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Review

Are endosomal trafficking parameters better targets for improving mAb pharmacokinetics than FcRn binding affinity?

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ABSTRACT

F.W.R. Brambell deduced the existence of a protective receptor for IgG, the neonatal Fc receptor (FcRn), long before its discovery in the early to mid-1990s. With the coincident, explosive development of IgG-based drugs, FcRn became a popular target for tuning the pharmacokinetics of monoclonal antibodies (mAbs). One aspect of Brambell's initial observation, however, that is seldom discussed since the discovery of the receptor, is the compliance in the mechanism that Brambell observed (saturating at 10s–100s of μM concentration), vs. the comparative stiffness of the receptor kinetics (saturating in the nM range for most species). Although some studies reported that increasing the already very high Fc–FcRn affinity at pH 6.0 further improved mAb half-life, in fact the results were mixed, with later studies increasingly implicating non-FcRn-dependent mechanisms as determinants of mAb pharmacokinetics. Mathematical modelling of the FcRn system has also indicated that the processes determining the pharmacokinetics of mAbs have more nuances than had at first been hypothesised. We propose, in keeping with the latest modelling and experimental evidence reviewed here, that the dynamics of endosomal sorting and trafficking have important roles in the compliant salvage mechanism that Brambell first observed nearly 50 years ago, and therefore also in the pharmacokinetics of mAbs. These ideas lead to many open questions regarding the endosomal trafficking of both FcRn and mAbs and also to what properties of a mAb can be altered to achieve an improvement in pharmacokinetics.

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1. Introduction

Unlike most other soluble proteins internalised by fluid-phase endocytosis, IgG is rescued from degradation in the lysosome by the neonatal Fc receptor, FcRn (Rodewald and Kraehenbuhl, 1984; Ober et al., 2004a). The FcRn binds IgG and recycles it to the plasma membrane and then back into the circulation. In endothelial cells, IgG is thought to follow a non-specific mechanism of uptake and transport to the recycling endosome (Maxfield and McGraw, 2004). IgG binds to FcRn after endosome acidification (pH 6.0–6.5) and the FcRn_IgG complex is sorted away from other fluid-phase solutes (Ober et al., 2004b). Although it remains unclear where FcRn initially binds IgG in the endocytotic pathway and how it traffics IgG back to the circulation (Ober et al., 2004a, b), it has been clearly demonstrated that one molecule of IgG binds to a single FcRn (with 1:1 stoichiometry) (Popov et al., 1996) under non-equilibrium conditions or two FcRn (with 1:2 stoichiometry) at equilibrium (Sanchez et al., 1999). It has also been demonstrated that a complex of IgG bound to a single FcRn molecule is not fully protected from degradation, and trafficking of 1:1 complexes to the lysosome has also been observed. Formation of a one to two (IgG:FcRn) complex can have a large influence on both the total binding affinity – with increases of up to four orders of magnitude (Gurbaxani, 2007) reported – and the effectiveness of IgG trafficking (Tesar et al., 2006).

To determine whether equilibrium or non-equilibrium binding is more important to IgG salvage, we need to understand more fully the dynamics and duration of transit of IgG through the cell. Ober et al. (Ober et al., 2004b) and Hopkins and Trowbridge (Hopkins and Trowbridge, 1983) demonstrated that the half-life of endosomal transit of IgG is around 7.5 minutes in human carcinoma cells, however the time duration of individual steps which are involved in

Abbreviations: IgG, immunoglobulin G; FcRn, neonatal Fc receptor; Fc, fragment crystallisable (antibody constant region); Fab, fragment with antigen binding (antibody variable region); $F(ab')_2$, covalently bound Fab portions of an antibody; PBPK, physiologically based pharmacokinetics; SPR, surface plasmon resonance; mAb, monoclonal antibody; nM, nanomolar; μM, micromolar; k_{on}, binding rate; k_{off}, dissociation rate; k_{int}, internalisation rate; k_{rec}, recycling rate; K_D, equilibrium binding affinity; pH, negative $\log_{10}$concentration of solvated hydrogen ions/acidity; MW, molecular weight; Da, Daltons; kDa, kilo Daltons; μm, micrometer; nm, nanometer.

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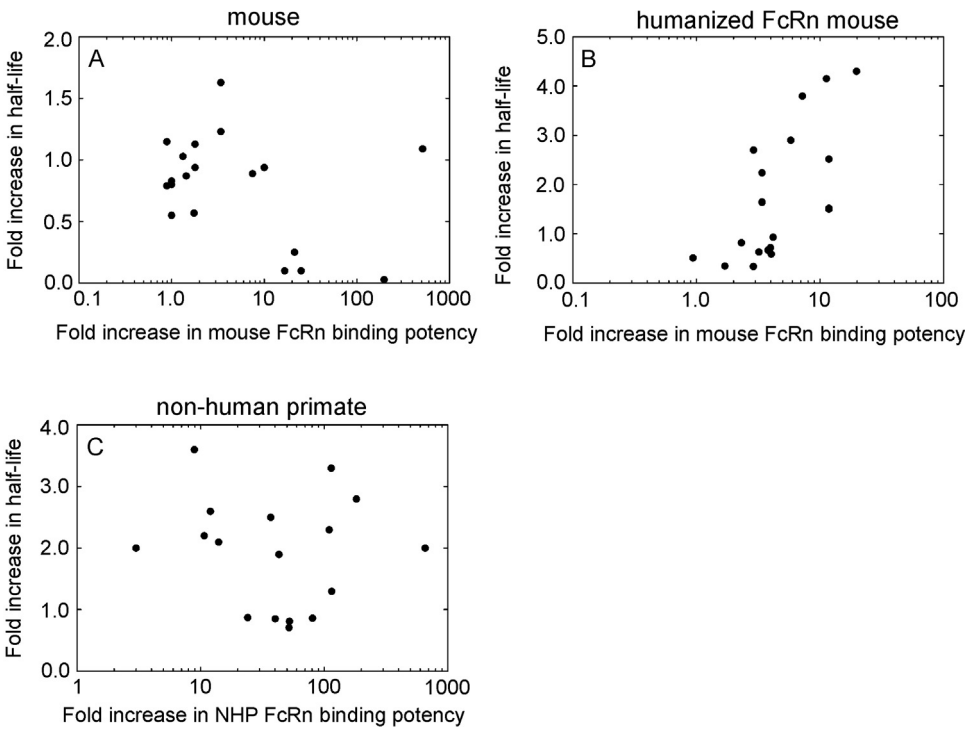

Fig. 1. The effect of fold increase in FcRn binding potency on fold increase in elimination half-life. The figure illustrated the effect of fold increase in FcRn binding potency on fold increase in elimination half-life in wild-type mouse (A), transgenic humanised FcRn mouse (B) and non-human primates (C).

the recycling process within these 7.5 minutes remains unclear. It is also unclear what determines the endosomal transit pathway of FcRn while carrying its cargo to its final destination. Data from light and electron microscopy tomography studies support the notion that the complex can take multiple paths to their target destinations and the trafficking is precisely regulated by signals from the receptors themselves and the cytosolic trafficking machinery (Tesar and Bjorkman, 2010).

Many studies have suggested that improvement in the pharmacokinetics of monoclonal antibodies (mAbs) may be gained through modification of the interaction of the Fc region of IgG with FcRn (Vaughn et al., 1997). Specifically, it has been proposed that increased affinity of the interaction at pH 6.0 may alter the intracellular trafficking resulting in reduced clearance and a prolongation in elimination half-life (Ober et al., 2004a, b; Ward et al., 2003). Work carried out in mouse/rat (Ghetie et al., 1997; Medesan et al., 1998; Datta-Mannan et al., 2007b) and non-human primates (Datta-Mannan et al., 2007b; Hinton et al., 2004; Hinton et al., 2006; Dall'Acqua et al., 2006; Yeung et al., 2009) also suggested that increased binding to FcRn may represent a strategy to increase half-life in humans. Specific Fc variants (T250Q/M428L, M428L, M252Y/S254T/T256E, M428L/N434S, N434A, and N434H) have demonstrated that improving IgG affinity for FcRn at pH 6.0 with a little or no change of binding at pH 7.4 can result in approximately 2–4-fold longer elimination half-life in non-human primates (Datta-Mannan et al., 2007b; Hinton et al., 2004; Hinton et al., 2006; Dall'Acqua et al., 2006; Yeung et al., 2009). Because these improvements in pharmacokinetics can be translated to enhanced, broadened therapeutic utility of a particular mAb (Zalevsky et al., 2010), it was thought that better understanding of Fc–FcRn binding can serve as a universal protein engineering strategy (Datta-Mannan et al., 2007b) to improve pharmacokinetics. While individual examples of engineered mAbs with higher affinity for FcRn at pH 6.0 and with longer half-life have been presented in the literature, a clear correlation between the two parameters has not been established and there are conflicting findings published (Gurbaxani et al., 2006; Datta-Mannan et al., 2007b; Datta-Mannan et al., 2012b; Datta-Mannan et al., 2007a; Igawa et al., 2010).

The published data relating to changes in FcRn binding in mouse, in mice with human FcRn receptors, in non-human primates and in man and subsequent changes in pharmacokinetic parameters are summarised in Table 1 and in Fig. 1. Taken as a whole these data do not support a simple relationship between FcRn binding and changes in pharmacokinetic parameters in either mouse or non-human primates. In humanised FcRn mice there does appear to be a weak trend shown between increased binding to FcRn and an increase in half-life or decrease in clearance, but in the only published study in humans an antibody modified to have a 3-fold increased affinity to human FcRn did not show improved pharmacokinetics compared to the wild-type antibody (Zheng et al., 2011). Furthermore, while a retrospective study of several marketed mAbs and Fc fusion proteins published by Suzuki et al. (Suzuki et al., 2010) showed a weak correlation between elimination half-life in human and fold-change in FcRn affinity, the correlation disappears when the Fc fusion proteins are removed, suggesting a lack of correlation between FcRn binding and pharmacokinetics, at least for full mAbs in humans. One possible explanation for the apparently different relationship between FcRn binding and pharmacokinetics between humanised FcRn mice and humans is that in the humanised animals there are low levels of murine IgG. The murine IgG present has low affinity for the human receptor so that there is little competition for binding to FcRn. In contrast in humans high levels of endogenous IgG can compete with the mAb for binding to the FcRn receptor.

Given the discrepancy between the nM binding affinity of Fc for FcRn and the circulating concentration of IgG at which the Brambell mechanism begins to saturate, it could be argued that seeking to improve mAb half-life by further increasing the already very tight Fc–FcRn affinity was not a good strategy to begin with. For the mAbs

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