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Elimination mechanisms of therapeutic monoclonal antibodies

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Targeted therapies using monoclonal antibodies have achieved important therapeutic applications in the treatment of various human diseases. Understanding the factors that impact the pharmacokinetics of monoclonal antibodies is of high importance for effective therapy. Many factors related to the target antigen, antibody and patients can affect antibody elimination. Evaluation of these factors will facilitate the understanding of the processes involved in antibody elimination.

Targeted therapies using monoclonal antibodies (mAbs) have gained increased therapeutic application in recent years. Seventeen[1] mAbs are currently approved in the USA in various therapeutic areas, such as oncology, inflammation, infectious disease and cardiovascular disease. All approved mAbs are of the IgG class. Thirteen are intact mAbs, three are conjugated and one is a mAb fragment (Fab). In the next five years the number of approved mAbs might potentially double [1]. The clinical pharmacology of therapeutic mAbs has been reviewed in a recent article [2]. A feature of mAb therapeutics is the high specificity conferred by the antibody interaction (variable region paratope) with a specific region on the targeted antigen (epitope). Hence, it is not surprising that among the factors regulating mAb pharmacokinetics, antigen properties, such as antigen distribution (soluble versus membrane associated) and antigen concentration, can influence mAb pharmacokinetics. Other factors, such as mAb structure and engineering, host factors, concurrent medications and immunogenicity, can alter the pharmacokinetic profile [2–4]. Understanding the factors that affect the pharmacokinetics of mAb is of high importance for effective therapeutic application.

Antibody structure and function

Antibodies serve two important functions: they bind and modulate antigens and they bind complement and immune effector cells, such as natural killer cells and monocytes. Each IgG molecule contains two identical heavy chains and two identical light chains (Figure 1). Antibody structure has evolved to accommodate the diverse antigen binding specificities through the 'variable region'. The antigen binding site is formed by the intertwining of the light chain variable domain (V_L) and the heavy chain variable domain (V_H). Each V domain contains three short stretches of peptide known as the complementarity determining regions (CDRs); the CDRs are the prominent determinants of antigen binding affinity and specificity. The light chain contains one constant domain: C_L. The heavy chain contains three constant domains: C_H1, C_H2, and C_H3. The C_H2 and C_H3 domains allow interactions of the IgG molecule with various components of the immune system by either binding C1q, which activates the complement cascade and elicits complement-dependent cytotoxicity, or by binding to Fcγ receptors on immune effector cells, which elicits antibody-dependent cellular cytotoxicity. These same variable and constant domains of the molecule also affect IgG catabolism and elimination [2,4,5].

Major determinants of monoclonal antibody elimination

Constant region: interaction with Fc receptors

Salvage pathway

IgG is the most abundant serum immunoglobulin (average concentrations ~11–14 mg/ml [6]) and serum IgG homeostasis is of

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[1]The total number of approved therapeutic monoclonal antibodies in the USA reached eighteen in 2005; however, one antibody was withdrawn from the market in the same year.

1359-6446/06/$ – see front matter PII: S1359-6446(05)03638-X

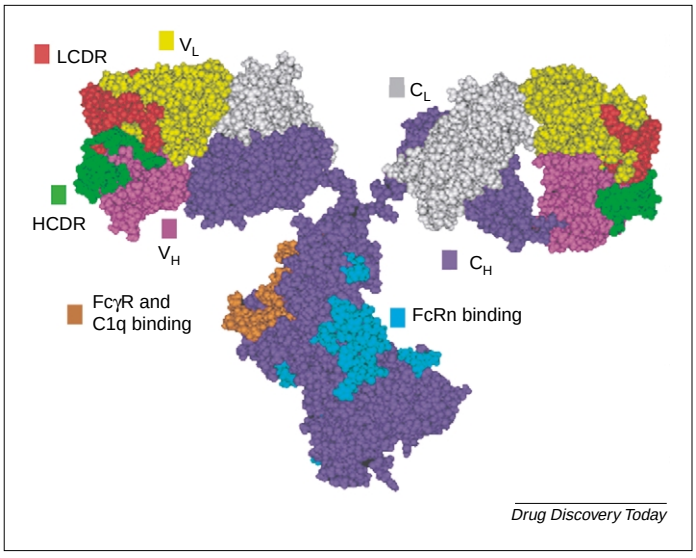

FIGURE 1

Representation of the space-filling model of an IgG molecule. Abbreviations: LCDR and HCDR, complementarity determining regions on V_L and V_H domain.

particular importance in mediating humoral immunity. The protective role of neonatal Fc receptor (FcRn), a major histocompatibility complex class-1-related receptor, in regulation of IgG homeostasis was postulated by Brambell [7]. Recent studies have further clarified the details of Brambell hypothesis and indicated that FcRn functions as a salvage receptor which regulates IgG catabolism [8–10]. Mice genetically lacking expression of FcRn demonstrated IgG hypercatabolism and faster IgG elimination [11].

Engineered human IgG antibodies with altered affinity to human FcRns [12–15] have altered elimination rates. Binding of IgG to FcRn is pH dependent: IgG binds to the receptor under mildly acidic conditions and is released under slightly basic conditions [14]. Mutation of IgG Fc residues (amino acid positions 428 and 250, alone or in combination) that increased the binding affinity of the antibody for FcRn (4- to 27-fold better binding affinity to rhesus FcRn than the wild-type antibody at pH = 6.0) without impacting the pH-dependent binding properties resulted in a twofold increase in serum half-lives of the mutant IgG2 antibodies [13]. The rapid clearance of murine IgGs from human circulation [16,17] has been attributed to the selectivity of human FcRn binding to human IgG. Administration of a murine anti-FcRn antibody against rat β_2-microglobulin transiently increased the clearance of a murine IgG antibody [18], which also supports the significance of FcRn in regulating antibody catabolism. In addition, antibody fragments, such as Fab (monovalent antibody fragment), $F(ab')_2$ (divalent antibody fragment) and scFv (single chain variable fragment) that lack the Fc domain and do not bind to FcRn, have substantially shorter half-lives (0.5–30 h) than the intact IgG. The low molecular weight antibody fragments are also subject to renal clearance [2].

Further evidence for the regulatory role of FcRn on IgG clearance is provided by studies involving patients with autoimmune disorders, who have received intravascular immunoglobulin treatment [19]. High levels of IgG saturate FcRn and block the salvage pathway. Earlier investigations demonstrated that the clearance rate of IgG was greatly dependent on its serum concentration, whereas the concentration impact on clearance did not apply to other immunoglobulin subclasses, such as IgM and IgA [20]. Longer IgG half-lives were reported at lower IgG concentrations, consistent with Brambell hypothesis for the protective role of FcRn on IgG homeostasis [7,20]. The impact of serum IgG concentrations on IgG clearance was recently demonstrated in experimental models. Administration of a large dose of purified human IgG (~2 g/kg) in mice resulted in a rapid decrease (>60%) in baseline mouse IgG1 and IgG3 serum concentrations [21]. Recently, similar results were reported for the effect of large dose of human IgG (2 g/kg) on the clearance of an anti-platelet antibody in rats [22].

Normal variation in endogenous IgG levels might not affect the elimination rate of therapeutic antibodies; likewise, the usual therapeutic doses of mAbs [2] are not expected to increase total IgG levels to the point that IgG clearance is affected. Recently, we had the opportunity to examine the impact of baseline serum IgG concentrations on clearance of a fully human IgG2 antibody against human interleukin (IL)-8 generated using Xenomouse® technology [23,24]. Following administration of multiple doses of the antibody (200 to 400 mg/patient, administered monthly or every three weeks, for three or four doses) in patients with inflammatory diseases, such as psoriasis, rheumatoid arthritis (RA) and chronic obstructive pulmonary disease (COPD), steady-state serum antibody concentrations (200–50 μg/ml) were achieved [25]. Baseline serum IgG concentrations ranged between 10 mg/ml and 50 mg/ml in patients with psoriasis and RA (Figure 2). However, no correlation between serum IgG and the steady-state antibody clearance was observed. Population pharmacokinetic analysis further verified the lack of correlation between serum IgG and steady-state antibody clearance.

Impact of effector function on pharmacokinetics and pharmacodynamics

In addition to FcRn, three classes of Fc receptors (FcγRs) for IgG interactions have been identified in humans. These receptors are expressed by various phagocytic cells, such as monocytes, macrophages, neutrophils and eosinophils, and other cells of the immune system, such as B and T cells, as well as platelets [26]. However, expression profiles and variability in distribution of the three FcγRs on various cell types are heterogeneous and complex and further compounded by genetic polymorphism (characterized by multiple sub-isoforms) observed among different individuals [27,28]. Human FcγRs bind IgG with various degrees of affinity, ranging from low ($>10^{-7}$ M) for FcγRII (CD32), medium ($=10^{-7}$ M) for FcγRIII (CD16), to high (10^{-8}–10^{-9} M) for FcγRI (CD64) [28,29].

Different IgG isotypes, such as IgG1, 2, 3, and 4, demonstrate unique recognition and activation profiles when interacting with various FcγRs [2,28–30]. Because of different interaction profiles with FcγRs, IgG1 subclass has proved to be most effective in complement dependent (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). This, indeed, is inline with the function of this highest-circulating serum IgG subclass (IgG1; 60–70% of total serum IgG [6,29]) for binding exogenous pathogens and for effective destruction and clearance of antigens via activation of various effector mechanisms [28,29]. With respect to effector functions, IgG3 has been shown to be as effective as IgG1 in complement activation and cell-mediated toxicity, whereas IgG2 and IgG4 isotypes are relatively inactive in eliciting effector functions [28–30]. In addition to their contributions to mAb pharmacological activities (pharmacodynamics), the FcγRs could also regulate elimination and pharmacokinetics (PK) of mAbs.