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Emerging Highlights of Antibody Therapy in Oncology

*Chen D**

Research Institute of Biological Medicine, Yiling Pharmaceutical, China

Abstract

As a hallmark of biological medicine, monoclonal antibody (mAb) therapy has evolved into the mainstream treatment in clinical oncology at a relatively fast pace. Whereas a therapeutic mAb was traditionally designed to block signaling molecules driving malignant cell growth or tumor angiogenesis, mAb-based agents are currently explored further in comprehensive contexts of disease biology, including immune checkpoint blockade, antibody-drug conjugates, Fc region modification, bispecific antibody, among others. Herein, this article outlines an updated understanding of these emerging avenues derived from mAb platforms, which are coming up with better innovative medicines to fight cancer.

Introduction

Since the first monoclonal antibody (mAb)-bearing hybridoma was invented four decades ago by Georges Kohler and Cesar Milstein [1], mAb-based therapeutic approaches have been going through a long evolving journey, and then successfully translated from bench to beside, to play an unique role in improving clinical outcomes particularly in the field of oncology. To date, more than sixty mAb-derived drugs have been approved for clinical use of which the majority belongs to oncology indications (en.wikipedia.org), and of note among the top ten best-selling drugs in 2015, seven are biomedicines out of which five fell impressively into mAb category (www.biodiscover.com), reflecting a dominating trend in the medical need-driven pharmaceutical innovation. Accordingly, the technology of antibody production has been optimized beyond hybridoma generation, taking the advantages of recombinant DNA engineering, immunoglobulin (Ig) humanization, phage display and transgenic animals, to circumvent the challenges such as immunogenicity and affinity issues [2,3]. Interestingly in recent years, mAb-based agents are being explored deeper in comprehensive contexts of disease biology for delivering further therapeutic benefits to the patients, which appear opening several avenues of great potentials for better medicines to emerge (Table 1).

Immune checkpoint blockade

Whereas mAb-based approaches have been previously developed to block secreting ligands or cell surface receptors in the signaling pathways that drive cancer cell growth or tumor angiogenesis, the renaissance of cancer immunology in recent years dramatically inspires oncology with several immune checkpoint-targeting antibodies to deliver additional clinical benefits through relieving immune suppression by the negatively regulatory pathways. The successes of blocking antibodies (ipilimumab and pembrolizumab/nivolumab) against co-suppressing molecules cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), respectively, in immune cells have validated a novel concept of checkpoint blockade to augment anti-neoplasm immunity through neutralizing immune inhibitory signaling activities induced by tumor cells [2,4]. The anti-CTLA-4 antibody ipilimumab was revealed to be able to prolong overall survival in a fraction of the patients with metastatic melanoma, triggering the curiosity of search for other immune-modulators as innovative medicines to fight cancer. In this regard, the anti-PD-1 antibody nivolumab has been subsequently demonstrated to confer efficacious clinical responses in melanoma including some patients free from disease progression for years, while causing less autoimmunity-associated adverse events than ipilimumab [3-5]. Moreover, nivolumab is also approved for therapeutic application in non-small cell lung cancer (NSCL) and renal carcinoma, suggesting extensive anti-tumor roles [5]. Most recently, according to the breaking news from Bio-World Today, an anti-PD-ligand1 (PD-L1) antibody atezolizumab has just been approved by Food Drug Administration (FDA) of USA to treat advanced bladder cancer. In this light, it is anticipated that the above approved antibodies will be tested in a broader spectrum of cancer types to expand their clinical indications. Meanwhile, following newer immune co-regulatory molecules to be identified more checkpoint modulating mAbs are going to come forth accordingly.

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Correspondence:
Daohong Chen, Research Institute of Biological Medicine, Yiling Pharmaceutical, Shijiazhuang, Hebei 050035, P.R. China,
E-mail: daohong@hotmail.com

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Table 1: Representative therapeutic antibodies of new mechanisms.

Group	Name	Mechanism of action	Clinical indication
Immune checkpoint blockade	Ipilimumab	Blocking CTLA-4	Metastatic melanoma
	Nivolumab	Blocking PD-1	Metastatic melanoma, NSCL, renal cancer
	Atezolizumab	Blocking PD-L1	Advanced bladder cancer
ADC	Brentuximab vedotin	Anti-CD30, tubulin inhibition	Hodgkin lymphoma
	Trastuzumab emtansine	Anti-HER2, tubulin inhibition	Refractory Her2+ breast cancer
Third generation	Mogamulizumab	Anti-CCR4, ADCC	Acute T-cell leukemia/lymphoma
	Obinutuzumab	Anti-CD20, ADCC	Refractory lymphocytic leukemia/lymphoma
BsAb	Blinatumomab	Anti-CD19 and CD3	Refractory B-acute lymphoblastic leukemia
	Catumaxomab	Anti-EpCAM and CD3	EpCAM-positive tumor, malignant ascites

CTLA-1 cytotoxic T-lymphocyte-associated protein 4, *PD-L1* programmed cell death- protein-ligand1, *NSCL* non-small cell lung cancer, *ADC* antibody-drug conjugate, *CD* cluster of differentiation, *HER2* human epithelial growth factor receptor2, *CCR4* CC chemokine receptor 4, *ADCC* antibody-dependent cell-mediated cytotoxicity, *BsAb* bispecific antibody, *EpCAM* epithelial cell adhesion molecule

Antibody-drug conjugate

Historically, cytotoxic medicines played a substantial role in controlling tumor progression and are particularly efficacious in certain types of hematological malignancies, through killing rapidly dividing (cancer) cells by means of inhibiting DNA synthesis or the related enzymes. Unfortunately, some normal cells, for example bone marrow and hair cells in the body, also divide very rapidly and were coincidently affected, resulting in severe adverse effects [3]. One possible solution for this problem is to conjugate certain potent cytotoxic compounds to tumor-specific antibodies, which has been termed antibody-drug conjugates (ADCs), thereby directing the cytotoxic effects to be concentrated on cancer cells while improving the pharmacokinetic profile of these compounds such as the long half-life time upon binding to a large protein like Ig. Currently, there are over fifty ADCs targeting numerous tumors in clinical development ranging from phase one to phase three, beyond which two of them have been approved for use in oncologic patients [6,7]. Brentuximab vedotin was designed to conjugate the anti-CD30 mAb with a highly potent tubulin inhibitor, for treating conventional drug-resistant CD30+ Hodgkin lymphoma (HL), and revealed to significantly improve response rates and progression free duration of the HL patients [8]. On the other hand, trastuzumab emtansine, consisting of the anti-Her2 mAb (trastuzumab) conjugated with a tubulin inhibitor (emtansine), has been demonstrated to be efficacious against the trastuzumab-resistant Her2+ breast cancer patients with better progression free and overall survival [3,6]. As such, ADCs can inhibit the growth of cancer cells expressing a selective antigen at a lower dosing of cytotoxic agents, and thus result in fewer systemic adverse events. Upon upgrading the technology such as optimized molecular linkers and minimized off-target effects, more ADCs will reach the clinic to deliver further therapeutic benefits to the patients in oncology, particularly those with refractory cancer.

Third-generation antibody

The first-generation mAbs were produced from mouse B-cell hybridomas, and can be recognized by human body defensive system as foreign proteins to mount immune responses against murine Ig, thus resulting in immunity-associated side effect and short half-life time in plasma. To deal with these challenges, the second-generation of therapeutic mAbs has come up with higher target antigen affinity and lower immunogenicity through genetic engineering to generate the Ab variants with human or humanized amino acid sequences. Recently to fully exploit biological potentials of a whole Ig molecule in the *in vivo* physiological contexts, there have been over twenty mAbs of the third generation in development through Fc region modification or/and glyco-manipulation to augment the cellular immune activities such as antibody-dependent cell-mediated cytotoxicity (ADCC). For example, the V158 site of IgGFcRIIIa, and defucosylated/low fucosylated mAbs have been identified to bind to the Fc receptor on immune cells such as natural killer cells with higher affinity which in turn induce stronger ADCC [9,10]. Mogamulizumab, a defucosylated anti-CC chemokine receptor 4 (CCR4) mAb, has achieved the clinical success as evidenced by conferring an impressive therapeutic response rate and extending the overall survival in the patients with acute T-cell leukemia/lymphoma. Later on, a Fc region-modified anti-CD20 mAb obinutuzumab has also been approved to treat drug-resistant chronic lymphocytic leukemia/lymphoma, upon delivering much better response rate and progression free survival than the old generation mAb rituximab [11]. Thus, being superior to small chemical compounds in this case therapeutic mAbs can not only block the signaling pathways driving tumor growth, but also simultaneously motivate several components of body's defense system to fight cancer. It is quite plausible that comprehensive characterization of the functional sites and post-translational situations of the IgG Fc region will inspire more third generation mAbs to overcome resistance to those of the second generation.

Bispecific antibody

Although in contrast to small chemical compounds therapeutic antibodies have a few superior properties such as prolonged half-lives in plasma and highly molecule-targeting specificity with minimized off-target toxicity, there are several limitations for mAb agents. A number of severe diseases like cancer usually involve multiple biological pathways in the pathogenesis, and thus single-targeted therapy may not be able to deliver the ideal clinical benefits. Even if certain groups of patients showed an impressive response to single pathway-blocking-based treatment initially, the majority of them relapsed due to the drug resistance resulted from target gene mutation(s) or/and alternative signaling pathway activation [3]. To address this issue, one possible approach is bispecific antibody (BsAb) therapy which has recently achieved some clinical success [12]. Blinatumomab, a T-lymphocyte-engaging BsAb simultaneously binding CD3-positive cytotoxic T cells and CD19-positive malignant cells, has been approved to treat relapsed/refractory B-acute lymphoblastic leukemia based on a responsive rate of 43% in a phase 2 clinical trial after 2 cycles of the treatment [13]. In addition, catumaxomab, targeting EpCAM and CD3, is clinically available

for the indications of EpCAM-positive tumors with malignant ascites, and particularly efficacious in treating peritoneal spread of gastrointestinal or gynecologic neoplasms [12]. Currently there are over 20 therapeutic BsAbs in the clinical trials [12], which will hopefully bring fresh waves of therapeutic benefits to the patients with a variety of tumor types in the coming years.

New strategy of combination

Although the etiology of neoplasm is yet to be precisely deciphered, it has been well documented that onco-pathogenesis is orchestrated through complex processes of multiple biological pathways in a dynamic manner, going beyond malignant cells to involve stromal components and even systemic factors [14], which underscores a rationale for combinational regimens-based therapy. One traditional protocol of combinational therapy was composed of a cytotoxic medicine plus a therapeutic mAb, such as 5-fluorouracil plus bevacizumab for colon cancer and doxorubicin plus trastuzumab for Her2+ breast cancer, in which the mAbs were added to enhance the direct killing malignant cells by the small chemical compounds. Interestingly in recent years, combinational strategies are also being extended to more comprehensive contexts of the disease biology, to improve the therapeutic efficacy via augmenting anti-tumor immunity. Combination of nivolumab and ipilimumab for immune checkpoint blockade in patients with metastatic melanoma raised the response rate to 61% dramatically, which was much higher than that of using each mAb alone [15]. Alternatively in case of increased side-effects and toxicities resulting from autoimmunity upon combined blocking of the immune co-inhibitors, one of hopeful options to circumvent this issue has been proposed to combine nivolumab or ipilimumab with an immune co-stimulatory mAb such as that of inducing OX40 receptor [5]. Intriguingly, some cytotoxic compounds were serendipitously noticed to exert certain positive regulatory effects on the immune environment at low dosages. Cyclophosphamide and doxorubicin up-regulate anti-cancer immune responses to eliminate malignant cells, through enhancing immunogenicity or lowering Fox3p+/CD8+ ratio in tumor-infiltrating lymphocytes, while sunitinib blocks STAT3 to diminish myeloid-derived suppressor cell (MDSCs) and negatively regulatory T (Treg) cells, and bevacizumab promotes dendritic cell (DC) maturation for antigen-presentation to prime anti-cancer immune activities [5,16]. In corollary, there have been several on-going clinical trials that combine immune checkpoint mAbs with these cytotoxic compounds to boost the anti-tumor immunity-resulted therapeutic efficacy [5].

Conclusion

The last two decades have witnessed a dramatic translation of mAb platform from a scientific breakthrough to a mainstream therapy in clinical oncology. Whereas the technology of antibody production has been modernized due to a series of impressive progresses in molecular and cellular biology during this period of time to meet the standards of pharmaceutical industry, the emerging waves of efforts are recently being made on further exploiting the functional potentials of a full antibody molecule and its derivates in comprehensive patho-biological contexts *in vivo*, including immune checkpoint blockade, ADC, Fc region modification, BsAb, new strategies of combinational therapy, among others. It is highly expected that more and better innovational medicines will be developed following the earlier successes from these recently highlighted avenues, to continuously address the unmet clinical needs of oncology in the era of precision medicine.

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