Advanced Drug Delivery Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

The neonatal Fc receptor, FcRn, as a target for drug delivery and therapy ☆

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ARTICLE INFO

Available online xxxx

Keywords:
Albumin
Immunoglobulin G
FcRn
Nanoparticle
Protein engineering

ABSTRACT

Immunoglobulin G (IgG)-based drugs are arguably the most successful class of protein therapeutics due in part to their remarkably long blood circulation. This arises from IgG interaction with the neonatal Fc receptor, FcRn. FcRn is the central regulator of IgG and albumin homeostasis throughout life and is increasingly being recognized as an important player in autoimmune disease, mucosal immunity, and tumor immune surveillance. Various engineering approaches that hijack or disrupt the FcRn-mediated transport pathway have been devised to develop long-lasting and non-invasive protein therapeutics, protein subunit vaccines, and therapeutics for treatment of autoimmune and infectious disease. In this review, we highlight the diverse biological functions of FcRn, emerging therapeutic opportunities, as well as the associated challenges of targeting FcRn for drug delivery and disease therapy.

Contents

1.1. Introduction

It has now been 50 years since the remarkable foresight by F.W.R. Brambell, who put forth the hypothesis that there exists a specific receptor responsible for the salvage of IgG from catabolism [1], eventually identified as the neonatal Fc receptor (FcRn). Originally discovered in the rat as the receptor responsible for the transmission of maternal

☆ This review is part of the Advanced Drug Delivery Reviews theme issue on "Editor's Choice 2015".

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http://dx.doi.org/10.1016/j.addr.2015.02.005
0169-409X/

antibodies from mother to pup [2–5], FcRn is now known to be involved in a multitude of critical biological functions throughout human life [6]. The most recognized of these functions is the FcRn-mediated recycling and transcytosis process that results in the extraordinarily long, ~21 day serum persistence of IgG and albumin in humans [7]. In addition to regulating IgG and albumin homeostasis, FcRn participates in a plethora of immunological processes critical to the maintenance of human health [8]. Thus, FcRn has become an attractive target for drug delivery and disease therapy. In this review, we highlight the aspects of FcRn biology that have enabled the development of FcRn targeted therapeutics for the treatment of autoimmune and infection disease, as well as the expanding drug delivery approaches that hijack FcRn functions (Table 1). For more information regarding basic FcRn biology, we direct readers to a number of excellent past [6,9–12] and recent [7,13,14] reviews. We conclude this review by putting forth a hypothesis regarding the FcRn-dependent regulation of IgG homeostasis and echoing the words of a recent opinion by Clark Anderson [15]; 'we may still have much to learn about the FcRn'.

1.2. FcRn structure, biology, and function

1.2.1. FcRn structure and mechanism of IgG and albumin binding

FcRn is structurally homologous to the MHC Class I heterodimeric receptor family [16] consisting of a type I transmembrane heavy chain that non-covalently associates with the soluble light chain, β2-microglobulin (β2m). β2m is absolutely necessary for the proper folding, transport, and function of FcRn, as well as other MHC Class I homologs, both *in vitro* and *in vivo* [17–20]. The FcRn heavy chain contains three soluble domains (α1, α2, and α3), a single transmembrane helix, and a cytoplasmic tail (Fig. 1). Unlike MHC Class I molecules, FcRn does not directly present antigen to T-cells due to point mutations on the top face of FcRn that disrupt peptide binding.

The ability of FcRn to protect IgG from intracellular catabolism is the result of a specific, pH-dependent interaction with the Fc portion of IgG (Fig. 1). IgG binds FcRn in a strictly pH-dependent manner at acidic (<6.5) but not neutral pH (>7) mediated by electrostatics between titratable histidine residues in the Fc C_H2–C_H3 domains of IgG and acidic residues on the α2-domain of FcRn [21–25] (Fig. 2). Binding is further stabilized by a series of hydrophobic interactions and hydrogen bonds between Fc and residues within the FcRn α2-domain and the β2m light chain N-terminus [26]. One IgG molecule can simultaneous bind two FcRn molecules due to the homodimeric nature of IgG [27,28] resulting in a high affinity interaction between FcRn and IgG at pH 6 due to avidity. The 2:1 interaction between FcRn and IgG is critical for efficient binding, recycling, and transcytosis *in vitro* [29] and to preserve the long serum persistence of IgG *in vivo* [22].

The FcRn binding site on IgG overlaps with the staphylococcal protein A (SpA), streptococcal protein G (SpG), and rheumatoid factor binding site [30], but is distinct from the classical Fcγ receptors [25] and the C1q component of complement [31,32] that bind near the upper C_H2 domain and hinge region. IgG binding to FcRn is independent of glycosylation [33] in contrast to glycan dependent IgG binding to classical Fcγ receptors [34].

Table 1
Summary of drug delivery approaches and therapeutic modalities that target the FcRn.

Protein half-life extension			
Strategyc	Mechanism	Effect	Reference
1. Fc-fusion	Hijacking FcRn recycling, increased molecular weight (MW)	Half-life extension by reducing catabolism and renal clearance	[14,77]
2. Albumin fusion	Hijacking FcRn recycling, increased MW	Same as Fc-fusion	[136]
3. IgG–Fc or albumin engineering	Increased mAb/albumin affinity for FcRn at pH 6	Half-life extension by reducing catabolism	[39,40,63,64,66,70–74,78,81,139]
4. Monomeric Fc and CH domains	Hijacking FcRn recycling, increased MW	Increased half-life by reducing catabolism and potentially renal clearance	[146–150]
5. Fusion to alternate FcRn binding ligands	Hijacking FcRn recycling	Half-life extension by reducing catabolism (only validated *in vivo* in ref. [147])	[151,152]
Non-invasive protein delivery			
1. Fc-fusion	FcRn-mediated epithelial transcytosis	Increased pulmonary/oral protein absorption	[101–103,112,118]
2. Fc-decorated protein nanocontainers	FcRn-mediated epithelial transcytosis, protection of protein cargo from degradation by encapsulation	Oral insulin delivery that improves glucose tolerance dependent on FcRn	[123]
Mucosal vaccination			
1. Fc-antigen fusion	FcRn-mediated transcytosis, FcγR-mediated delivery to phagocytic cells, FcRn potentiation of antigen presentation	Improved innate and adaptive immune response against protein antigens	[128,129,131]
2. bnAb-Fc engineering	Increased FcRn-dependent deposition and/or retention of engineered IgG in mucosal tissues	Enhanced protection against intrarectal HIV challenge	[133]
Inhibitors of the IgG–FcRn interaction			
1. IVIG	Saturation of FcRn	Accelerated clearance of endogenous IgG	[83,85]
2. FcRn antagonists (α-β2M mAbs, α-FcRn mAbs, Abdegs, synthetic peptides, small molecules)	Blocking IgG binding site on FcRn and/or competing with endogenous IgG for binding to FcRn	Accelerated clearance of endogenous IgG	[87–89,91,93]
3. IgG antagonists	Blocking FcRn binding site on IgG	Inhibits FcRn–IgG interaction *in vitro*. Not tested *in vivo*. May accelerate IgG clearance.	[30,97]
Inhibitors of the IgG-albumin interaction			
1. α-FcRn mAbs	Blocking albumin binding site on FcRn	Not determined. May enhance clearance of albumin or albumin bound toxins	[40]
Increased tumor/tissue accumulation, distribution, and/or retention			
1. IgG–Fc engineering	Presumably increased FcRn transport via increased affinity for FcRn	Improved anti-tumor effect in mice potentially mediated by tumor cell FcRn expression, increased amount of IgG in bronchio-alveolar lavage of monkeys	[64,79]

Please cite this article as: J.T. Sockolosky, F.C. Szoka, The neonatal Fc receptor, FcRn, as a target for drug delivery and therapy, Adv. Drug Deliv. Rev. (2014), http://dx.doi.org/10.1016/j.addr.2015.02.005