCs using anti-Gr1 antibody can markedly decrease tumor volume and tumor weight in CARD9^{-/-} mice. Finally, the tumor regulatory mechanism was studied using CARD9^{-/-} mice-derived MDSCs. This study found that the non-canonical NF- κ B pathway in MDSCs was activated in CARD9^{-/-} mice and that this enhanced expression IDO. IDO, an enzyme responsible for metabolism of tryptophan and one of the most important immunoregulatory enzymes, was critical to tumor development by regulating T cells [34–36]. Thus, within the TME, CARD9 promoted tumor growth via activation of the CARD9/NF- κ B/IDO signaling cascade in MDSCs (Fig. 2A).

CARD9 protein was also found to be expressed in lung cancer cell lines PC9, H1299, and HBE [30], suggesting its potential participation in tumorigenesis. *In vitro* experiments showed that CARD9 knockdown in PC9 cells significantly promoted cell proliferation, invasion, migration, and inhibited cell apoptosis. Furthermore, reduced CARD9 expression activated p38 and contributed to tumor development in a p38-dependent manner. Contrary to previous findings regarding CARD9-induced p38 activation [37–39], in this study CARD9 deficiency upregulated

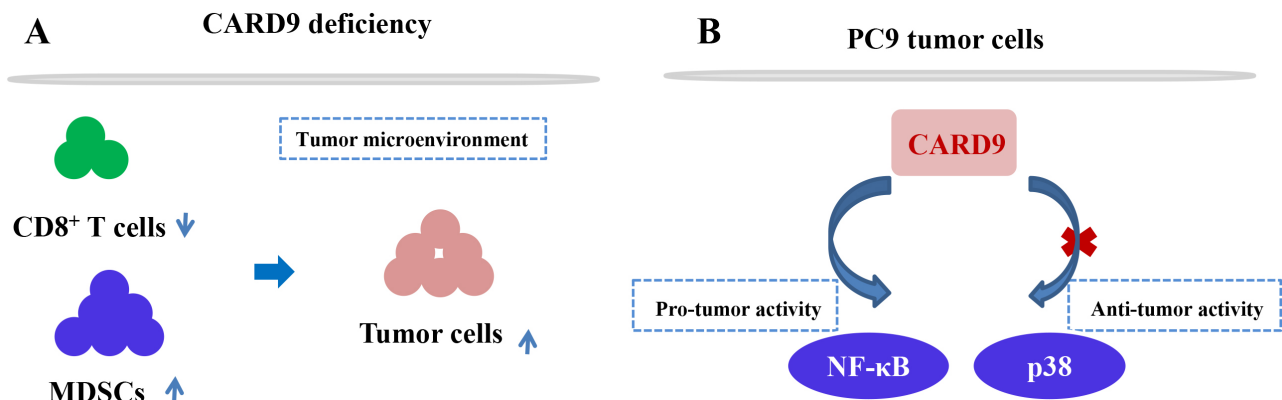


Fig. 2. The molecular mechanism of CARD9 in lung cancer. (A) CARD9-mediated immune response in the tumor microenvironment; (B) CARD9-induced signalling pathway in the PC9 cell line.

p38 expression and the underlying molecular mechanism for this finding will need to be elucidated in the future. Nevertheless, CARD9 has a significant anti-tumor response in lung tumors via downregulation of p38 signaling.

In this study, the investigators also showed that CARD9, in lung cancer cell lines, had a critical role in facilitating the progression of lung cancer [13]. CARD9 was upregulated in various lung cancer cell lines including PC9, A549 and H1975. Furthermore, CARD9 was found to activate the canonical NF- κ B pathway in the PC9 cell line and, of note, CARD9 knockdown in PC9 cells inhibited cell proliferation, invasion, and migration. These findings are in contrast to previously outlined studies regarding CARD9 deficiency promoting tumor growth. This paradox may be attributable to CARD9 function via two distinct molecular mechanisms in PC9 cells, specifically, CARD9-induced NF- κ B activation resulting in enhanced tumor cell growth versus CARD9-induced p38 deactivation resulting in inhibited cell growth (Fig. 2B). Nevertheless, this paradox suggests that CARD9 may play a dual role in lung tumor progression.

6. CARD9 as a potential therapeutic target in lung cancer

CARD9 expression in myeloid cells has been linked to tumor-related inflammation, tumor immune microenvironment, and intestinal microecology, suggesting that CARD9 may represent a potential target for anti-tumor immunotherapy [17].

Ganoderma lucidum polysaccharide (GLP), isolated from the fungus *Ganoderma lucidum*, serves as an effective anti-tumor agent that significantly inhibits tumor growth in the Lewis lung cancer mouse model. Moreover, GLP administration to these mice [40] can effectively suppress the accumulation of MDSCs in the spleen and tumor tissues, increase the percentage of CD4⁺ and CD8⁺ T cells in the spleen, and reverse the attenuated expression of CARD9 and p65 in MDSCs. Furthermore, GLP can ele-

vate expression of IDO in MDSCs, suggesting an activation of the CARD9/NF- κ B/IDO signaling cascade in MDSCs within the TME. Collectively, targeting CARD9 with GLP can prevent lung cancer development by suppressing accumulation and differentiation of MDSCs in tumor-bearing mice.

β -glucan, a natural polysaccharide compound, binds to C-type lectin receptors and subsequently activates CARD9-dependent signaling [41]. β -glucan was found to reduce tumor burden with less vascular structure in the Lewis lung carcinoma mouse model [41]. Mechanistically, β -glucan converts tumor-associated macrophages into anti-tumor macrophages of the M1 phenotype via activation of the Dectin-1/CARD9 signaling pathway.

7. Conclusions

CARD9 is a central integrator of innate immunity in myeloid cells and plays a key role in lung cancer pathogenesis. However, some important questions regarding CARD9 remain unknown. First, it is unclear whether CARD9 is protective against lung cancer development. A total of three papers have been published that report on the clinical significance of CARD9 in lung cancer. Of these, two indicate CARD9 possesses pro-tumor activity, and one paper suggests anti-tumor activity. Of note, *in vivo* studies in mice support an anti-tumor function for CARD9 and this contradicts clinical data obtained from humans. This discrepancy may be due to high expression of CARD9 in patient samples because of the increased proportion of myeloid cells within the tumor [1]. Future studies will be needed to fully understand CARD9 pro-tumor versus anti-tumor functions using a large cohort of patients.

Second, the cellular distribution of CARD9 in lung cancer remains controversial; specifically at question is whether CARD9 is expressed in MDSCs and/or lung tumor cells. As previously reported [42–44], investigators documented that CARD9 expression was limited to tumor-

infiltrating macrophages in colon cancer. In contrast, studies of oral squamous cell carcinoma [45] and renal cell carcinoma [44] revealed CARD9 expression within tumor cells. Others documented CARD9 expression, at both the protein and mRNA levels, is upregulated in various cultured lung cancer cell lines, suggesting that CARD9 is not only expressed in MDSCs but also in lung tumor cells. In contrast, some clinical data gathered from lung cancer patients clearly show that CARD9 was only expressed in MDSCs rather than in tumor cells [1].

Despite the uncertainties outlined in this review, the bulk of studies support an anti-tumor function for CARD9 in lung cancer. More studies, focused on the biological function of CARD9, will be required to better determine how MDSCs interact with tumor cells in a CARD9-dependent mechanism.

8. Author contributions

RS—writing-original draft preparation; ZY—writing-review and editing. All authors have read and agreed to the published version of the manuscript.

9. Ethics approval and consent to participate

Not applicable.

10. Acknowledgment

Not applicable.

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12. Conflict of interest

The authors declare no conflict of interest.

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