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Myeloid cells as effector cells for monoclonal antibody therapy of cancer

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ABSTRACT

Monoclonal antibodies (mAbs) have become an important addition to chemo- and/or radiotherapy for the treatment of cancer. They have multiple effector functions that can lead to eradication of tumor, including induction of apoptosis, growth inhibition, and initiation of complement-dependent lysis. Furthermore, mAbs can recruit immune effector cells. Traditionally, natural killer cells have been considered as the main effector cell population in mAb-mediated tumor killing. Myeloid cells have potent cytotoxic ability, as well. Monocytes and macrophages have been shown to induce antibody-dependent cytotoxicity and phagocytosis of tumor cells in the presence of IgG anti-tumor mAb. Furthermore, neutrophils are the most abundant population of circulating white blood cells, and as such may constitute a formidable source of effector cells. However, when targeting neutrophils for tumor therapy, antibodies of the IgA subclass may be more effective. This article focuses on enlisting myeloid effector cells for mAb-based immunotherapy of cancer. Additionally, methods to study mAb-dependent phagocytosis of tumor cells by macrophages are compared.

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1. Introduction

Monoclonal antibodies (mAb) are increasingly used as therapeutic agents in autoimmune diseases, chronic inflammation and cancer. They can be used to deliver therapeutic drugs (including toxins or chemokines/cytokines) or as diagnostic tool (e.g. radioisotopes) [1,2]. However, mAbs additionally induce multiple cytotoxic effects. For instance, they can directly inhibit tumor growth by apoptosis induction, neutralizing growth stimulatory molecules like vascular endothelial growth factor (VEGF) or by blocking specific growth factor receptors (such as epithelial growth factor receptor; EGFR) (Fig. 1A). It has been shown that direct effects can play a prominent role in clinical successes of mAb therapy. Anti-EGFR mAbs are for example used to treat patients with head and neck cancer or colorectal cancer, but are only effective in patients that express wild type KRAS, whereas mutations in the EGFR signaling pathway seriously interfere with therapeutic success [3].

Tumor-targeting mAbs can furthermore induce indirect cytotoxicity by activating components of the immune system. Most clinically used mAbs are of the IgG subclass, which have the potential to bind C1q (Fig. 1B). This will activate the complement cascade through the classical pathway, thereby opsonizing targets by deposition of C3b, which can lead to tumor lysis through the lytic pathway (complement-dependent cytotoxicity; CDC). The role of CDC in patients is not yet completely clear. It has however been shown that polymorphisms in the C1QA gene correlated with clinical responses in patients with follicular lymphoma after rituximab treatment, supporting the importance of CDC [4]. Both direct effects of mAbs and CDC have recently been reviewed elsewhere [1,2,5].

The Fc domain of IgG mAbs interacts with IgG Fc receptors (Fcγ receptors) (Fig. 1C). As such, mAbs form a bridge between tumor cells and Fcγ receptor-expressing immune effector cells, which can lead to tumor cell death that is generally referred to as antibody dependent cellular cytotoxicity (ADCC). Four IgG subclasses have been defined in humans (IgG1, IgG2, IgG3, IgG4). Additionally, the human IgG receptor family includes several members (FcγRI,

Abbreviations: ADCC, antibody dependent cellular cytotoxicity; ADPh, antibody dependent phagocytosis; BsAb, bispecific antibody; CDC, complement dependent cytotoxicity; CEA, carcinoembryonic antigen; CR3, complement receptor 3; CTL, cytotoxic T-lymphocyte; DC, dendritic cell; E:T, effector to target ratio; EGFR, epithelial growth factor receptor; Ep-CAM, epithelial cell adhesion molecule; FcαR, IgA Fc receptor; FcγR, IgG Fc receptor; G-CSF, Granulocyte-colony stimulating factor; GM-CSF, granulocyte macrophage-colony stimulating factor; Her-2, human epidermal growth factor receptor 2; IFN-γ, Interferon-γ; Ig, immunoglobulin; LTB4, leukotriene B4; mAb, monoclonal antibody; M-CSF, macrophage-colony stimulating factor; NET, neutrophil extracellular trap; NK cell, natural killer cell; PRR, pattern recognition receptor; ROS, reactive oxygen species; SCID, Severe combined immunodeficiency; SIRPα, signal regulatory protein α; TAM, tumor associated macrophage; Th17, T helper 17 cell; TLR, toll like receptor; VEGF, vascular endothelial growth factor.

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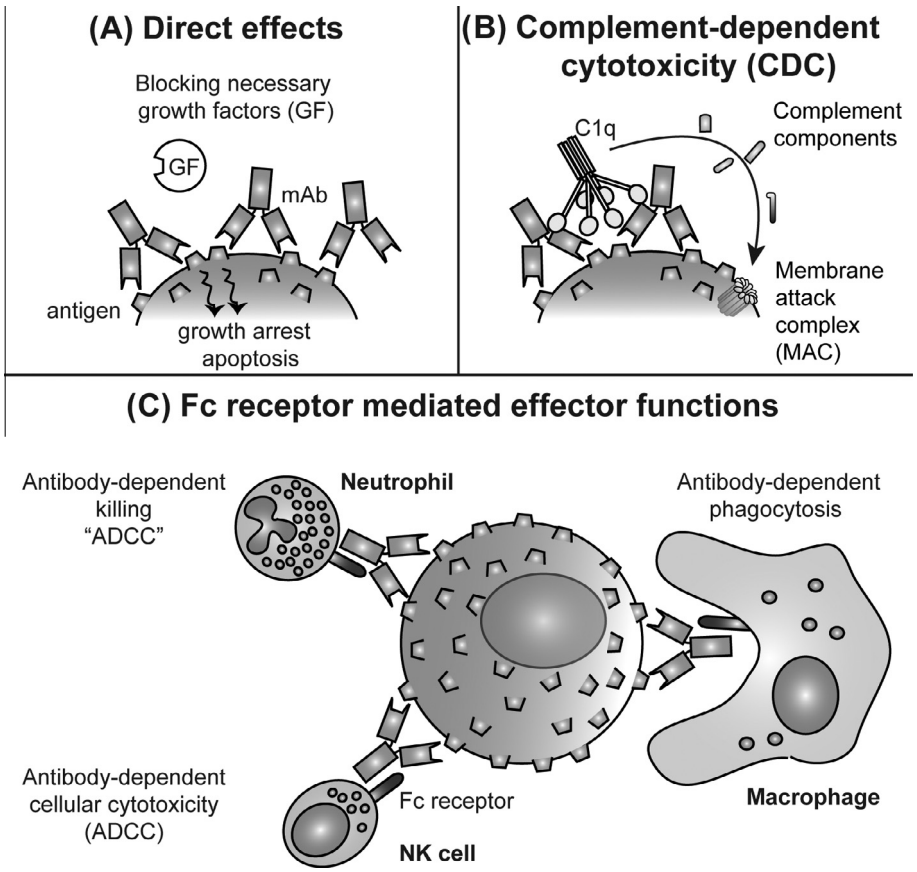

Fig. 1. Schematic and simplified model of mAb-induced effector mechanisms. (A) Direct effects induced by mAbs include blocking of growth factor receptors, or induction of apoptosis. (B) mAbs can initiate complement-dependent cytotoxicity (CDC) after binding of C1q to its Fc domain, which will initiate the classical complement pathway. (C) Opsonization of tumor cells with mAbs results in killing by immune effectors cells via different mechanisms. Of note: it is not clear yet via which mechanisms neutrophils kill tumor cells, but they likely differ from NK cell-induced classical antibody-dependent cellular cytotoxiciy (ADCC).

FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb), which can be activating or inhibitory and which differ in their affinities for the IgG subclasses (Table 1). Characteristics of human and mouse Fc receptors have recently been extensively reviewed elsewhere [6–8]. It has been demonstrated that Fcγ receptor-mediated mechanisms are involved in therapeutic efficacy *in vivo* for most mAbs. For instance, anti-gp75 mAb therapy did not prevent melanoma development in FcR γ chain deficient mice that lack the activating FcγRI, FcγRIII and FcγRIV [9]. Moreover, mAb therapeutic efficacy was absent in mice lacking FcγRI, or after blocking FcγRIV (or both), whereas murine FcγRIII was not involved [10–12]. By contract, anti-tumor mAbs were more effective in preventing tumor development in mice that were deficient for the inhibitory receptor FcγRII [13]. Fc receptor polymorphisms that affect affinity for IgG (FcγRIIa-131H/R and FcγRIIIa-158V/F) have been associated with clinical success of rituximab (anti-CD20), cetuximab (anti-EGFR) or trastuzumab (anti-HER-2; human epidermal growth factor receptor 2) therapy in lymphoma, colorectal or breast cancer, respectively [14–16], demonstrating that Fcγ receptor-mediated effector functions play an important role in cancer patients. It is not completely understood which Fcγ receptor-bearing cells provide cytotoxic activity *in vivo*. Traditionally, natural killer (NK) cells have been considered as main effector cells for ADCC [17]. NK cells are very effective killers of virus infected cells and tumor cells that lack MHC-I (Major Histocompatibility Complex-I) [18]. Furthermore, NK cells express FcγRIIIa, and the association between Fc receptor alleles (FcγRIIIa-**V**158 allotype versus FcγRIIIa-**F**158 allotype), and clinical success of mAb therapy has been attributed to NK cells [19]. However, other cell populations can act as potential effector cells for mAb-mediated tumor regression, including the myeloid effector cells monocytes/macrophages and neutrophils, which will be the focus of this manuscript.

Table 1
Interactions of Fcγ receptors with different IgG isotypes (reviewed in [6,7]).

Receptor	Function	Affinity	Interacting IgG (in sequence of affinity)
Human			
FcγRI	Activating	High	IgG1 = IgG3 > IgG4
FcγRIIa-H131	Activating	Low	IgG1 > IgG3 > IgG2 > IgG4
FcγRIIa-R131	Activating	Low	IgG1 > IgG3 > IgG4 > IgG2
FcγRIIb	Inhibitory	Low	IgG3 = IgG1 = IgG4 ≫ IgG2
FcγRIIIa-V158	Activating	Intermediate	IgG3 ≫ IgG1 ≫ IgG4 ≫ IgG2
FcγRIIIa-F158	Activating	Intermediate	IgG3 ≫ IgG1 ≫ IgG4 > IgG2
FcγRIIIb		Low	IgG3 > IgG1
Mouse			
FcγRI	Activating	High	IgG2a ≫ IgG2b, IgG3
FcγRII	Inhibitory	Low	IgG2a = IgG2b = IgG1
FcγRIII	Activating	Low	IgG2a = IgG2b = IgG1
FcγRIV	Activating	High	IgG2a = IgG2b

2. Macrophages as effector cells in mAb therapy of cancer

Macrophages are derived from circulating monocytes, and are potent regulators of the immune system in tissues during infections and wound healing [20,21]. Furthermore, it has been demonstrated that many tumors contain a considerable macrophage population, which are referred to as tumor-associated macro-

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