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Antibody therapies in cancer and autoimmune disease

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Abstract. Cancer and autoimmune diseases are gradually proven to be "two sides of the same coin". Many cancer patients develop manifestations of autoimmune diseases and rheumatism, especially those receiving immune checkpoint inhibitors. At the same time, patients with autoimmune diseases also have cancer combined, which may be related to chronic inflammation damage to DNA or clinical medication. Antibody therapies, pioneered by monoclonal antibody drugs, are now used extensively in the treatment of cancer and autoimmune diseases. The relationship between cancer and autoimmune diseases is gradually being discovered, and some antibody therapies have therapeutic effects on both types of diseases, perhaps because the two have common targets. In-depth study of the role of various targets in the occurrence and development of the two types of diseases, screen the common targets, and discover the antibody drugs that play an activation or inhibition role against the common targets, so as to achieve the effect of "same treatment for different diseases", which brings hope to patients with "cancer-autoimmune diseases". This paper discusses the relationship between the two types of diseases, summarizes the specific targets and corresponding diseases of some antibody therapies, and analyzes the current status of antibody therapy in the treatment of the two types of diseases, in order to explore the "dual therapy" potential of more antibody therapies in the future, and develop new targets and drugs.

Keywords: Antibody Therapy, Cancer, Autoimmune Disease, Monoclonal Antibody.

1. Introduction

Nowadays, cancer remains one of the principal contributors to patient deaths worldwide. The cancer system includes not only cancerous tumor components, but also non-cancerous components and their metabolites, also known as the tumor microenvironment (TME). The TME promotes immune escape of cancer cells, which ultimately leads to cancer tumor resistance.

Autoimmune diseases (AIDs) are diseases due to the bodies' loss of immune tolerance to their own antigens, producing autoantibodies and leading to inflammation production and tissue damage. AIDs are becoming increasingly common and include more than 100 different clinical entities, such as rheumatoid arthritis, dry syndrome, antiphospholipid syndrome, autoimmune thyroid disease and so on [1].

There are growing evidences that cancer and AIDs are "two sides of the same coin" and that they can occur simultaneously despite their opposite mechanisms of action. It has been found that cancer and AIDs share common targets. While antibody therapies targeting the respective disease targets are increasingly being investigated, antibody therapies targeting shared therapeutic targets remain to be

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explored. Therefore, this paper explores the association between the two types of diseases and summarizes the relevant antibody therapies in order to recommend some directions for progress.

2. Relationship between autoimmune disease and cancer

2.1. Systemic sclerosis and cancer

Systemic sclerosis (SSc), a systemic AID, causes vascular changes and tissue fibrosis, mainly due to immune irregularities, and cancer remains the number one non-SSc-related cause of death among SSc patients [2]. Carbonell et al. used standardized incidence testing and analyzed the risk and factors for cancer in SSc patients and found that SSc patients had an increased risk of cancer ($p < 0.001$), most commonly breast, lung, hematologic, and colorectal cancers [3]. In a regression study by Partouche et al. , breast cancer was the most common cancer among SSc patients within 5 years of being diagnosed with SSc, and gastrointestinal cancer or lung cancer was the most common cancer 10 years after being diagnosed [4]. The positivity of anti-RNA polymerase III (anti-RNAPIII) antibody and anti-Scl-70 antibody were considered as risk factors for cancer in SSc patients [5, 6], anti-SSSCA1 antibody status may also be used as a cancer biomarker in SSc [7].

2.2. Autoimmune thyroiditis and thyroid cancer

Autoimmune thyroiditis, also known as Hashimoto's thyroiditis (HT), is an organ-specific AID caused by the occurrence of an autoimmune process. In this process, two specific antibodies, anti-TPO and anti-Tg, are produced against two antigens, both of which are produced by the body itself, called thyroid peroxidase (TPO) and thyroglobulin (Tg) [8], although negative antibodies do not exclude the occurrence of HT [9]. The most prevalent endocrine malignancy is thyroid cancer(TC), of which nearly 90% is papillary thyroid cancer (PTC) [10]. In a study by Mao et al. HT was found to be a possible high risk factor for TC [9]. HT-associated B lymphocytes located in the secondary lymphoid capsule of the thyroid gland produce and release autoantibodies from inside, leading to shrinkage and fibrosis of the follicles;This stops the infiltration and spread of tumor cells [11], but also increases the false-positive rate during central lymph node ultrasonography [12], which affects the diagnosis and treatment of TC.

2.3. Inflammatory bowel disease and cancer

Inflammatory bowel disease (IBD) is a progressive, refractory disease. Crohn's disease (CD), ulcerative colitis (UC) and indeterminate enteritis are the three most common IBDs. During IBD disease, the intestinal microbial composition is altered, there is an accumulation of Th17 cells in the intestine and an increase in the associated cytokines [13]. IBD can progress to colitis-associated colorectal cancer (CRC) through a process of “chronic inflammatory response - low grade heterogeneous proliferation-high grade heterogeneous proliferative carcinoma” [14]. In this process, Th17 is activated by bacterial components that enter the host intestinal epithelium and lamina propria, promoting CAC tumorigenesis [15].

3. Antibody therapies

Cell surface receptors, such as interleukin, Fc, programmed death, tumor necrosis factor receptors, and leukocyte differentiation antigen, and protein receptors, such as immunoglobulin and complement protein receptors, regulate cell growth, proliferation, and apoptosis through MAPK, AR, Wnt, CASP and other pathways. These receptors and targets have critical effects on the development of cancer and AIDs, and blocking them from functioning has become a new hope for the treatment of cancer and AIDs. For example, immunotherapy approaches that block the PD-1/PD-L1 signaling pathway are used in the standard treatment of cancer [16].

Antibody (Abs) is a glycoprotein secreted by B cells to recognize and neutralize foreign organisms or antigens in humoral immunity. The monoclonal antibodies (mAbs) designed based on the characteristics and effects of antibodies have high specificity, stability and affinity. The mAbs consist of a heavy chain and a light chain, with the Fab segment recognizing cell surface receptors and free molecular surface

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targets, and the Fc segment recognizing Fc receptors on the surface of cells with the ability to kill. Killer cells include NK cells, macrophages and so on. The killing ability of killer cells is activated to achieve specific targeted killing effects through antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) [17].

Today, antibody-associated therapies are no longer only mAbs, but more and more engineered and modified antibodies are available in various coupled forms, such as antibody-drug conjugates (ADCs), bispecific antibodies (bsAbs), antibody fragments (AFs), Fc fusion proteins and so on. bsAbs have the ability to bind to two different epitopes, playing the role of T cell recruitment, double immune checkpoint blockade and so on. The first bsAbs to be authorized for use is Catumaxomab (CD3×EpCAM) [18]. bsAbs are also used for drug delivery, receptor inhibition and activation [19]. On the basis of mAbs, ADCs are coupled with small molecule drugs to form a class of antibody therapy that has both the tumor targeting property of mAbs and the killing effect of small molecule drugs on cancer. The representative ones are trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) for HER2 positive breast cancer. Their research and development is based on trastuzumab [20].

4. Antibody therapies in cancer

Specific receptors on cancer cells, such as the human epidermal growth factor receptor family (HER/ErbB), can activate downstream signaling pathways, including the PI3K/AKT signaling cascade, to regulate cell proliferation and differentiation, invasion and migration, and angiogenesis [21]. In this process, PD-L1, which is exposed on the tumor cell surface, binds to PD-1 on the T cell surface, thus resisting the killing effect of T cells [22]. Meanwhile, TME contains important cells of tumor immunity, such as Treg cells [23]. Treg cells are CD4+ T cells, which are responsible for suppressing autoimmunity when normally expressing CD25 [24]. Also, helper T cells become two subsets of Th1 and Th2 under the polarization of IL-12 and IL-4. Th2-related cytokines can antagonize Th1 and weaken cellular immunity. mAbs target cancer cell surface antigens, inhibit related downstream signaling pathways, suppress cancer cell proliferation, and kill cancer cells through various killing effects; or prevent the occurrence of immune escape and enhance the host's autoimmune cell-killing ability.

In Table 1, we summarize some of the commonly used antibody therapies and their antibody classes and corresponding cancer names. Nowadays, based on these drugs, more new antibodies are designed, such as the new anti-HER2 mAb H2Mab-181 [25], H2Mab-19 [26], novel mAb developed against KRAS mutations recognizing the extracellular structural domain of human ASCT2 [27]et al; Bispecific antibodies such as Mosunetuzumab, Glofitamab, Oronextamab and Epcoritamab, which target CD3 and CD20, have also emerged, showing good clinical effects in non-Hodgkin's lymphoma [28]. Combinations between different monoclonal antibodies have also demonstrated increased safety and efficacy, such as Epratuzumab, which targets CD22 and is complementary to the known effects of CD20 antibodies [29], the combination of Utomilumab and Rituximab, designed for tumor necrosis factor receptor superfamily member 4-1BB, has demonstrated positive safety and clinical activity in patients with therapeutically resistant/refractory CD20+ non-Hodgkin's lymphoma [30]. Also, certain monoclonal antibodies target targets that have been found in other diseases that have not been studied, and whether they can play a therapeutic role in these diseases remains to be investigated. For example, OX40 expression was found in triple-negative breast cancer (TNBC), and Ivuxolimab, which targets OX40, may be a new drug for TNBC.

However, antibody therapies for cancers may also have side effects. Mogamulizumab, an anti-CC chemokine receptor 4 antibody, has also been reported to induce mossy reactions in mucosal skin [31]; CD3, CD19 dual-target antibody Blinatumomab shows cytokine release syndrome (CRS) and neurotoxicity [32].

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Table 1. Antibody therapies in cancer.

Specific targets	Cancer Name	Drug Name
CD2	Non-Hodgkin lymphoma (NHL)	Siplizumab
CD3 BCMA	Relapsed/refractory multiple myeloma (RRMM)	Teclistamab
CD3 EpCAM	Hepatoblastoma, Non-muscle-invasive bladder cancer (NMIBC), Peritoneal carcinomatosis (PC)	Catumaxomab
CD3	B-cell lymphoma, NHL, Relapsed/refractory follicular lymphoma(FL)	Mosunetuzumab
CD20	Relapsed/Refractory B-cell non-Hodgkin lymphoma (B-NHL), Relapsed/Refractory Diffuse Large B-cell Lymphoma (DLBCL)	Glofitamab Odronextamab Epcoritamab
CD3 CD19	NHL, B-lymphocytic leukemia, Relapsed/Refractory DLBCL	Blinatumomab
CD19 CD22	B-lymphocytic leukemia, Relapsed/Refractory DLBCL	Inotuzumab
CD19	Relapsed/Refractory DLBCL	loncastuximab tesirine
CD20	Lymphoma, NHL	Rituximab Obinituzumab Ofatumumab Ocrelizumab Tositumomab
	NHL, Chronic lymphocytic leukemia (CLL), FL	Ocaratuzumab
	NHL	Veltuzumab
	NHL, CLL	Ublituximab
	Acute lymphocytic leukemia (ALL), NHL, follicular and DLBCL	Epratuzumab
CD22	Relapsed/Refractory hairy cell leukaemia	Moxetumomab pasudotox
	ALL	Inotuzumab Ozogamicin
CD30	Hodgkin's lymphoma(HL), NHL	Iratumumab
	HL, Systemic Mesenchymal Large Cell Lymphoma(ACLC), Cutaneous T-cell lymphoma(CTCL)	Brentuximab vedotin
CD33	Acute myeloid leukemia (AML)	Gemtuzumab Ozogamicin
CD38	Multiple myeloma(MM), RRMM, Newly diagnosed multiple myeloma(RDMM)	Isatuximab
	MM, RRMM, RDMM, Relapsed plasma cell lymphoma, AML, Mantle cell lymphoma(MCL), FL, DLBCL, Blastic plasmacytoid dendritic cell neoplasm (BPDCN)	Daratumumab
	RRMM	Elotuzumab
CD79b	DLBCL , Relapsed/Refractory FL, NHL	Polatuzumab vedotin
CD80	NHL, Relapsed/refractory FL, B-NHL	Galiximab
CTLA-4	Renal cell carcinoma (RCC), Advanced melanoma, Non-small cell lung cancer (NSCLC), Metastatic melanoma	Ipilimumab

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Table 1. (continued).

IL-6/IL-6R	MM, Triple-negative breast cancer(TNBC)	Atlizumab Tocilizumab
	Descending thoracic aorta aneurysm(dTAA)	Satralizumab
OX40	Hepatocellular carcinoma(HCC), Melanoma	Ivuxolimab
4-1BB	NSCLC, Small cell lung cancer(SCLC), Anaplastic thyroid carcinoma, Renal cell carcinoma, Squamous cell carcinoma of the head and neck (HNSCC), NHL , DLBCL, Breast Cancer(BC), FL	Utomilumab
	Urothelial Carcinoma, Bladder cancer(BCa), B-Cell Malignancies, Leukemia, Pancreatic Cancer, Colorectal Cancer(CRC), Head and neck cancer(HNSC), Solid tumors, B-Cell NHL, MM	Urelumab
CC chemokine receptor 4	T-cell lymphomas, T-cell leukemia, Mycosis fungoides (MF) , Sézary syndrome (SS)	Mogamulizumab
EGFR	CRC, BCa, Glioma	Cetuximab Panitumumab
	CRC, BCa, Glioma, Liver cancer	Bevacizumab
	HNSC	Akalux
EGFR MET	NSCLC	Amivantamab
HER2	BC, Stomach cancer	Trastuzumab Pertuzumab
	Metastatic BC	Trastuzumab Emtansine
	Metastatic HER2-positive BC	Trastuzumab Deruxtecan
	HER2-positive BC, Gastric cancer, Gastroesophageal junction cancer, HER2 low expression breast cancer, NSCLC	Enhertu
VEGF	CRC	Bevacizumab
VEGFR2	Stomach cancer, Liver cancer	Ramucirumab
GD2	Neuroblastoma	Dinutuximab
PD-1	Melanoma, NSCLC	Pembrolizumab Nivolumab
	RRMM, Melanoma, NSCLC, Colorectal cancer(CRC), Non-muscle invasive bladder cancer(NMIBC)	Cetrelimab
PD-L1	TNBC, BCa	Atezolizumab
	BCa	Durvalumab
	SCLC, NSCLC, Esophageal squamous cell carcinoma, BC, HCC, TNBC	Adebrelimab
	Soft tissue sarcomas, Biliary tract cancer	Envafolimab
CTLA-4	Metastatic melanoma	Lpilimumab
TROP-2	TNBC	Sacituzumab Govitecan
BCMA	RRMM	Belantamab Mafodotin
TF	Relapsed/Metastatic cervical cancer	tisotumab vedotin-tftv

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5. Antibody therapies in autoimmune disease

In contrast to cancer, most patients with AIDs have Treg cells in peripheral blood that are defective in number and/or function [24]. In many inflammatory and AIDs, CD4+ T helper (Th) cells are involved in tissue destruction [33],Th1-related inflammatory factors have been shown to be relevant with AIDs, for example, Type I Interferons (IFN) [34]. In addition, Th17 cells, which can produce IL-17, have a vital effect on AIDs, and IL-23 on their surface promotes the pathogenicity of Th17 cells in vivo by increasing the production of IL-17 and GM-CSF in RORγt-, STAT3- [35].

Conventional therapies for AIDs are usually glucocorticoids, immunosuppressants and so on. With the emergence of side effects and the development of mAbs, mAbs are also considered as treatments for AIDs. In Table 2, we summarize some information about antibody therapies that can be used to treat AIDs. Comparing Table 1, it can be seen that a variety of mAbs can treat not only oncological cancers but also AIDs, perhaps due to the overexpression of the same targets that can cause both cancer and AIDs. Thus mAbs for the same target may be able to achieve the effect of "treating the same disease",for example, MAP4K3 (also known as GLK) can activate PKCθ in T cells by phosphorylating PKCθ Ser-538 residues, thereby activating IKK/NF-κB, and can also be involved in cell proliferation through the mTOR signaling pathway, and overexpression of GLK can cause cancer, AIDs [36], antibody therapies targeting MAP4K3 (GLK) may offer a new way forward for patients with "cancer-AIDs". It is also worthwhile to investigate whether the existing targets and their corresponding mAbs have a "dual therapy" role in treating both types of diseases.

However, there are still some drawbacks to mAbs for AIDs, such as Alemtuzumab which is thought to be associated with the emergence of secondary AIDs [37]; anti-tumor necrosis factor (TNF) therapy is also not recommended in idiopathic inflammatory myopathy (IIM) because of the potential to induce systemic AID [38]. Even when different mAbs are designed for the same target, they have different efficacy and safety profiles, such as in psoriasis where Risankizumab has been found to have higher efficacy and lower risk [39].

Table 2. Antibody therapies in AIDs.

Specific targets	AIDs Name	Drug Name
CD19	Optic neuromyelitis optica spectrum disorder (NMOSD) , Multiple sclerosis(MS)	Inebulizumab
CD20	MS, Autoimmune encephalitis(AIE), Rheumatoid arthritis(RA)	Ocrelizumab
	MS, RA, Systemic lupus erythematosus(SLE), Anti-neutrophil cytoplasmic antibody-associated vasculitis	Ofatumumab
	SLE	Obinituzumab
	MS, NMOSD	Ublituximab
	Immune thrombocytopenia(ITP)	Veltuzumab
	RA, AIE, Graves' orbitopathy(GO), Myasthenia gravis(MG), Autoimmune blistering diseases(AIBDs)	Rituximab
CD22	SLE, Primary Sjögren's syndrome	Epratuzumab
CD25	MS	Daclizumab
CD28	RA, Juvenile idiopathic arthriti(JIA), SLE, Systemic sclerosis(SSc)	Abatacept
	RA	Belatacept
CD38	AIE, Immune thrombotic thrombocytopenic purpura (iTTP), Refractory autoimmune hemolytic anemia, SLE, Cold agglutinin disease, Autoimmune cytopenias	Daratumumab
CD49	SLE	Elotuzumab
	MS, RA, Crohn's disease(CD)	Natalizumab
CD52	MS, Sporadic inclusion body myositis	Alemtuzumab

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Table 2. (continued).

IGF-1R	Thyroid eye disease, Thyroid orbitopathy, Thyroid-associated ophthalmopathy (TAO)	Teprotumumab (Tepezza)
α4β7integrin	CD, Inflammatory bowel disease(IBD), Ulcerate colitis(UC)	Vedolizumab
TNF-α	RA, JIA, Psoriatic arthritis(PsA), AS, CD, Ulcerative colitis, Psoriasis, Pyogenic sweat glands, Uveitis	Adalimumab
	CD	Infliximab
	RA, Polyarticular JIA, Systemic JIA	Tocilizumab
	CD, UC, IBD, SLE	Golimumab
	CD, UC, Axial spondyloarthritis (axSpA), IBD, Plaque psoriasis(PsO)	Certolizumab Pegol
IFN-α	SLE	Rontalizumab
	SLE, Idiopathic inflammatory myopathies (IIM)	Sifalimumab
	SLE	Rontalizumab Anifrolumab
IL-4/IL-13	Asthma, Atopic dermatitis(AD)	Dupilumab
	SSc	Romilkimab
IL-6/IL-6R	CD, RA, SSc, Autoimmune eye disease, AIE, GO	Tocilizumab
	NMOSD, Myelin oligodendrocyte glycoprotein (MOG)-IgG-associated disease (MOGAD)	Satralizumab
	CD, RA	Atlizumab Sarilumab
IL-17	AS, Oderate to severe psoriasis, Hypertrophic palmoplantar psoriasis, Generalized pustular psoriasis, PsA, RA, SLE	Secukinumab
	PsO	Bimekizumab
IL-23	PsO, Palmoplantar pustulosis(PPP), CD, PsA	Guselkumab
	PsO	Tildrakizumab Risankizumab
IL-12/23	PsO, PsA, Non-infectious uveitis (NIU)	Adalimumab
	UC	Mirikizumab
	PsO	Briakinumab
	CD, UC, IBD, Psoriasis, PsA, AD, SLE	Ustekinumab
FcRn	MG, AIE, Autoimmune bullous diseases, Bullous pemphigoid, Chronic inflammatory demyelinating polyradiculoneuropathy, Chronic Autoimmune Demyelinating Neuropathies, ITP, Autoimmune myositis, Pemphigus(Pemphigus Vulgaris ,Pemphigus Foliaceus)	Efgartigimab
Complement protein C5	AIE, ITP, MG	Rozanolixizumab
	AIE, MG, Catastrophic antiphospholipid syndrome(CAPS), Paroxysmal nocturnal hemoglobinuria(PNH), Atypical hemolytic uremic syndrome(aHUS), Thrombotic microangiopathy(TMA), NMOSD	Eculizumab
	Paroxysmal nocturnal hemoglobinuria(PNH)	Ravulizumab
vWF	iTTP	Caplacizumab
BAFF	SLE, SSc	Belimumab

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6. Conclusion

Cancer and AIDs are both diseases caused by immune disorders, and in recent years, antibody therapies have become increasingly popular in the management of these two types of diseases, with mAbs being particularly outstanding. Despite the opposite pathogenesis of the two diseases, they share the same targets of action, which makes many mAbs have the potential to treat both diseases simultaneously. However, only a few mAbs have been studied for their "dual therapy" potential. At the same time, the side effects of mAbs are gradually being discovered, and the development of new mAbs for existing targets, the discovery of new specific targets, the design of bispecific antibodies, and the development of multi-drug combinations have become the direction of antibody therapies for cancer and AIDs. Future research is needed to further explore the potential of antibody therapies as "dual therapy" and develop new targets and drugs to bring more possibilities for clinical treatment.

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