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REVIEW

# The Role of Interleukin-9 in Cancer

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**Abstract**
Interluekin-9 (IL-9) is produced predominantly by helper T cells such as Th2 and Th9 cells. It normally functions through the activation of a JAK/STAT pathway and plays a critical role in immunity and the pathogenesis of cancer. In cancer, it yields different responses depending on the cancer cell line involved. This review is a summary of what is known about the involvement of IL-9 in various cancer cell lines as well as its role in immunity with a focus on allergic responses.

**Keywords** Interleukin 9 · Cancer · Inflammation

## Introduction

Human interleukin-9 (IL-9) was first identified in the late 1980s. Its gene is located on the long arm of chromosome 5. The IL-9 protein has 144 amino acid residues with a signal peptide of 18 amino acid residues. IL-9 is mainly secreted by Th2, Th9, and mast cells although many other cells could secret IL-9, such as Th17 cells, Tregs, CD8+ T cells, innate lymphoid cells, NKT cells, and dendritic cells [1–10].

IL-9 production may be promoted by IL-1β, IL-2, IL-4, IL-6, IL-9, IL-10, IL-12, IL-21, IL-25, IL-33, TGF-B, TSLP (thymic stromal lymphopoietin), and transcription factor PU.1 [11–21]. IFN-g represents a potential inhibitor for IL-9 expression [11, 12].

IL-9 signals through the IL-9 receptor and this receptor is composed of two subunits: IL-9Rα (IL-9–specific alpha-chain) and $\gamma_c$ (the common γ-chain) which is also a subunit of the IL-2, IL-4, IL-7, IL-15 and IL-21 receptors [22, 23]. IL-9Rα is constitutively bound to JAK1 and the $\gamma_c$ is constitutively bound to JAK3 [24]. The IL-9Rα can sufficiently bind IL-9 on its own but cannot mediate the signal any further without the $\gamma_c$ portion [25]. Upon the receptor ligation, a juxtaposition occurs between the 2 chains. This results in auto and or trans phosphorylation of JAK kinases. Specifically, there exists a proline rich box-1 region in the cytoplasmic domain of IL-9Rα, which is required for JAK binding and activation and mediates STAT phosphorylation [26]. The Tyrosine 407 residue is the cytoplasmic part of IL-9Rα phosphorylated upon ligand binding, and is the docking site for STAT −1, −3, and − 5 transcription factors. This residue is required for STAT transcription factor activation [24]. The phosphorylated STAT molecules dimerize and migrate to the nucleus, where they bind regulatory sequences for de novo gene expression and thus links IL-9 to its pleiotropic biological functions.

IL-9 is a pleiotropic cytokine that has both direct and indirect effects on hematopoietic progenitor cells, lymphocytes, mast cells, as well as airway smooth muscle cells and epithelial cells. IL-9 may have a role in Treg response and Th1/Th17-mediated inflammation, however, its major role in immunity is usually associated with allergic inflammation and immunity to extracellular parasites. Interestingly, in recently years, some studies have indicated IL-9 plays a role in the pathogenesis of neoplasia [27–32]. This review summarizes the latest advances regarding the role of IL-9 in the pathogenesis of cancer.

## Pro-Tumor Effect of IL-9

IL-9 was initially identified as a T cell growth factor with cell growth promotion potential. Thus, it is not surprising that IL-9

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might have pro-tumor effects. It has been found that IL-9 is involved in the pathogenesis of lung cancer, leukemia, breast cancer, thyroid cancer, colon cancer, as well as lymphoma.

## Lung Cancer

It has been shown that IL-9 substantially promotes the proliferation of A549 and SK-MES-1 lung cancer cell lines. Acting in tandem with IL-17, IL-9 secreted by Th9 cells phosphorylated the STAT3 protein on Serine 727. The phosphorylation of STAT3 activates a JAK/STAT pathway that eventually promotes the proliferation of lung cancer cell lines. IL-9 does not enhance the growth of the cells directly, but it is involved in the regulation of their proliferation. When the STAT3 pathway is activated, there is more migration by A549 and SK-MES-1 lung cancer cell lines. The deregulation of IL-9 is associated with continuous JAK/STAT3 signaling and gives rise to autonomous cell growth, malignant cell transformations, and better adhesion of lung cancer cells. Activation of the JAK/STAT3 pathway by IL-9 also protects lung cancer cells from apoptosis, which contributes to the accumulation of cancer cell population [33]. In fact, the differentiation and presence of Th9 cells in higher concentrations was indicative of lower patient survival [33]. These findings indicate that IL-9 promotes lung cancer growth through cancer cell proliferation and inhibition of cancer cell apoptosis.

## Leukemia

By using the human T Cell Leukemia Virus (HTLV-1) infected T cells, IL-9 was shown to be a key downstream target gene used in the pathway by which IL-17RB stimulates HTLV-1 infected T cell growth [1]. The first part of the pathway in IL-17RB mediated HTLV-1 infected T cell proliferation is: Act1 activates the ubiquitin ligase TRAF6 and the kinase TAK1 that in turn triggers NF-kB and MAP kinase activation to induce type 2 cytokines IL-4, IL-5, IL-13, as well as IL-9. TAK1 is known to stimulate IL-9 secretion. In experiments, it was shown that IL-9 was both necessary and sufficient to restore HTLV-1 cells in IL-17RB knockout experiments. The further downstream mechanism remains to be elucidated [1]. It has been shown that there are essential sequences in the IL-9 gene needed for its expression in HTLV-1 [34]. In another study, it was shown that overexpression of IL-9 is associated with the pathogenesis of chronic lymphoid leukemia. Additional study of downstream apoptosis proteins is needed to find the mechanism [35]. These suggest that IL-9 might play a pivotal role in leukemia.

## Breast Cancer

By using breast cancer cell lines, it has been shown that IL-9 is involved in tumor tolerance associated with cell proliferation. Recombinant protein TAT-NLS-BLBD6 interacts and interferes with B-catenin and inhibits breast cancer cell growth, invasion, migration, colony formation, and increased arrest of sub-G1 phase and apoptosis. IL-9 is a downstream target gene and is downregulated by the recombinant protein. This suggests that IL-9 is involved in the proliferation, invasion, migration, colony formation, and autonomous cell growth in a promoting fashion. IL-9 is downregulated by the Wnt gene in this signaling pathway [36]. In another experiment, IL-9 is a key factor in establishing permissive growth environment for CT26 (Colon cancer) and 2 murine breast cancers (Her21mu and 4TI). IL-9 enhances Treg cell suppressive potency in an autocrine fashion which promotes T- cell tolerance via a paracrine impact on mast cells. This was shown through an IL-9 deficiency experiment in which IL-9 was shown to play a role in secondary tumor rejection, where mammary carcinomas are rejected in IL-9 knockout mice. This could be due to T cell tolerance. This suggests IL-9 negatively regulates T cell function within tumor challenges. Additional information is needed to elucidate the mechanism such as a source of IL-9. The early secretion of IL-9 in the tumor microenvironment may prevent the activation of adaptive immunity [37–39].

IL-9 knockout mice show rejection of tumors for breast cancer lines; macroscopic tumor growth is delayed. The cells do not express high levels of IL-9R and do not directly secrete IL-9. CD4+ and CD8+ T-cells are needed for tumor eradication in IL-9 knockout mice, but the mechanism is not known. It is suggested that IL-9 could promote tolerance to tumor microenvironments or possibly mask malignancy. IL-9 is involved in early establishment of tolerogenic milieu and hampers the development of adaptive immunity response against the tumor challenge (memory response). In IL-9 knockout mice, both splenocytes and lymphocytes are activated and tumor specific, but it is not known if this is true in IL-9 mice. The Treg cell response of tumor tolerance raises the question of how secretion by each different cell affects the given cancer cell line [5].

## Thyroid Cancer

Papillary thyroid cancer (PTC) patients with Hashimoto thyroiditis (HT) produce significantly higher concentration of IL-9 than PTC patients without HT. This is significant because HT has higher concentrations of inflammatory cytokines, and IL-9 functions widely in inflammation. There is a higher concentration of IL-9 in PTC patients than controls and sole HT patients which had normal IL-9 levels. It is known that HT affects cytokine profiles of patients with PTC by stimulation secretion of Th1/Th2 and Th9 types of cytokines. The primary sources of IL-9 are Th2 and Th9 cells. HT is characterized by infiltration of the thyroid gland by immune cells, mainly Th2 cells. The mechanism is assumed to mimic the Th9 general mechanism of the JAK/STAT pathway of a phosphorylation

cascade. The downstream mechanism and associated affected proteins by IL-9 remain to be discovered [40].

### Colon Cancer

IL-9 is a key factor in establishing a permissive cell growth environment for CT26, a colon cancer cell line. This study used a murine model. In this particular experiment, the murine models with CT26 colon cancer were injected with IL-9 knockout mice, and the difference in colon cancer growth between wild type and knockout mice was significant, with higher growth shown in IL-9 wild type mice. This suggests that IL-9 produces a tolerogenic response to tumors and inhibits adaptive immunity by promoting an environment in which cancer cells can grow. The mechanism underlying this pathway is related to the cells that secrete the IL-9. Treg cells are imperative to have tumor rejection in IL-9 knockout mice. This possibly suggests that IL-9 could be associated with CD4+ and CD8+ T cell differentiation into Treg cells that inhibit adaptive immunity or hide malignancy. Time is also a factor in this experiment, and the timing with which IL-9 is secreted should be studied. It is thought that early IL-9 secretion prevents adaptive immunity by Treg cells. This could mean that if IL-9 is secreted before the Treg cells are able to respond to tumor microenvironments, the IL-9 is able to hide the malignancy of the cancer itself [5].

### Lymphoma

IL-9 promotes the progression of lymphoma cancer cell lines, particularly: Hodgkin's Lymphoma, Anaplastic large cell lymphoma (ALCL) and NK/T Cell Lymphoma. In ALCL it stimulates the pathogenesis of anaplastic lymphoma kinase positive (ALK+) ALCL via the activation of JAK3/STAT3 pathways. In many of the ALK+ lymphomas, the ALK gene is translocated and subsequently fused with the nucleophosmin (NPM) gene. This fusion protein plays an important role in the pathogenicity of ALK+ ALCL via the activation of JAK-3. JAK-3 is itself activated by gamma-c cytokines like IL-9. In this study, IL-9 and its alpha receptor were shown to be present in ALK+ ALCL. IL-9 blockade by antibodies in turn inhibits the activation of STAT3 and JAK3. Blockade of IL-9 also reduced kinase activity of JAK3 and ALK significantly. The blockade of IL-9 with antibody also decreased cell proliferation in Hodgkin and ALK+ lymphoma cells [41]. In concordance with the JAK/STAT mechanism, it has also been shown that mutations in the JAK3 genes are involved in the pathogenesis of NKT-Cell lymphoma [42, 43].

In an additional study, IL-9 is overexpressed in lesional skin and contributes to the survival of neoplastic cells which is a process regulated by the STAT3/5 pathways. IL-9R positive cells were frequently present in lesional mycosis fungoides skin. This was found on mycosis fungoides cell line MyCa2000. IRF4 is a transcription factor expressed in lesional skin of mycosis fungoides patients and regulates IL-9 production in neoplastic cells. IRF4 is a Th9 transcription factor which gives light to the mechanism. STAT3 is recruited upon binding of IL-9 to its receptor via SH2 domain and is crucial for apoptosis inhibition [44]. There exists a hypothesis that says malignant clones that produce significant amounts of IL-9 polarize cytokine secretion towards Th9 cells. IL-9 thus contributes to the replication of malignant cells [45] and modulates an inflammatory microenvironment. There is a possible self-regulatory loop of IL-9 production in MyCa2000 cells because of the silence of STAT3/5. IL-9 depleted mice exhibited reduction in tumor growth, higher frequencies of regulatory T cells and activated CD4/CD8 T/t lymphocytes. Mycosis fungoides is the most common form of cutaneous T cell lymphoma [46].

Finally, IL-9 participated in the pathogenesis of B cell Non-Hodgkin Lymphoma through upregulation of immunosuppression mediated by Treg cells and mast cells. Dysregulated expression of IL-9 can be detected in Hodgkin's Disease, anaplastic large cell lymphomas [47], and nasal Natural killer T cell lymphoma [48, 49].

## Anti-Cancer

IL-9's extensive record with pro-cancer effects makes it very interesting to discover that it also has anti-tumor capabilities. More so, the mechanism by which it exerts these effects has been shown to be both direct and indirect, depending on the cell line used, indicating the pleiotropic nature of this cytokine.

### Melanoma

IL-9 has a variable effect on melanoma depending on the cell line used. In melanoma, IL-9 only inhibits growth and induces apoptosis in certain melanoma cell lines, and the mechanism by which this result is achieved is diverse. In two melanoma cell lines, HTB-65 and CRL-11147 cell growth was neither promoted nor inhibited. In SK-Mel-5 melanoma cell lines, IL-9 significantly inhibited the growth of melanoma cells in vitro. The mechanism of this growth inhibition is unclear but thought to be correlated to the upregulation of p21 [50]. In the HTB-72 melanoma cell line, IL-9 inhibited melanoma cell growth and additionally, IL-9 also induced apoptosis. In HTB-72 cells, cell growth inhibition was correlated to the upregulation of the anti-proliferative molecule, p21. Additionally, IL-9 goes further in its anti-cancer effects in that it induces apoptosis of HTB-72 melanoma cells through the upregulation of the pro-apoptotic molecule, TRAIL. This study found the first direct anti-tumor effects of IL-9 on a cell line. In most other

cancer cell lines, the proliferative effects of IL-9 are seen through an indirect mechanism; however, this study shows a very direct effect [50].

This conflicts with the results of another study which states that in a mouse model of melanoma, the effects of IL-9 are indirect. Melanoma tumor cells did not express IL-9R which suggests that IL-9 exerts anti-tumor activity by activating effector cells rather than directly on tumor cells. DTA-1 is an agonistic antibody that exerts anti-tumor activity by triggering IL-9 production from CD4+ t cells. DTA-1 improves anti-tumor activity of Th9 cells in melanoma via IL-9 dependent mechanism. Th9 recipients showed considerably delayed tumor growth. IL-9 did not directly affect CD8+ T cell cytotoxicity in vitro. IL-9 induced by DTA-1 potentiated tumor specific CTL responses by enhancing dendritic cell function. Addition of agonistic antibody to human GITR promotes IL-9 production by CD4+ T cells in a T cell intrinsic manner. This production of IL-9 by CD4+ T-cells increases their differentiation into Th9 cells; this is how DTA-1 delays tumor growth in an IL-9 dependent fashion. DTA-1 enhances cytotoxic T lymphocyte responses in an IL-9 dependent manner and possibly IL-21 dependent manner. It was shown that neutralizing IL-9 with an antibody did not completely abrogate the effects of DTA-1 induced CTL responses. This indicates that IL-9 works not independently but with other mechanisms to delay tumor growth. Finally, the mechanism by which IL-9 mediates this response is through a co-stimulation by GITR agonistic antibody that drives the differentiation of CD4+ T-cells to Th9 cells. The TRAF6–NF-kB pathway is required for GITR-induced TH9 cells. Further studies need to be done to elucidate the details of this mechanism [51].

Other studies also offer additional support of an indirect mechanism for IL-9 mediated antitumor activity. In a B16 melanoma cell line, antibody-neutralized IL-9 was associated with increased tumor cell growth. The presence of the IL-9 receptor was not investigated in this study, but, cells with lower levels of IL-9 had less leukocyte infiltration into the lung tumor tissues. IL-9 neutralized mice show decreased CCL20 expression in lung tumor melanoma tissues. CD8+ T-cells are less activated in IL-9 neutralized mice and associated with decreased leukocyte infiltration. Further, IL-9 secreting Th9 cells were shown to also secrete the recruiting chemokines CCL20 and CCL6, indicating an indirect mechanism through which IL-9 mediates an antitumor response. The presence of these chemokines suggests that IL-9 secreting Th9 cells recruit and augment the activation of numerous leukocytes, specifically CD8+ T cells. IL-9 favors tumor protection possibly via CCL20 mediated leukocyte recruitment in tumor tissues. The anti-tumor effect is based on a strong CD8+ cytolytic T cell response and recruitment of dendritic cells and cytotoxic CD8+ t-cells into tumor tissue. These studies show the indirect, T cell mechanism in which IL-9 inhibits tumor cell growth. IL-9 induced apoptosis was not seen; however, inhibited growth associated with the T-cells that secrete IL-9 has been shown [52]. There is additional supporting evidence that shows Th9 cells are not directly involved in cytolysis of tumor cells, but that IL-9 provokes a unique inflammatory environment in tumor tissues favoring CD8+ CTL activation in melanoma models [53]. Finally, IL-9 is shown to have a critical role in migration of Th9 to tumor sites to exert effector functions. In the murine melanoma model B16, IL-9 was needed to promote Tc9 cell migration to tumor sites but had no direct effect on the tumor cell death. It acts chiefly as a homing mechanism which demonstrates yet another function of IL-9 in melanoma models that is inconsistent with other studies [54].

Another murine model study looks at the process of IL-9 transcription through DNA binding proteins to find a possible mechanism by which Th9 cells are differentiated and produce the anti-tumor IL-9 activity. This study does not look at the mechanism by which IL-9 inhibited the anti-tumor effects themselves; it analyzes the DNA binding protein Id3 and its regulation in tandem with transcription factors E2A and GATA-3 that bind the IL-9 promoter. Deletion of Id3 DNA binding protein causes an upregulation of IL-9 in CD4+ T-cells, which induces their differentiation into Th9 cells [55].

## Conclusion

Interleukin-9 is not limited to any one function and has been shown to induce various physiological responses in both innate and adaptive immunity. Its extensive involvement in various aspects of immunity suggests widespread application to various ailments. Its relationship with cancer is not well understood because it has been shown to both promote and inhibit tumor cell growth and migration. Clearly, IL-9 has a complicated dual function depending on cell line, tumor microenvironment, and other experimental conditions. Further complicating our understanding of the role of IL-9 in cancer pathogenesis is the limited knowledge of the pathways that it influences, and the downstream effects of these influences. Further investigation is needed to isolate the pathways through which IL-9 induces its effects, and the proteins it influences in these pathways. Further experiments must be careful to ensure similar experimental parameters to control for compounding variables such as differences in tumor microenvironment and other growth conditions. Because IL-9 is pleiotropic in function, these experiments must be conducted across many different cell lines and in many different cellular conditions in order to comprehend all of this complicated molecule's diverse functionality.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors have no conflict of interest.

**Ethical Approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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