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Interleukin-35: Immunosuppressive mechanisms in cancer and autoimmune diseases

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ABSTRACT

Interleukin-35 (IL-35) causes cancer to become more tumorigenic, prevents cancer cells from dying, and accelerates the spread of the disease. Cancer is a significant cause of morbidity and mortality and is one of many side effects of immunosuppressants. The increasing use of immunosuppressants in non-transplant patients especially helps define the effect of mild to moderate immunosuppression more precisely. This review examined the relationship between IL-35 immunosuppression, cancer, and autoimmune diseases, and the new types of diseases it creates.

Keywords: Autoimmune disease, cancer, IL-35, immunosuppression.

Interleukin-35 (IL-35) is a cytokine mainly produced by regulatory T (Treg) cells and consists of the Epstein-Barr virus-induced gene 3 beta chain (EBI3) and the IL-12 p35 alpha chain. Interleukin-35 induces tumorigenicity in cancer, protects cancer cells from apoptosis, and promotes cancer progression. However, several reports point out its contradictory role in cancer prevention. Thus, the exact purpose of this cytokine in cancer development remains a fundamental question to be answered. This review describes the structure of IL-35 and its receptors and their various signaling pathways.[1]

Interleukin-35 is a cytokine of the IL-12 family, composed of a heterodimeric combination of α (p40 and EBI3) and β (p19, p28, and p35) chain subunits. Other members of this family include IL-12 (p35 and p40), IL-23 (p19 and p40), IL-27 (p28 and EBI3), IL-35 (p35 and EBI3), and the newly discovered member IL-39 (IL-23p19 and EBI3). In contrast to other members of the IL-12 family, IL-35 has been shown to have immunosuppressive activity. Since then, IL-35 has emerged as a key regulator of tumor progression since it can promote the establishment of an immunosuppressive microenvironment. The expression of IL-35 in the tumor microenvironment (TME) can promote the proliferation of primary tumor cells and metastatic colonization at secondary sites. The receptor, consisting of gp130 and IL-12Rβ2, signals the induction of downstream transcription of EBI3 and IL-12a and the activation of the classical Janus kinase (JAK) transducers and activators of transcription-STAT signaling pathway.[1]

Interleukin-35 has been shown to play an important role in the development of benign and malignant tumors, such as hepatocellular carcinoma, advanced breast cancer, pancreatic ductal adenocarcinoma, non-small cell lung cancer (NSCLC), and prostate cancer. Studies have demonstrated that IL-35 is mainly produced by Tregs, and in recent years, the expression of IL-35 in tumor cells has been gradually confirmed by western blot and reverse transcription polymerase chain reaction (RT-PCR) analysis. IL-35 could enhance the malignant biological behavior of RM-1 cells *in vitro* compared with treatment with IL-35 neutralizing antibodies. *In vivo*, IL-35 has been shown to promote tumor growth, progression, and metastasis by

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enhancing the secretion of other cytokines, such as IL-6 and granulocyte colony-stimulating factor. It has also been confirmed that IL-35 inhibits several cytokines, including interferon-gamma, producing tumor-promoting effects.[1]

As several IL-35+ immune cell types, such as M1 tumor-associated macrophages and dendritic cells (DCs), have been discovered and isolated, current evidence suggests that tumor-derived IL-35 is significantly involved in the tumor-promoting properties of various cellular contexts, possibly by suppressing the infiltration of tumor-infiltrating lymphocytes and the proliferation of effector cells. Overall, IL-35 produced by malignant tumor cells and surrounding stromal cells contributes to immune suppression within the tumor microenvironment, thereby supporting sustained tumor growth and metastasis.[2]

The tumor microenvironment, particularly that of advanced cancers, is especially immunosuppressive and is equipped with various immunosuppressive mechanisms, one of which is the recruitment of immunoregulatory populations of immune cells that dampen anti-tumor immunity. Previous studies have verified that IL-35+ Tregs are especially enriched inside the TME, and IL-35 blockade caused superior effector anti-tumor immune responses with ultimately reduced tumor burden and metastasis. More recently, it has been determined that Treg-derived IL-35 directly induces inhibitory receptor expression while limiting the differentiation of an essential memory CD8+ T cell population through a STAT1/4-BLIMP1 axis.[3]

However, Tregs aren't the only source of IL-35, and various molecular kinds have been suggested to deliver IL-35 within the TME. For instance, it has been suggested that tumor cells in breast cancer and pancreatic ductal adenocarcinoma can produce IL-35, and that expression correlates with worse prognosis in patients with these cancers. A study using a murine model of transplantable cancers with transgenic IL-35 expression has shown that increased cytokine production within the TME is associated with increased recruitment of myeloid-derived suppressor cells and angiogenesis, which collectively promoted tumor growth.[4]

An observation has suggested that metastatic TME-associated macrophages produce IL-35 in boT-celery in humanistic head and neck cancers and mice (orthotopic mammary gland tumor model). Initial inflammation caused by tumor growth *in situ* upregulated IL-12Rβ2 expression in tumor cells, conferring responsiveness to IL-35. Macrophage-derived IL-35 can induce a mesenchymal-epithelial transition in tumor cells, facilitating metastasis. It can suppress anti-tumor responses and promote myeloid-derived inhibitory cell accumulation, which can be improved by blocking IL-35. Further, even though B cell infiltration within the TME has been correlated with better patient outcomes in various cancers, including pancreatic cancer and head and neck squamous cell carcinomas, it has been shown that IL-35+ Bregs promote cancer cell proliferation and accelerate the development of pancreatic ductal adenocarcinoma. Tumor-associated IL-35 enrichment hinders effective cancer immunotherapy, making it a promising therapeutic target. However, the IL-35 chain's promiscuity in sharing multiple receptors complicates mechanistic dissection and therapeutic development due to its promiscuity.[5]

Interleukin-35 in autoimmunity

Regarding the role or effect of IL-35 in six autoimmune and inflammatory diseases, some of the diseases known to be causal or related are; type 1 diabetes, rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), inflammatory bowel diseases (IBD), primary Sjögren's syndrome (pSS) and atherosclerosis.[1]

THE RELATIONSHIP BETWEEN AUTOIMMUNE DISEASES AND CANCER

Patients with IBD, such as ulcerative colitis and Crohn's disease, are at increased risk for colon cancer. Celiac disease is also associated with an increase in all intestine cancer, although this malignancy is rare in healthy individuals. Excessive inflammation was observed in intestinal mucosa samples taken from these patients. In the 19th century, Rudolf Virchow reported that leukocyte infiltration within tumors is a common feature of cancer. It is now recognized that inflammation plays an important

role in carcinogenesis. In particular, chronic inflammation caused by infections (e.g., from hepatitis B or C viruses, *Helicobacter pylori*), chemicals (e.g., tobacco and inhaled pollutants), or obesity-related factors (e.g., hormones, growth factors, adipokines, inflammatory mediators) may increase the risk of cancer growth and metastasis. Autoimmune diseases unrelated to the gut have also been widely studied for their association with cancer. Rheumatoid arthritis is caused by dysregulation of the immune system, including cytokines and related cells, and is involved in the development of cancer. However, primary RA does not seem to significantly increase the risk of cancer, although this issue remains controversial. In contrast, there is consensus that treating RA with the anticancer drug methotrexate increases the risk of secondary cancers, especially lymphomas. In contrast to RA, pSS increases the risk of cancer overall and lymphoma, particularly non-Hodgkin's lymphoma (NHL). Systemic lupus erythematosus is associated with the risk of several types of cancer, including vulvar, lung, thyroid, and possibly liver cancer. In addition, lymphoma, particularly NHL subtypes, and diffuse large B-cell lymphoma are commonly associated with SLE. Diffuse large B-cell lymphoma develops from activated lymphocytes, suggesting that chronic inflammation may increase the risk of lymphoma in autoimmune diseases such as IBD. On the other hand, these patients have a lower risk of breast, uterine, and possibly ovarian cancer. Systemic sclerosis is also associated with the risk of some cancers, including lung cancer, NHL, and hematopoietic cancers, but not breast cancer. Both dermatomyositis and polymyositis increase the risk of nasopharyngeal cancer, lung cancer, and hematopoietic cancers. Interestingly, the risk is highest in the first year after diagnosis and then decreases with age. B-cell lymphoma associated with autoimmune diseases. T-cell lymphomas are also associated with autoimmune diseases and reported that 13 patients with metastatic melanoma received immune-depleting chemotherapy followed by immunotherapy combining specifically responsive tumor-reactive T cells with high doses of IL-2. Tumor shrinkage or regression correlated with the development of autoimmunity manifested as a sign of autoimmune melanocyte destruction, including in four patients with vitiligo and one with anterior uveitis. This study demonstrated that self-antigens on cancer cells, even when normally expressed, can be useful targets for human tumor immunotherapy, provided that the treatment is tolerated or locally controllable. Cancer and autoimmune diseases are closely related, and anti-IL-7R targeted antibody therapies that suppress the pathophysiological condition, as in IL-35, are useful in the treatment of both diseases.[6]

Immunosuppression and cancer

Although great strides have been made in understanding the mechanisms leading to tumor immunity, many obstacles stand in the way of successfully translating mechanistic insights into effective tumor immunotherapy. These obstacles include the ability of tumors to promote a permissive microenvironment and the activation of various immunosuppressive mechanisms that may collectively hinder effective immune responses. Here, we discuss the different strategies that tumors use to prevent immune responses, including tumor-associated impaired antigen presentation, activation of negative costimulatory signals, and the generation of immunosuppressive factors. Furthermore, we highlight the influence of regulatory cell populations that may contribute to this immunosuppressive network. These include Treg, natural killer (NK) T cells, and specific subsets of immature and mature DCs. The current wealth of preclinical information promises future scenarios in which simultaneous blockade of immunosuppressive mechanisms in combination with other traditional strategies may be effective in overcoming immune tolerance and promoting tumor regression.[4] Our perspective on tumor immunology changed radically in the early 1990s after the surprising discovery that most antigens expressed by tumor cells are not necessarily neoantigens occurring exclusively on cancer cells, but rather tissue differentiation antigens also expressed on normal cells. These unexpected findings led to the hypothesis that perhaps the biggest obstacle in harnessing the immune system to fight tumors is the immune system itself, in particular, its complex mechanisms for establishing T cell tolerance to self-antigens and, more broadly, to tumors and antigens, a process that is usually considered to be “physical”. Experimental evidence supporting

this hypothesis was provided by the groups of scientists, who independently demonstrated that antigen-specific CD4+ T cells indeed become tolerant during tumor growth *in vivo*. After this phenomenon, called “tumor-induced anergy”, was first reported, several studies demonstrated that this T cell insensitive state occurs during the growth of hematologic or solid tumors expressing a model or real tumor antigens, as well as during tumor progression, in naturally occurring tumors, and, more importantly, during the progression of human cancers as well. Therefore, it cannot now be denied that induction of tolerance to tumor antigens by mechanisms similar to those that control responses to self-antigens is an important immunosuppressive strategy that allows tumor cells to evade T cell-mediated antitumor responses. This different view of tumor immunity is also raising the bar for cancer immunotherapy, as the immune system must overcome the barriers created by immune tolerance to effectively detect and eliminate tumors that primarily express the "body's own" substances that represent cancer immunotherapy.[7]

Cancer is a major cause of morbidity and mortality and is one of the many side effects of immunosuppressants. Epidemiological studies and cancer registries have consistently shown an increased risk of malignancies in transplant patients, although the calculated risks (four to 500-fold increase) vary widely between studies, mainly due to differences in methodology and patient selection. Skin cancer, lip cancer, lymphoma, and Kaposi's sarcoma are the most common cancers in these patients. Many risk factors have been identified, including underlying viral infections, treatment regimens, and levels of immunosuppression. The increasing use of immunosuppressants in non-transplant patients helps to define more precisely the impact of mild to moderate immunosuppression. Since the discovery of effective immunosuppressants, extensive experience has been gained in the fields of transplantation and autoimmune diseases. In both fields, new immunosuppressants are on the market or still under clinical investigation. The increasing use of immunosuppressants in non-transplant patients indeed offers an opportunity to more accurately delineate the impact of mild to moderate immunosuppression on cancer risk.[5]

It is known that the risk of cervical cancer is significantly increased in women whose immune systems are weakened by acquired immunodeficiency syndrome or treatment after organ transplantation. Patients with end-stage renal failure appear to be at increased risk of cervical cancer. Patients with some autoimmune diseases are at increased risk of precancerous changes in the cervix, especially if they are treated with immunosuppressants. Among behavioral factors that weaken the immune system, smoking appears to significantly increase the risk of cervical cancer, while an inadequate diet only moderately increases the risk. It is difficult to determine whether sexually transmitted diseases are an independent risk factor other than human papillomavirus infection. Identifying groups of women who are more likely to fail to overcome persistent human papillomavirus infection will help individualize screening guidelines and help more specifically identify immune-related factors in the pathogenesis of cervical cancer.

Antibody therapies of cancer

The anti-CD20 antibody rituximab is a chimeric murine antibody approved in 1997 for the treatment of NHL. The CD20 is expressed on malignant B cells but is also a pan-B cell marker. Nevertheless, the side effects of anti-CD20 antibody therapy are clinically tolerable since the absence of plasma cells limits host damage in B cell-dependent immune responses and allows T cell-mediated mechanism of actions immunity and peripheral antibody production. In addition, repopulation of the B cell compartment can occur after the end of treatment. The combination of rituximab with chemotherapy has significantly improved the prognosis of T-cells mechanism of action of rituximab includes both an apoptosis-inducing effect and activation of antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and antibody-dependent celular cytotoixicity (ADPC) effector pathways. In addition, rituximab may increase sensitivity to chemotherapy or passive immunization. A variety of therapeutic anti-CD20 antibodies are currently in clinical use or clinical trials. Interestingly, in some autoimmune diseases, CD20 is expressed on

pathogenic activated B cells, so anti-CD20 antibodies can be used to treat autoimmune diseases. b. Ocrelizumab in MS. The humanized anti-human epidermal growth factor receptor 2 (HER2) antibody trastuzumab has been approved for the treatment of metastatic breast cancer. Neutralization and ADCC are considered the most important mechanism of actions. Before the clinical introduction of trastuzumab, HER2-positive breast cancer had a significantly worse prognosis than HER2-negative breast cancer.[8,9]

However, treatment with trastuzumab improved the prognosis of patients with HER2-positive tumors to the same level as that of patients with HER2-negative tumors. This discovery has changed the paradigm of breast cancer treatment. Interestingly, the relationship between HER2 and trastuzumab is considered to be an ideal combination of target antigen and therapeutic antibody. The former is highly expressed in tumors, while the latter is hardly immunogenic. Therefore, much basic research and development work on antibody therapy has focused on trastuzumab.[10,11]

The anti-epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab are chimeric immunoglobulin G1 (IgG1) and fully human IgG2 antibodies, respectively. According to the IgG subclass, cetuximab shows a stronger immune response compared to panitumumab (ADCC mediated by the Fc portion).[12]

Natural killer cells are important for recruiting cytotoxic T cells to tumor sites. Interestingly, Wang reported that cetuximab triggered the activation of not only NK cells but also cytotoxic T cells in peripheral blood mononuclear cells of colorectal cancer (CRC) patients. Thus, cetuximab provides greater health benefits than panitumumab in head and neck cancer patients. Interestingly, only mutations in Kirsten rat sarcoma viral oncogene homolog or B-raf proto-oncogene, serine/threonine kinase, downstream molecules of EGFR signaling associated with resistance to EGFR inhibitors, have been used to indicate anti-EGFR antibody therapy. The EGFR expression level is not an indicator of a good response to cetuximab or panitumumab. Panitumumab, through its IgG2 moiety, can enhance the alternative pathway of ADCC by T-cellating myeloid cells. Therefore, it is becoming increasingly important to understand the immune regulation of antibody therapy and use predictive methods to select appropriate antibodies. Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal IgG1 approved for the treatment of various types of cancer, including CRC, NSCLC, breast cancer, and kidney cancer. It binds to VEGF and disrupts VEGFR signaling in tumor vasculature, which may attenuate tumor growth by reducing nutrient and oxygen supply.[13]

In the treatment of metastatic colorectal cancer, bevacizumab in combined immunoglobulin entional chemotherapy improves outcomes compared with standard chemotherapy alone or cetuximab or panitumumab. Immune checkpoint inhibitors (ICIs), such as ipilimumab, nivolumab, and atezolizumab, have ushered in a new era of cancer monoclonal antibody therapy.[14-17]

Ipilimumab is a fully human monoclonal IgG1 that inhibits cytotoxic T-lymphocyte antigen-4 (CTLA-4) and increases T-cell activation. Nivolumab is a fully human IgG4 monoclonal antibody, and atezolizumab is a humanized IgG1 antibody. These antibodies block programmed death-1 (PD-1) or programmed death ligand-1 (PD-L1), which also enhance T cell activation. The biology and mechanism of action of these antibodies have been studied in detail elsewhere. However, to date, no studies have been performed that have investigated both drug delivery and efficacy in human tumor tissue to clarify the exact mechanism of action of these agents. ICIs may have multiple mechanisms of action, including ADCC, CDC, ADPC, and induction of apoptosis.[18,19]

Antibody therapies in autoimmune disease

Many therapeutic antibodies have been approved for clinical use against autoimmune diseases. In 1986, the anti-CD3 antibody muromonab-CD3, a murine IgG2 antibody (clone OKT3), was the first antibody approved by the Food and Drug Administration as an immunosuppressive therapy against transplant rejection.[20-22]

It was also thought to be useful in treating autoimmune diseases such as MS, but clinical trials were halted due to toxicity, especially allergic reactions to the murine antibody.[20-22]

The OKT-3 first activates T cells, causing apoptosis or inducing energy or tolerance. Finally, it removes T cells from the host's circulation. Recently, OKT-3 has been used in several BsAb formats to activate T cells. Thus, OKT-3 has multiple effects and is useful for various applications. Anti-CD25 antibodies daclizumab and basiliximab, humanized IgG1, and chimeric IgG1, respectively, are also used to control transplant rejection. IL-2/IL-2Rα signaling controls T cell proliferation and activation, and anti-IL-2Rα antibodies inhibit T cell activity in tissue inflammation and acute rejection.[23]

Both antibodies are thought to be useful in the treatment of MS. Daclizumab was approved for the treatment of MS but was withdrawn from the market worldwide due to safety concerns, including encephalitis and hepatitis. These are likely secondary autoimmune diseases caused by the inhibition of Treg cells and the proliferation of NK cells. Regarding NK cells, daclizumab increased the CD56 bright population. Interestingly, the frequency of CD56 bright NK cells did not change significantly between MS patients and healthy controls, but the number of these cells increased in patients who responded well to MS treatment. Taken together, these results suggest that Treg impairment caused by daclizumab treatment may lead to secondary autoimmune diseases. Two active ingredients have already been approved for the treatment of MS: the anti-VLA-4 antibody natalizumab and the anti-CD52 antibody alemtuzumab. Natalizumab is a humanized IgG4 without ADCC and CDC activity, whereas alemtuzumab is a humanized IgG1 with ADCC and CDC activity. Thus, natalizumab blocks the migration of VLA-4 (α4β1 integrin) positive leukocytes into the central nervous system by inhibiting their interaction with vascular cell adhesion molecule-1 and mucosal adressin cell adhesion molecule-1 positive endothelial cells, thereby reducing disease activity. Natalizumab can cause serious side effects, such as John Cunningham virus-mediated progressive multifocal leukoencephalopathy. Sabol et al.[25] reported an association between natalizumab treatment and a potential risk of melanoma. Alemtuzumab can deplete CD52-positive leukocytes, mainly composed of T and B cells, through ADCC and CDC activity. Secondary infections (Listeria monocytogenes and cytomegalovirus) and malignancies (thyroid cancer and melanoma) are rare, but certain secondary autoimmune diseases such as thyroid disease, immune thrombocytopenia, and nephropathy may be observed. The most common malignancies were papillary thyroid carcinoma and melanoma.[6,24]

Anti-CD20 antibody therapy, based on the elimination of autoantibody-producing B cells or T cell-activated B cells, is used to treat some autoimmune diseases. One such antibody, rituximab, was approved in 2006 for the treatment of RA but has immunogenicity issues due to its chimeric composition (i.e., human anti-chimeric antibodies). Ocrelizumab, a humanized IgG1, has also been approved for the treatment of MS.[26]

However, all IgG subclasses can exhibit autoimmune disease prevention center activity and trigger macrophage-dependent killing or secondary immune responses. The ADPC may be an important factor in the paradoxical feature of antibody therapy, where treating an autoimmune disease may trigger a secondary autoimmune disease.[27]

Anti-tumor necrosis factor (TNF) antibodies such as infliximab and adalimumab, and the biologic anti-TNF drug etanercept, are breakthroughs in the treatment of autoimmune diseases. As a regulatory cytokine, TNF plays an important role in inflammation and autoimmune diseases, reducing clinical symptoms. Patients' quality of life is dramatically improved. However, there are concerns about the side effects of anti-TNF therapy, as pro-TNF therapy was originally intended to treat cancer. In the treatment of RA, anti-TNF therapy increased the risk of cancer and serious infections, with pooled odds ratios of 3.3 and 2.0, respectively.[28]

In Crohn's disease, anti-TNF drugs significantly increased the risk of lymphoma, with standardized incidence ratios of 3.23 compared with Surveillance, Epidemiology, and End Results program controls and 1.7 compared

with no anti-TNF drugs. Active ingredient. Immunomodulatory therapy.[29]

With anti-TNF therapy, the most common cancers are lymphoma and melanoma, and the most common infection is pneumonia.[30]

Skin infections such as boils, erysipelas, and herpes infections can be caused by anti-TNF antibodies. However, anti-TNF therapy is not associated with an increased risk of severe skin infections, as occurs with non-biologic systemic therapies such as methotrexate, cyclosporine, and acitretin.[31]

Interestingly, ulcerative colitis patients with breast cancer resistant to non-biologic drugs can be well controlled by anti-TNF therapy without causing tumor growth. The anti-IL-6R antibody tocilizumab is a humanized IgG1 that suppresses cytokines released by synovial cells and activated T cells that destroy cartilage. Tocilizumab does not increase the risk of cancer.[32]

Appropriate host immune management can save you from the emergence of most cancer cells and autoreactive lymphocytes, while impaired immune management due to inner or outside elements permits the improvement and development of each disease.[33]

Anti-PD-1/PD-L1/CTLA-four antibodies can repair antitumor immune responses and launch the brakes on immune checkpoints; on the other hand, immoderate immune responses can cause autoimmune conditions.[34]

For example, anti-IL-6 antibodies can suppress cytokine release syndrome resulting from antibody remedy. The idiotype community additionally suppresses the unfold of autoreactive immune responses. Therefore, if we can assemble a choice tree for suitable immune management in step with character pathophysiological conditions, it could be viable to accurately manage most cancers and autoimmune diseases.[35]

Anti-IL-7R antibody remedy can assist set up this strategy

Moreover, sufferers with autoimmune diseases have an excessive chance of growing lymphoid malignancies, and in a few sufferers, the improvement of autoimmune diseases is located after normal antibody remedy treatment.[36]

Therefore, precise removal of lymphocytes with greater IL-7R signaling might be a concern with inside the pathogenesis of each lymphoid malignancy and autoimmune disease in excessive-chance sufferers.

In conclusion, the review emphasizes the intricate relationship between IL-35 immunosuppression, the advancement of cancer, and autoimmune disorders. It underscores that IL-35 doesn't just promote tumor growth and spread by creating an immunosuppressive environment but also has a substantial impact on the development of different autoimmune conditions. Recognizing these connections could lead to new treatment options for addressing cancer and autoimmune diseases.

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