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Review

Mechanisms of action of therapeutic antibodies for cancer

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ABSTRACT

The therapeutic utility of antibodies and their derivatives is achieved by various means. The FDA has approved several targeted antibodies that disrupt signaling of various growth factor receptors for the treatment of a number of cancers. Rituximab, and other anti-CD20 monoclonal antibodies are active in B cell malignancies. As more experience has been gained with anti-CD20 monoclonal antibodies, the multifactorial nature of their anti-tumor mechanisms has emerged. Other targeted antibodies function to dampen inhibitory checkpoints. These checkpoint inhibitors have recently achieved dramatic results in several cancers, including melanoma. These and related antibodies continue to be investigated in the clinical and pre-clinical settings. Novel antibody structures that target two or more antigens have also made their way into clinical use. Tumor targeted antibodies can also be conjugated to chemo- or radiotherapeutic agents, or catalytic toxins, as a means to deliver toxic payloads to cancer cells. Here we provide a review of these mechanisms and a discussion of their relevance to current and future clinical applications.
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1. Introduction

Antibodies have proven to be powerful additions to the therapeutic armamentarium for a wide range of human diseases, including many types of cancer. The class of antibody most frequently used clinically is IgG. IgG is further divided into subclasses, each with unique and sometimes overlapping properties, including the ability to not only target and interfere with cell signaling but also induce CDC, ADCC, and ADPh (Schneider-Merck et al., 2010; Weiner et al., 2010; Hudis, 2007). While antibodies are commonly thought of in terms of their antigen specificities, native IgG is a bifunctional protein. It is becoming increasingly evident that the anti-tumor effects of Ab are driven both by their antigen-binding regions and by the properties of their Fc domains.

Several FDA approved antibodies target the receptors of the epidermal growth factor family and are mainstays of some breast and colon cancer treatment algorithms. By directly binding to these membrane bound receptors, these Abs inhibit their activity, resulting in dampened function of the downstream signaling cascades that promote cell cycle and function. However, in addition to signaling blockade, some members of this family of antibodies can also mediate ADCC of tumor cells (Kohrt et al., 2012; Scheuer et al., 2009). Other antibodies such as rituximab, targeting CD20 expressed on B cells/B cell malignancies, are also capable of inducing a signaling mediated death. However a growing body of work has demonstrated that both the variable and constant regions mediate the effects of rituximab by inducing CDC, ADPh and ADCC (Kaminski et al., 1993; Shan et al., 2000; Semac et al.,

Abbreviations: Ab, antibody; Ag, antigen; ADCC, antibody-dependent cell mediated cytotoxicity; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AKT, protein kinase B; APC, antigen-presenting cell; Apo2L/TRAIL, tumor necrosis factor-related apoptosis inducing ligand; BiTE, bispecific T cell engager; BTK, Bruton's tyrosine kinase; CDC, complement-dependent cytotoxicity; CEA, carcinoembryonic antigen; CHOP, cyclophosphamide, Daunorubicin, Vincristine, Prednisone; CR, complete response; CS1, signaling lymphocytic activation molecule-F7; CTL, cytotoxic lymphocyte; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DART, Dual Affinity ReTargeting; DC, dendritic cell; DR4, death receptor-4; DR5, death receptor-5; EGFR, epidermal growth factor; Fab, immunoglobulin antigen binding fragment; Fc, fragment crystallizable; FcγR, Fcγ Receptor; FOLFIRI, folinic acid, fluorouracil and irinotecan; GITR, glucocorticoid-induced tumor necrosis factor receptor; GPNMB, glycoprotein non-metastatic-b; HCC, Hepatocellular carcinoma; HER2, human epidermal growth factor; HGFR, hepatocyte growth factor receptor; HGF, hepatocyte growth factor; IGF, insulin like growth factor; IGFR, insulin-like growth factor receptor; IGF-1R, insulin like growth factor 1 receptor; IGF-2R, insulin like growth factor 2 receptor; Ig, immunoglobulin; IR, insulin receptor; KIR, killer-cell immunoglobulin-like receptors; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; LAG-3, anti-lymphocyte-activation gene 3; MAC, membrane attack complex; MAPK, Mitogen-activated protein kinase, MET oncogene; MHC, major histocompatibility complex; MM, Multiple Myeloma; MMAE, monomethyl auristatin; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK cells, natural killer cells; NSCLC, non small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand; PET, positron emission tomography; PFS, progression free survival; PI3-K, phosphoinositide 3-kinase; PLGA, Poly(D,L-lactic-co-glycolic acid); RANK, receptor activator of nuclear factor-κB; scFv, short chain variable fragment; T-DM1, trastuzumab emtansine; TandAb, tetravalent tandem antibody; TCR, T cell receptor; TIL, tumor infiltrating lymphocyte; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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Table 1
FDA approved antibodies for the treatment of cancer.

Generic name (trade name)	Origin	Isotype (conjugate)	Target	Approved uses/trials	Initial approval
Unconjugated MAbs					
Rituximab (Rituxan)	Chimeric	IgG1	CD20	Various leukemias and lymphomas	1997
Ofatumumab (Arzerra)	Human (XenoMouse)	IgG1	CD20	CLL/NHL	2009
Obinutuzumab (Gazyva)	Humanized	IgG1	CD20	CLL/NHL	2013
Alemtuzumab (Campath-1H)	Humanized	IgG1	CD52	CLL (no longer in clinical use)	2001
Trastuzumab (Herceptin)	Humanized	IgG1	HER2	Breast and gastric cancer/esophageal	1998
Pertuzumab (Perjeta)	Humanized	IgG1	HER2	Breast/esophageal, neuroendocrine, gastric	2012
Cetuximab (Erbitux)	Chimeric	IgG1	EGFR	Colorectal, HNSCC, lung	2004
Panitumumab (Vectibix)	Humanized	IgG2	EGFR	Colorectal/pancreatic	2006
Bevacizumab (Avastin)	Humanized	IgG1	VEGF-A	Colorectal, NSCLC, glioblastoma, RCC, cervical, ovarian	2004
Denosumab (Xgeva)	Human	IgG2	RANKL	GCTB	2010
Ramucirumab (Cyramza)	Humanized	IgG1	VEGFR2	Gastric cancer, NSCLC/HCC, RCC, Breast	2014
Ipilumimab (Yervoy)	Human	IgG1	CTLA-4	Melanoma	2011
Nivolumab (Opdivo)	Human	IgG4	PD-1	Melanoma	2014
Pembrolizumab (Keytruda)	Humanized	IgG4	PD-1	Melanoma/NSCLC, glioblastoma, ovarian, colon, RCC	2014
Dinutuximab (UNITUXIN)	Humanized	IgG1	GD2	High risk neuroblastoma	2015
Immunoconjugates					
Ibritumomab Tiuxetan (Zevalin)	Murine	IgG1 (^{90}Y)	CD20	Non-Hodgkin's lymphoma	2002
Brentuximab vedotin (Adcetris)	Chimeric	IgG1 (MMAE)	CD30	Hodgkin's lymphoma, SALCL	2011
Ado-trastuzumab emtansine (Kadcyla)	Humanized	IgG1 (DM1)	HER2	Breast cancer	2013
Gemtuzumab ozogamicin (Mylotarg)	Humanized	IgG1 (calicheamicin)	CD33	AML	2000[a]

MAb, monoclonal antibody; IgG, immunoglobulin-G; CLL, Chronic Lymphocytic Leukemia; NSCLC, Non-Small Cell Lung Cancer; ^{90}Y, yttrium-90; ^{131}I-Iodine-131; MMAE, monomethyl auristatin E; DM1, Mertansine; HNSCC, head and neck squamous cell carcinoma; SRE, skeletal-related event; GTCB, giant cell tumor of bone; SALCL, Systemic Anaplastic Large Cell Lymphoma.

[a] Withdrawn in 2010, currently reentered clinical trials for AML in France.

2003; Bonavida, 2007; Di Gaetano et al., 2003; Koene et al., 1997; Lefebvre et al., 2006). This information has led to development of novel anti-CD20 Abs selected for their superiority in inducing CDC and ADCC based on their physical properties that may alter binding with Fc receptors on immune effector cells.

Immune checkpoint inhibiting antibodies have produced some of the most striking results within recent years. By essentially taking the brakes off of T cells, treatment with these antibodies is creating durable responses in patients with advanced melanoma (Hodi et al., 2010; Wolchok et al., 2013a; Prieto et al., 2012; Postow et al., 2015) and other diseases, including renal cell carcinoma, non-small cell lung cancer and Hodgkin's Disease. Agonist antibodies to immune activating molecules are also under investigation.

Antibody structural derivatives also contribute to the growing clinical immunotherapy arsenal. The first clinically approved bispecific T cell engager is able to redirect the killer T cells of cancer patients directly to tumor cells via two engineered antigen binding sites. Various other platforms are in development and clinical trials for multiple malignancies. Anti-tumor agents can also be ferried by antibodies to tumor cells and exert their effects with decreased collateral damage to healthy tissue (Tables 1 and 2).

We will discuss the many antibodies relevant to cancer therapy with the aim of highlighting their basic mechanisms of action. Bearing in mind that several antibodies have multiple mechanisms of action, we have grouped antibodies into sections, based upon predominant mechanism or structure. This approach provides a glance at the rapidly evolving clinical landscape.

We searched for relevant articles on PubMed. In order to guide selection of PubMed searches regarding agents under development by private companies terms, Google searches were also employed. References to clinical trials are verified as cited or by searching clnicaltrials.gov.

2. Antibody structure

Antibodies, or immunoglobulins (Igs) exist in five distinct forms: IgA, IgD, IgE, IgG and IgM. Each of these has unique properties and functions determined by the constant region of the Ig. IgG is the class of Ig most often used in cancer therapy (Shuptrine et al., 2012). IgG consist of two identical antigen binding fragments (Fab) and one Fc region. While the Fab regions bind the target of the antibody (Ab), the Fc region binds to multiple molecules. These include components of the complement cascade, neonatal Fc receptors and Fcγ receptors present on neutrophils, monocytes, eosinophils, NK cells, and DCs (Weiner et al., 2010; Goebl et al., 2008). Classes of antibodies are further divided into subtypes. Different subtypes of Ig vary in their ability to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). For example, human IgG2 can recruit myeloid cells for ADCC but does not activate complement (Schneider-Merck et al., 2010). Human IgG4 does not activate ADCC or CDC, while human IgG1 can activate complement and recruit immune effector cells for ADCC (Weiner et al., 2010; Hudis, 2007). Further, posttranslational modification of the Fc region can also influence the function of antibodies (Kubota et al., 2009). Therapeutic antibodies are also distinguished by the method in which they were produced. In addition to producing purely mouse monoclonal antibodies, a wide array of contemporary antibody engineering techniques have led to the ability to generate Abs that are human and mouse chimeras, humanized or completely human. Chimeric Abs consist of murine derived variable regions and human constant regions. Humanized Abs are completely human, except for the complementarity determining regions (Imai and Takaoka, 2006).

3. Signaling disruption

Targeted antibodies affect tumor cells via multiple mechanisms. Tumor signaling can be perturbed when targeted Abs disrupt growth signaling pathways by manipulating the activation state of membrane bound receptors or neutralizing cytokines that are critical to cellular growth and proliferation. Several targets have been extensively validated in the clinic, some of which are highlighted below. Of note, interactions between the Fc portion of these antibodies and FcR on immune effector cells play an additional role in anti-tumor activity, i.e. induction of antibody-dependent cell-mediated cytotoxicity (ADCC). See the Fc mediated section for more information regarding ADCC.

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