Complement function in mAb-mediated cancer immunotherapy

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Complement activation by mAbs can cause direct tumor cell lysis or enhance antibody-dependent cell-mediated cytotoxicity. However, tumor cells are protected from complement-mediated injury by membrane-bound complement regulatory proteins (mCRP) that are often expressed at elevated levels on tumor cells. Recent studies indicate that blocking or overwhelming the function of tumor cell mCRP might substantially improve the efficacy of monoclonal antibody (mAb) immunotherapy. In addition, the use of β-glucan as an adjuvant for mAb immunotherapy enables iC3b deposited on tumor cells by mAbs to activate complement receptor 3 (CR3) on effector cells, thus inducing CR3-dependent cellular cytotoxicity. These strategies provide novel cell-mediated mechanisms of tumor cytotoxicity that are additive to all other mAb effector mechanisms.

Immunotherapy using monoclonal antibodies (mAbs) holds great promise as an anti-cancer therapeutic strategy because of its ability to target cancer cells specifically and spare surrounding normal tissue. This is an important advantage over relatively non-specific chemo- and radiotherapeutic treatments. This Review will describe antibody-induced complement-mediated effector mechanisms, evasion of complement injury by tumor cells and how complement activation or regulation can be manipulated to enhance the clinical efficacy of therapeutic mAbs. Until now, there has been some success with the treatment of hematological malignancies with mAbs, although, in general, clinical results have fallen short of expectations. Only seven mAbs have been approved for use in the clinic and five of these are directed against hematological tumors. This Review summarizes data that explain why results might have been disappointing and how improvements might be achieved through modifications of therapy that better use the complement system.

mAb-induced complement-mediated effector mechanisms

Most mAbs that mediate antibody-dependent cellular cytotoxicity (ADCC) also activate the complement system (Box 1 and Figure I in Box 1) [1]. In particular, chimerized or humanized mouse mAbs containing the human IgG1 Fc-region trigger both ADCC and complement activation. Complement initiates three mechanisms that can be used against mAb-coated tumor cells (Figure 1). The first is direct complement killing of tumor cells by the

Figure 1. Effector mechanisms of monoclonal antibodies (mAbs). mAbs bound to target antigen can be recognized by Fc-receptors (FcRs) expressed on immune cells, such as granulocytes, natural killer (NK) cells, monocytes and macrophages, leading to antibody-dependent cellular cytotoxicity (ADCC). mAbs can also activate the complement system following binding of C1q to the mAb Fc region. Complement activation results in the deposition of C3b, which is subsequently converted to iC3b, and can lead to the formation of the cytolytic membrane attack complex (MAC or C5b-9), resulting in complement-dependent cytotoxicity (CDC). ADCC can be enhanced by complement receptor 3 (CR3) binding to iC3b, thus enhancing FcγR-mediated effector-cell binding. Ligation of iC3b by CR3 can, on CR3 priming with β-glucan (βG), induce CR3-dependent cellular cytotoxicity (CR3-DCC).
Box 1. Activation and regulation of the complement system

The classical pathway of the complement system is activated following binding of monoclonal antibodies (mAbs) to tumor cells (Figure I). This pathway is initiated on binding of the C1 complex to mAbs (in close proximity) on the tumor-cell membrane. The lectin pathway and alternative pathways are generally activated by pathogens and not by cell-bound mAbs and are therefore not further discussed. Complement activation on a cell surface results in the formation of the membrane bound C3- and C5-convertases, which are enzyme complexes that cleave and activate C3 and C5, respectively. The cleavage of C3 results in the generation of C3b, a small number of which become covalently attached to the cell surface. Cell-surface bound C3b is involved in amplifying the complement cascade, however, because complement activation is tightly regulated on host tissue, including host-derived tumor cells, C3b is rapidly degraded into the fragments iC3b and C3dg. These cell-bound fragments can function to promote complement receptor-enhanced antibody-dependent cellular cytotoxicity (ADCC) through binding to CR3 on leukocytes [2]. C5 cleavage by the C5-convertase results in fragmentation into C5a and C5b. C5a is the most important inflammatory mediator of the complement system and it functions to recruit and activate immune effector cells at the site of complement activation. C5b binds to the cell membrane and initiates formation of the membrane attack complex (MAC or C5b-9). This complex can cause direct complement-dependent cytotoxicity (CDC) through the formation of membrane-penetrating pores.

To prevent uncontrolled activation and consumption of complement components, complement activation is tightly regulated by complement regulatory proteins (CRPs). CRPs are present as soluble proteins in the fluid phase and as membrane-bound complement regulatory proteins (mCRPs) on most cell types. The mCRPs comprise CR1, CD46, CD55 and CD59 (Figure I). CR1 and CD46 are cofactors for factor I-mediated degradation of C3b and C4b (to iC3b and iC4b, respectively), preventing formation of new convertases, whereas CD55 accelerates the decay of C3- and C5-convertases, thereby preventing activation of downstream complement proteins [1]. Rodents express an additional mCRP, termed Crry, a structural and functional analogue of CR1 but with a wider cell type distribution [35]. Thus, by inhibiting complement activation, CR1, CD46 and CD55 (and Crry in rodents) limit the generation of the opsonic fragments C3b and iC3b and of the chemotactic factors C3a and C5a. Finally, CD59 binds to complement proteins C8 and C9 during MAC assembly and prevents complement (MAC)-dependent cell lysis (CDC).

**CR3-DCC as an anti-tumor effector mechanism**

The C3 receptors on human leukocytes, CR1 and CR3, do not trigger the killing of tumor cells coated with their respective ligands, C3b and iC3b. However, considerable evidence has now been reported that CR3 (CD11b–CD18), expressed by phagocytes and natural killer (NK) cells, can be manipulated in such a way that it will trigger cytotoxicity of iC3b-coated tumor cells. CR3-DCC is normally reserved for yeast and fungi that bear β-glucan as an exposed component of their cell wall. Induction of cytotoxicity by iC3b-coated yeast requires the dual ligation of CR3 to both iC3b and cell wall β-glucan. Yeast cell wall β-glucan binds to a C-terminal lectin domain of CD11b, priming CR3 for efficient cytotoxic degranulation responses after it also binds iC3b by a N-terminal I-domain binding site of CD11b [2]. In contrast to microorganisms, tumor cells, as well as other host cells, lack β-glucan as a surface component and therefore cannot trigger CR3-DCC, even when heavily coated with iC3b. Soluble β-glucan binds to CR3 and primes the receptor in a way that enables it to trigger cytotoxic degranulation of iC3b-coated tumors that lack endogenous β-glucan [3,4]. Mice injected intravenously with soluble yeast β-glucan exhibit tumor regression and long-term survival [5,6]. This activity of β-glucan requires that tumor cells be coated with iC3b through the action of either naturally occurring anti-tumor Abs or intravenously administered anti-tumor mAbs that activate complement. This adjuvant activity of β-glucan did not occur with a mouse IgG1 mAb that did not activate complement but did occur with an IgM complement-activating mAb [7]. Also, tumor regression by combined mAb and yeast β-glucan therapy did not occur in mice deficient in either C3 or CR3, highlighting the requirement for both iC3b deposited on tumor cells (by complement-activating mAbs) and its receptor CR3 on the phagocytes [5,6].

**Anti-tumor mAbs in clinical use**

Seven anti-cancer mAbs are now approved for clinical use and another ten are currently being tested in Phase III clinical trials [8,9] (Table 1). Each of these mAbs has been examined to determine their mechanism of action in mediating therapeutic responses. Many mAbs have been modified with the objective of improving ADCC mediated...
by Fcγ-receptors (FcγR) expressed on leukocytes. The importance of ADCC as a cytotoxic mechanism of antitumor mAbs has been demonstrated in animal studies. Ravetch et al. showed that the tumoricidal effect of a humanized anti-HER2/neu mAbs (epithelial growth factor receptor 2, Trastuzumab) was significantly reduced in FcγR knockout nude mice as compared to wild-type nude mice [10]. Similarly, the tumor regression activity of a chimeric anti-CD20 mAb (Rituximab) was significantly reduced in FcγR deficient mice as compared to wild-type mice [10,11]. Further support for an important role for ADCC was provided by a study of Cartron et al., who found that in patients with a polymorphism in FcγRIIIa leading to increased binding of IgG1, therapy with an anti-CD20 mAb produced a 90% response rate (patients with complete remission or partial response) at 12 months, compared to a 51% response rate in individuals not expressing this polymorphism of FcγRIIIa [12]. Others have shown that this FcγRIIIa polymorphism and also a polymorphism in FcγRIIA are associated with the response rate to therapeutic mAbs [13]. In contrast to ADCC, there is a paucity of information regarding complement-activation by these clinically used mAbs.

### Complement recruitment by clinically approved mAbs

<table>
<thead>
<tr>
<th>Isotype/origin</th>
<th>Target</th>
<th>Mab names</th>
<th>Conjugated</th>
<th>Cancer type</th>
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<tbody>
<tr>
<td>hlgG1</td>
<td>HER2/neu</td>
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<td>No</td>
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<td>hlgG1</td>
<td>VEGF</td>
<td>Bevacizumab</td>
<td>No</td>
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<td>hlgG1</td>
<td>CD33</td>
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<td>clgG1</td>
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*Abbreviations: CEA, carcino-embryonic antigen; clg, chimerized lg; EGFR, epithelial growth factor receptor; Ep–CAM, epithelial cell adhesion molecule; HER2/neu, EGFR2; hlg, humanized lg; mAbs, monoclonal antibodies; mlg, mouse lg; MUC1, human mucin 1 (episialin) VEGF, vascular endothelial growth factor.

*In general, the following isotypes efficiently fix human complement: mlgG2a, mlgG2b, mlgG3, mlgM, hlgG1, hlgG4, hlgM.*

Improving the efficiency of CDC or CR3-DCC in vivo, and these effects would be additive to all the existing effector mechanisms of these mAbs. Other than isotype, one reason why a mAb might not efficiently activate complement is that the tumor cell antigen density might be too low to enable the formation of IgG dimers, which are required for the attachment of C1q and activation of the classical pathway. In this context, a recent publication showed that low HER2/neu antigen density could be circumvented by the use of a cocktail of mAbs that were specific for multiple epitopes on the HER2/neu antigen [19]. This strategy elicited a more efficient CDC in vitro and an increase in tumor reduction in vivo. For other mAbs, such as humanized anti-vascular endothelial growth factor (VEGF; Bevacizumab), the role of complement activation has not yet been properly investigated, although these mAbs are of a complement activating isotype and activate complement in vitro.

### Complement regulation on tumor cells

Complement activation seems not to be an important effector mechanism of mAbs, which can be explained by the expression of mCRPs. Both normal and tumor cells are highly resistant to homologous complement attack owing to the expression of mCRPs (Box 1 and Figure 1 in Box 1). An important role for tumor mCRPs in immune evasion is indicated by the finding that tumor cells often overexpress one or more of the mCRPs [20,21]. The ability of mCRPs to protect tumor cells from complement-mediated effector mechanisms has been studied extensively on numerous types of cancer cell lines in vitro. These studies have demonstrated the potent inhibitory effect of mCRP on mAb-induced C3b deposition, C5a generation and MAC-mediated lysis [22–25]. Tumor cells might also protect themselves by binding soluble complement inhibitory factors from serum, such as complement factor H (fH), a protective mechanism also used by some microorganisms [26,27]. Sialic acid-rich proteins that bind fH are upregulated by many tumors and overexpression of sialic acid has...
been associated with clinical severity [27]. It is also
interesting that fH or a related protein is a marker for
bladder cancer, suggesting a link between complement
resistance and escape from immune surveillance [28].

Overexpression of a particular mCRP has been reported
for each tumor type against which a therapeutically
approved mAb is directed [20,29,30]. Furthermore, CDC
mediated by four of the seven approved mAbs is inhibited
in vitro by mCRPs expressed on tumor cells. In the case of
anti-HER2/neu-mediated cytotoxicity (Trastuzumab),
there was an increase from 10% to 80% in CDC following
inhibition of mCRP function on tumor cells [25]. Similarly,
CD55 and CD59 limit complement-mediated injury and
their expression on tumor cells determines the response
rate in vitro for mAbs against Ep-CAM and CD20 [24,31].
These data suggest that mCRPs indeed inhibit therapeutic
effect of mAbs.

Role of mCRPs expressed on tumor cells in experimental
animal models and in clinical immunotherapy

Although in vitro studies indicate a role for mCRPs in
determining the outcome of mAb immunotherapy, only a
few studies have investigated the role of mCRPs in
appropriate experimental animal cancer models. Because
mCRPs act in a species selective fashion [32,33], hetero-
logous animal models involving complement and mCRPs
of different species might not be clinically relevant. For
example, an anti-tumor mAb might be effective in a rodent
model of human cancer because the human mCRPs
expressed on the tumor cell are not effective against
rodent complement. Such protocols that mix human
tumors and rodent complement [e.g. human tumors in
nude or severe combined immunodeficient (SCID) mice]
might explain why the same antibody that was active
against tumors in mice is ineffective in a clinical
(homologous) setting. Thus, to investigate mAb efficacy
and the effect of mCRP expression, a syngeneic model is
more clinically relevant [32–34].

However, data on the effect of mCRPs on mAb therapy
in syngeneic models are scarce. Di Gaetano et al. recently
reported the development of a mouse model of human
B-cell lymphoma and demonstrated that complement
activation was required for the therapeutic activity of
Rituximab in this model [16]. It should be noted that
rodents express, in addition to the mCRP described above,
an additional C3 regulatory protein, Crry/p65 (Crry) [35].
Crry is the major C3 regulatory protein in rodents (Box 1).
Using metastatic murine EL4 cells transfected with
human CD20, it was shown that humanized anti-CD20
(Rituximab) and a murine anti-CD20 mAb were therapeu-
tic in wildtype syngeneic mice but not in C1q-deficient
syngeneic mice. In another report, a rat model was used
that incorporated human breast cancer cells expressing
rat Crry or CD59. Crry, but not CD59, expression
prevented host regression of tumors as compared to
mock-transfected cells [36,37]. However, in a rat model
of human neuroblastoma homologous for rat CD59,
expression of CD59 promotes tumorigenesis [38]. In
these models, complement was activated on the tumor
cells by naturally occurring rat anti-tumor antibodies, and
the data indicated that different complement-dependent
mechanisms were involved in controlling growth of the
different types of tumors. In another study, populations of
a rat hepatoma cell line expressing either low or high
levels of Crry were injected into syngeneic rats, and Crry
expression levels were found to correlate inversely with
tumor-free survival [39]. In this study, inhibition of Crry
with anti-Crry F(ab)2 substantially increased survival
rate, confirming an important role for Crry in promoting
tumor growth.

There are several clinical studies indicating that
mCRPs expressed on tumor cells provides protection
from immune attack. On human tumor cells it is believed
that CD55 and CD46 perform the same type of complement
inhibitory function that Crry does on rodent cells. CD55
has been identified as a tumor-associated antigen and high
expression levels of CD55 on colorectal cancer tissue is
correlated with a significant decrease in survival [40]. The
functional significance of mCRP on tumor cells in humans
is also indicated by the correlation of low CD46 expression
with high levels of C3 deposition on renal and cervical
cancer tissue [41,42]. Furthermore, peripheral blood
leukocytes isolated from patients with chronic lymphocytic
leukemia (CLL) who had a poor response to anti-CD20
(Rituximab) treatment, were more sensitive to comple-
ment lysis on in vitro neutralization of CD55 and CD59
than were leukocytes isolated from patients who did
respond to Rituximab therapy [43]. In addition, signifi-
cantly higher levels of CD59 have been found on CLL cells
that were not cleared from the circulation following
Rituximab therapy [44]. These data suggest that mCRPs
have an important role in inhibiting an optimal clinical
effect of Rituximab treatment. However, this is contro-
versial. For example, it has been reported that tumor cell
expression levels of CD55 and CD59 do not correlate with
percentages of lysis [41] and another study reported that
mCRP expression levels do not predict the clinical outcome
of Rituximab treatment [43]. Nevertheless, the consensus
among different reports favors an important role for
complement, and therefore probably mCRPs, in the
mechanism of action of Rituximab. The precise details
and relative contributions of complement relative to ADCC
remain unresolved.

In summary, data from experimental models of cancer
and clinical studies suggest that modulating complement
susceptibility of a tumor cell has the potential to increase
therapeutic efficacy of a mAb by triggering complement-
dependent effector mechanisms, whether or not the
primary mechanism of action is complement-dependent.

Enhancing mAb immunotherapy by improving
complement-mediated effector mechanisms

mAb-mediated immunotherapy might be enhanced by
improving complement-mediated effector mechanisms
through modulating mCRPs or by application of the
adjuvant β-glucan.

Overcoming tumor cell mCRPs

Overwhelming mCRP function (Figure 2) could be
achieved by increasing the complement activating
capacity of mAbs by changing the isotype or by humaniza-
tion. These approaches increase complement activation
Other ways to increase complement activation include amplification of the amount of mAb deposited on tumor cells by use of a secondary mAb directed against either the anti-tumor mAb or against the iC3b deposited on tumor cells by the primary mAb. Injection of an anti-iC3b mAb following Rituximab (humanized anti-CD20) treatment in a cynomologous monkey model of lymphoma indeed resulted in enhanced iC3b deposition on the tumor cells. Another potential strategy to enhance complement activation and overwhelm mCRPs is to conjugate an anti-tumor mAb to a complement-activating protein, such as cobra venom factor (CVF) or C3b. The effectiveness of this approach has been shown in vitro using either colorectal cancer cells coated with anti-Ep/CAM–CVF conjugates, or neuroblastoma cells coated with anti-GD2–CVF conjugates. To reduce the expected immunogenic reactions against CVF, the active part of CVF can be genetically inserted in the region coding for the Fc-tail of the appropriate immunotherapeutic mAb.

Downregulating the expression of mCRPs has the capacity to enhance mAb-mediated complement activation and some success using various cytokines has been reported in vitro and in vivo. Upregulating the expression levels of tumor antigen might also result in increased complement activation. For example, it has been reported that the MUC1 (human mucin 1; episialin) antigen, the target for Pentumomab, can be upregulated in vitro by dexamethasone on myeloma cells and by interferon-γ (IFN-γ) on a broad range of cancer cell lines. Another way to circumvent the effect of mCRP on mAb-induced complement activation is by using mAbs that block the function of mCRPs to enhance the complement susceptibility of tumor cells. However, such an approach cannot be used readily in vivo because of the widespread expression of mCRPs on normal tissue. In vitro experiments have shown that a bispecific mAb that recognize both a tumor antigen and a mCRP can selectively target tumor cells and enhance their susceptibility to complement deposition and lysis. Also, in vivo, these bispecific mAbs prevent tumor outgrowth in a syngeneic rat model. Ideally, these bispecific mAbs need to have a higher affinity for the tumor cells than for normal cells expressing the targeted mCRP.

Use of β-glucan to prime CR3-DCC
Soluble yeast β-glucan induces CR3-DCC of tumor cells in vitro and in vivo. CR3-DCC is additive to all other effector mechanisms of the mAb. Initial reports showed this adjuvant activity with intravenously administered soluble yeast β-glucan, however, it now appears probable that certain large molecular size β-glucans can have this same complement-dependent adjuvant function when given orally. This is an advantage when being clinically administered. Cheung et al. showed that large molecules of barley β-glucan given orally to mice functioned as adjuvants that greatly promoted the tumor regression activity of mAbs that activated complement. Moreover, studies with mouse tumor models showed that oral β-glucan therapy could greatly augment tumor regression mediated by anti-CD20, anti-HER2/neu and anti-EGFR1. The combined use of oral or
intravenous β-glucans with mAb therapy recruits granulocytes as tumor killer cells [6,7]. The current data suggest that orally administered β-glucan functions through anti-tumor mAbs and the complement system to recruit CR3+ effector cells that produce tumor regression and tumor-free survival [7,63]. As with intravenously administered soluble yeast β-glucan, the therapeutic benefit of oral β-glucan was lost in C3- or CR3-deficient mice, confirming a similar requirement for iC3b on tumors and CR3 on granulocytes [63]. Clinical trials of the oral barley β-glucan given in combination with an anti-GD2 ganglioside mAb to patients with neuroblastoma are currently in progress at Memorial Sloan-Kettering Cancer Center (New York, USA). This trial has yielded encouraging preliminary results (G.D. Ross, pers. commun.).

Concluding remarks

There is now substantial evidence that the complement system can be manipulated in such a way that it can substantially contribute to the efficient elimination of mAb opsonized tumor cells. Such manipulation could be achieved either through the blockade or overwhelming of mCRP function to enhance CDC, or through the use of β-glucan to enable CR3 positive effector cells to eliminate iC3b-opsonized tumors. The experimental and clinical observations showing that modulating the function of mCRP increased the therapeutic effectiveness of immunotherapeutic mAbs not only improves the prospects of immunotherapeutic treatment but also increases the number of mAbs that can be useful in the clinic. Moreover, mAbs that have virtually no tumor regression activity when used alone are able to mediate complete regression when given in combination with β-glucan. Awareness of the mechanisms responsible for effective mAb-mediated cancer immunotherapy might finally enable mAb immunotherapy to fulfill its expectations and in many cases replace non-specific chemotherapy.

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