



Review article

FcRn expression in cancer: Mechanistic basis and therapeutic opportunities



Imke Rudnik-Jansen, Kenneth A. Howard *

Interdisciplinary Nanoscience Center (iNANO), Department of Molecular Biology and Genetics, Aarhus University, DK-8000 Aarhus C, Denmark

ARTICLE INFO

Keywords:

Neonatal Fc Receptor
Targeted cancer therapy
Tumour metabolism
Albumin-drug designs
Antibody-drug designs
Cancer immunotherapy

ABSTRACT

There is an urgent need to identify new cellular targets to expand the repertoire, potency and safety of cancer therapeutics. Neonatal Fc Receptor (FcRn)-driven cellular recycling plays a predominant role in the prolonged serum half-life of human serum albumin (HSA) and immunoglobulin G (IgG) exploited in long-acting cancer drug designs. FcRn-mediated HSA and IgG uptake in epithelial cells and dendritic cell antigen presentation offers new therapeutic opportunities beyond half-life extension. Altered FcRn expression in solid tumours accounting for HSA catabolism or recycling supports a role for FcRn in tumour metabolism and growth. This review addresses the mechanistic basis for different FcRn expression profiles observed in cancer and exploitation for targeted drug delivery. Furthermore, the review highlights FcRn-mediated immunosurveillance and immune therapy. FcRn offers a potential attractive cancer target but in-depth understanding of role and expression profiles during cancer pathogenesis is required for tailoring targeted drug designs.

1. Introduction

Cancer remains one of the leading causes of death worldwide [1]. A paradigm shift in cancer therapy is precision medicines that aim to maximise selective cancer targeting and concomitant reduced off-target toxicity [2,3]. Targeted therapy has made promising advances over recent years, but tumour heterogeneity, cellular mutagenesis and drug resistance are remaining challenges [4]. Moreover, a limited panel of receptors and ligand targets involved in tumour growth and/or progression has been the focus of targeted therapeutic intervention. The identification of novel targets to expand the repertoire of cancer therapeutics is needed. Dysregulation of Neonatal Fc Receptor (FcRn) cellular recycling may account for enhanced intracellular albumin uptake associated with metabolic reprogramming of cancers [5,6], supporting involvement of FcRn in tumour growth. This review focusses on FcRn and its relatively underexplored role in tumour progression that may offer targeted anti-tumour approaches dependent on FcRn expression levels.

1.1. The Neonatal Fc Receptor

The Neonatal Fc Receptor was first shown to facilitate transport of maternal immunoglobulin G (IgG) to pre- and neonatal mammals [7]. Thereafter, it has been found in a variety of adult tissues and cell types [8] and to be involved in the maintenance of serum IgG and albumin

levels [9,10]. The *FCGR1A* gene encodes the type I glycoprotein with a heavy chain consisting of three extracellular domains ($\alpha 1$, $\alpha 2$, and $\alpha 3$), a transmembrane region and a cytoplasmic tail that associates non-covalently with the extracellular $\beta 2$ -microglobulin light chain [9,11]. The FcRn is an atypical Fcγ-receptor, structurally related to MHC class I molecules [12], but with the peptide binding groove occluded FcRn lacks peptide binding properties [13]. Oganesyan et al., first reported the 3D structures of human FcRn bound to the human Fc region of IgG and human serum albumin (HSA) alone, or concurrently to both ligands binding non-overlapping sites on the FcRn heavy chain [14] (Fig. 1). Histidine residue 310 on FcRn becomes protonated at pH ~ 6 that plays a direct role in the pH-dependent binding of Fc regions, while the loss of histidine protonation upon an increase in pH releases IgG from FcRn [15]. In a similar manner, HSA binding relies on protonation resulting in charge-stabilized hydrogen bonds formed in the crucial histidine residue 116 that constrains the position of the heavy chain loop, leading to a pH dependent hydrophobic interaction between HSA and FcRn [14,16].

1.2. FcRn-mediated cellular transport of IgG and albumin

HSA is the most abundant plasma protein serving as a natural transport protein for endogenous ligands such as bilirubin and fatty acids facilitated by its multiple ligand-binding sites [17,18]. Whilst, IgG is the most common antibody type accounting for ~10–20% of plasma proteins [19]. FcRn expressed in the vascular endothelium maintains

* Corresponding author.

E-mail address: kenh@inano.au.dk (K.A. Howard).

serum IgG and HSA levels through a cellular recycling endosomal sorting mechanism that diverts the ligand from lysosomal degradation [10,20]. HSA and IgG are internalised by pinocytosis and subsequently bind to FcRn in the acidic endosomal compartment, recycled to the cell surface and dissociate at a physiological pH. This results in a prolonged serum half-life for HSA of ~19 days [21] and IgG of ~21 days, dependent on IgG isotype [22].

FcRn is also involved in the bidirectional transcytosis of IgG and HSA across polarised cellular barriers. Epithelial FcRn expression has been reported in the intestine [23], placenta [24], respiratory tract upper airway [25] and genitourinary system [26,27]. The prominent role of IgG in mucosal humoral responses suggest IgG gains access to the lumen by FcRn-mediated transcytosis. Indeed, FcRn-driven bidirectional transcytosis transport of IgG-bacterial antigen immune complexes across the mucosal epithelial barrier was necessary for CD4+ T-cell-mediated mucosal immunity in mice [28]. Evidence for FcRn-mediated albumin transcytosis is more recently established [29,30]. In hepatocytes, FcRn was shown to regulate albumin recycling and transport in polarised hepatocytes and enhance liver sensitivity to albumin-bound hepatotoxins *in vitro*. Blocking the FcRn-mediated trafficking of albumin-

bound hepatotoxins was shown to prevent liver damage [29]. In addition, FcRn-mediated transcytosis enables HSA recycling within the kidney tubular system, thereby, preventing HSA excretion [30].

2. FcRn-driven half-life extension of cancer therapeutics

2.1. Albumin-based cancer therapeutics

The basis for albumin-based cancer therapeutics is supported by the demonstration of passive albumin entry into solid tumours by the enhanced permeability and retention (EPR) effect first described in mice by Matsumura and Maeda in 1986 [31]. Half-life extension mediated by FcRn engagement likely increases the passive tumour accumulation process of both endogenous HSA binding drugs and HSA drug conjugates. Cytotoxic drugs modified with a maleimide side chain have been designed to bind to the endogenous HSA pool for enhanced tumour accumulation. This is exemplified with Aldoxorubicin assessed in clinical trials [32], a thiol-reactive doxorubicin prodrug that binds to the free thiol on HSA and is released at the prostate tumour target site by a prostate-specific protease cleavable bond [33]. Another example is an

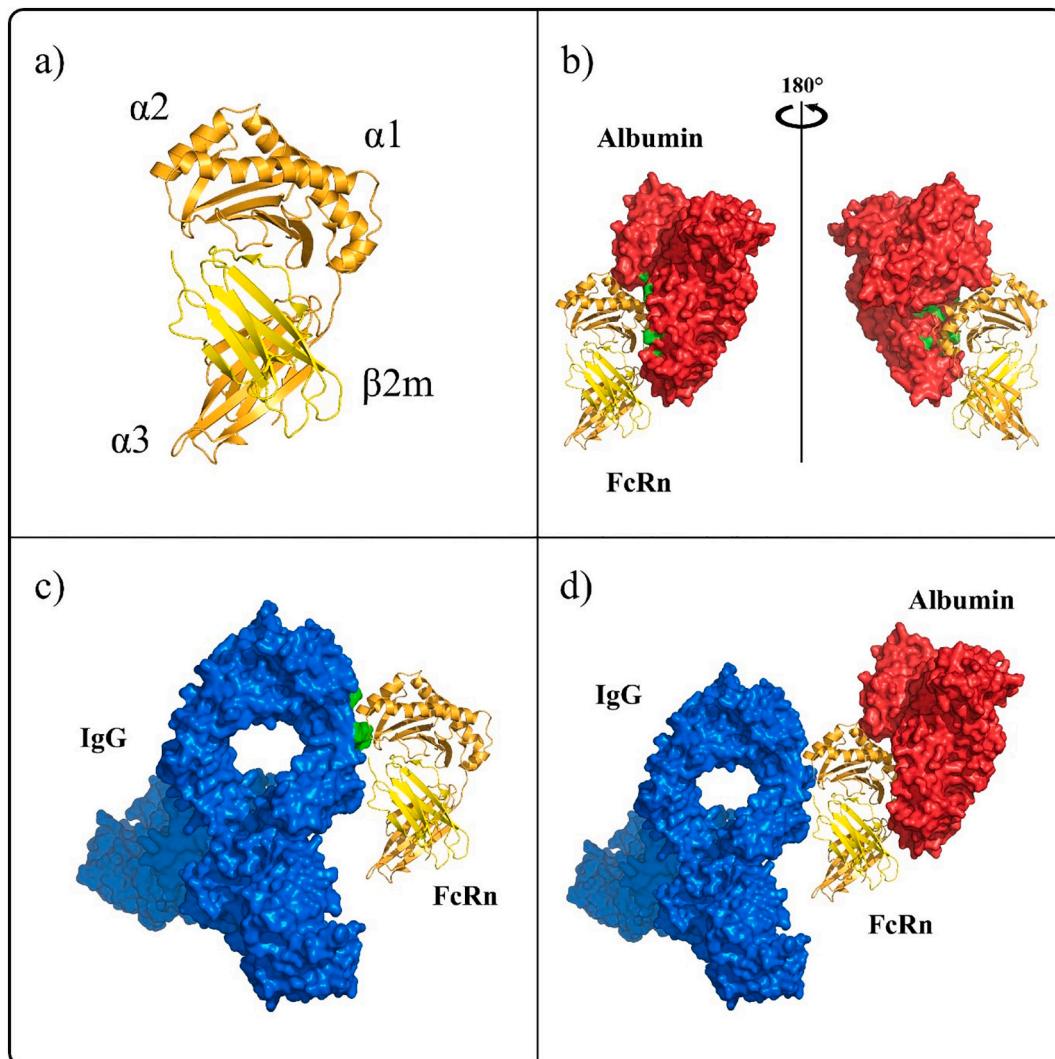


Fig. 1. Human FcRn interaction with ligands IgG and albumin. a) Crystal structure of FcRn composed of the three extracellular domains ($\alpha 1$, $\alpha 2$, and $\alpha 3$, depicted in orange) in the heavy chain and the extracellular $\beta 2$ -microglobulin ($\beta 2m$) light chain (depicted in yellow). b) FcRn binding interaction with albumin (depicted in red), viewed at different angles to show the full binding interface. Albumin residues important for FcRn binding are depicted in green. c) FcRn binding interaction with IgG (depicted in blue). IgG residues important for FcRn binding are depicted in green. d) FcRn interaction with both ligands binding on opposite faces of the heavy chain. Illustration was made using PyMol software, reference 4N0U and 1HZH. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

enzyme responsive albumin-binding prodrug based on endogenous albumin binding and subsequent β -glucuronidase-activated drug release in the tumour microenvironment (TME) [34]. The enzyme-responsive albumin-binding prodrug was less toxic than the free drug in mice with orthotopic mammary and pancreatic tumours [35]. Tasquinimod is a small molecule inhibitor interfering with tumour angiogenesis and establishment of the TME, whose effects were potentiated through reversible binding to HSA and consequent enhanced tumour uptake [36]. Tasquinimod has shown to display a high affinity binding to histone deacetylase 4 (HDAC4) overexpressed on prostate cancer cells [36] and to S100A9 expressed by regulatory myeloid cells [37]. Tasquinimod has been shown to double the median progression-free survival of patients with metastatic, castrate resistant prostate cancer in randomized prospective clinical trials [38,39]. The albumin/drug associate Abraxane®, an albumin formulation containing paclitaxel is approved for treatment of advanced non-small cell lung cancer, and metastatic pancreatic and breast cancer [40–42]. Active Gp60 and SPARC-mediated cellular uptake is the proposed targeting mechanism, however, FcRn-driven albumin half-life extension likely contributes to drug efficacy.

2.2. Antibody-based cancer therapeutics

Full size monoclonal antibodies (mAbs) that engage with FcRn and cancer cell receptors offer long-acting targeted therapy [43]. Currently, cetuximab, panitumumab, nimotuzumab, and necitumumab are the four major epidermal growth factor receptor (EGFR) mAbs used in the clinic [44]. Antibody-drug conjugates combining the specificity of mAbs with a cytotoxic drug offer increased potency [45]. Ado-trastuzumab emtansine is an antibody-drug conjugate approved for the treatment of advanced breast cancer. It comprises of the full size HER2 mAb trastuzumab conjugated to the maytansinoid DM1 through a non-reducible thioether linkage [46]. MAb-dependent effector cell activation relies on Fc binding to the Fc-gamma Receptor (Fc γ R) resulting in antibody-dependent cellular phagocytosis and antibody-dependent cell-mediated cytotoxicity [19]. Complement-dependent cytotoxicity is another mechanism by which mAbs can exert their function [19]. Conversely, possible adverse effects can result from excess cytokine release due to Fc interaction with Fc γ R ubiquitously expressed on immune cells [47] or classical complement system activation upon interaction with the C1q component [48]. The Fc-engagement of mAbs in cancer therapeutics might not be a major concern since the utilisation of Fc-engagement, in particular Fc multimerization of proteins, has shown to be promising in anti-tumour therapeutics [49,50]. MAbs targeting antigens overexpressed in tumours such as EGFR, however, can mediate on-target off-tumour immune effects in healthy tissues that express basal EGFR levels that might aggravate Fc-mediated cytokine release. Antibodies engineered without the Fc component is a method to circumvent this, however, with the caveat of reduced circulatory half-life due to loss of FcRn-mediated recycling [51]. High and frequent dosing is, therefore, required, exemplified with the immunotherapy blinatumomab requiring continual infusion per 28-day treatment cycle [52]. Efforts have focused on silencing Fc regions to reduce adverse immune activation whilst retaining FcRn-mediated half-life extension [53]. It is a challenge, however, to develop truly ‘silent’ IgG variants lacking Fc γ R binding and the number of mutations needed to achieve this can further affect stability and immunogenicity of the altered Fc regions [54]. Therapeutic antibodies generated with increased affinity for FcRn have shown to substantially increase circulatory half-life in transgenic mice and cynomolgus monkeys with improved anti-tumour efficacy [55,56]. *Hitherto*, ravulizumab is the single approved therapeutic antibody with modified FcRn affinity, used for treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uremic syndrome [57].

3. FcRn-mediated immunosurveillance and anti-tumour immunity

The expression of FcRn has been identified in professional antigen presenting cells (APCs) such as macrophages to maintain serum albumin and IgG levels [58,59]. Mice harbouring FcRn-deficient macrophages, unable to recycle IgG, show abnormally low serum IgG levels as result of IgG hypercatabolism. Conversely, depletion of the FcRn-deficient macrophage population rescued IgG serum levels [59,60]. The extended half-life of IgG is favourable for antibody-based therapies, but causes detrimental effects in IgG-mediated autoimmune disorders such as myasthenia gravis, rheumatoid arthritis or pemphigus vulgaris. FcRn-IgG interactions have been targeted to prevent circulating pathogenic IgGs using FcRn blockers with an engineered Fc region to bind FcRn with higher affinity and reduced pH dependence [61]. FcRn blockers currently being evaluated in clinical trials include orilanolimab [62], efgartigimod [63] and nipocalimab [64]. Another role of FcRn expression in APCs is FcRn-mediated recognition of pathogens and antigen presentation to T-cells needed for subsequent activation of immune responses [65]. FcRn enhances MHC class II and MHC class I cross-presentation of antigen-antibody complexes by dendritic cells (DC). Decreased MHC class II antigen presentation *in vitro* occurred in FcRn-deficient DCs, or in healthy DCs that cannot interact with IgGs due to site-directed FcRn binding site mutagenesis [66]. The importance of FcRn function in DC-mediated adaptive immune responses was further confirmed *in vivo*, as antigen presentation to CD4+ T-cells was markedly blunted in FcRn-deficient DC mice [66]. Similarly, FcRn plays a role in the antigen cross-presentation of DC to CD8+ T-cells [67]. Extracellular antigens normally internalised, processed and presented by MHC class II to CD4+ T-cells, can be internalised into specialised vacuoles and loaded onto MHC class I molecules for processing and presentation by the process of cross-presentation. Recent work showed FcRn traps IgG immunocomplex-antigens (IgG-IC) in an atypical acidic loading compartment and protects it from lysosomal degradation, enabling peptide processing and cross-presentation in a subset of DCs (CD8+, CD11b+ cells) [67]. The involvement of FcRn in the uptake of antigens trapped in the IgG-IC and subsequent cross-presentation of processed antigen peptides was further validated *in vivo*. Mice containing FcRn-deficient DCs showed inadequate cross-priming of CD8+ T-cells that resulted in hampered CD8+ T-cell induction [67]. Another study has shown that FcRn can induce adaptive immune responses to IgG-IC, and FcRn blockage could decrease IC-mediated inflammation in autoimmune diseases without affecting IgG clearance [68].

Tumour-associated immunity typically involves IgG responses [69] and recent work suggests an important role of FcRn in anti-tumour immunity [70,71]. Mice with an abnormal copy of the adenomatous polyposis coli (APC) gene *Apc*^{Min/+} that spontaneously develop large numbers of small intestine adenomas, were shown to develop a significantly increased number of large intestinal tumours when crossed with *Fcgtr*^{-/-} mice [70]. Furthermore, *Fcgtr*^{-/-} mice were more susceptible to the development of sporadic colorectal cancers [70] or lung cancer metastasis [71] due to decreased numbers of infiltrating DCs, CD8+ T-cells and NK cells in the TME. Moreover, NK cells had an immature phenotype suggesting that FcRn-deficiency restricts NK cell maturation. Adoptive transfer experiments of primed DCs with or without functional FcRn were performed to validate that FcRn-mediated tumour protection was dependent on activated CD8+ T-cells by DC cross-priming. DCs lacking FcRn were unable to provide the necessary cytokine environment needed to promote CD8+ T-cell activation *in vivo* [70]. These results suggest that FcRn could be involved in early stage anti-tumour immunosurveillance for immune detection of tumour development and cross-priming of CD8+ T-cells needed for an anti-tumour immune response (Fig. 2). Interestingly, FcRn-expressing DCs are shown to localise in human colorectal tissue cancers and correlate with CD8+ T-cell infiltration, while signs of CD8+ T-cell-mediated immune responses in colorectal cancer patients are associated with better

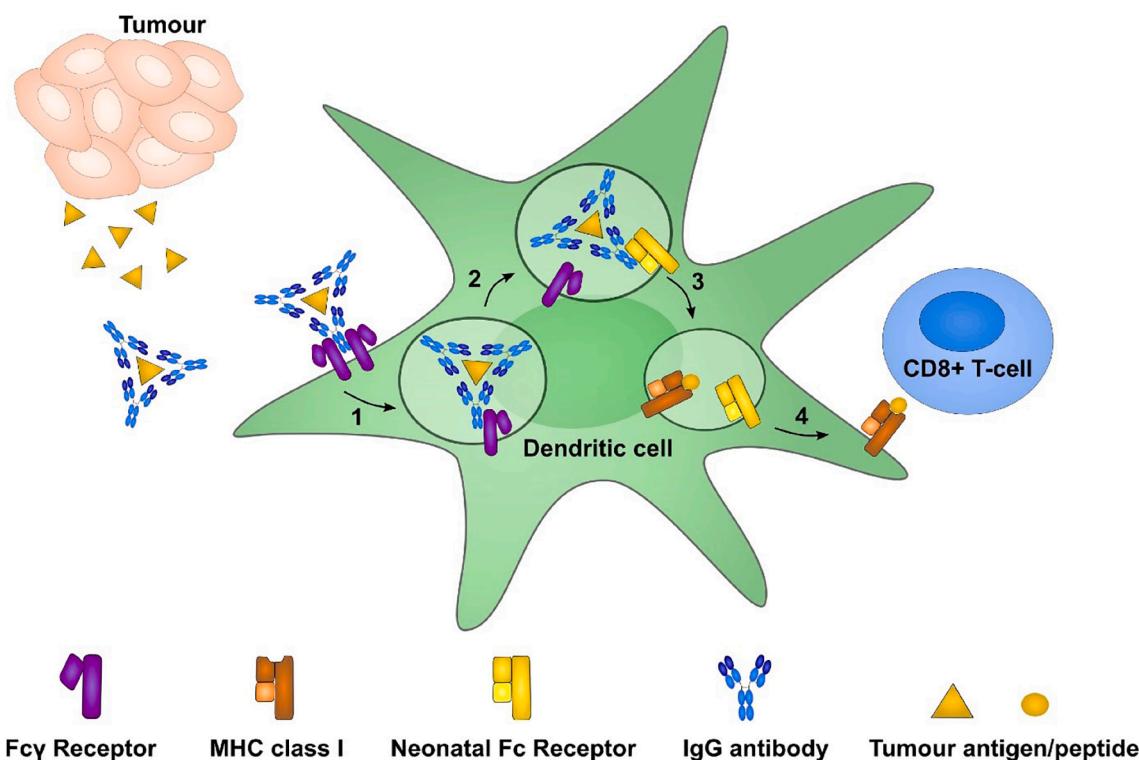


Fig. 2. FcRn-mediated immunosurveillance priming effective anti-tumour immunity. FcRn expressing dendritic cells take up tumour antigen-IgG immune complexes upon binding Fc γ R (1). The immune complexes dissociate from Fc γ R and bind FcRn (2). The immune complexes are then shuttled into the antigen processing pathways and the peptides loaded on MHC molecules (3) to prime CD8+ T-cells for an anti-tumour immune response (4). Concept proposed by Baker et al. [70].

prognosis [72]. Targeting FcRn-expressing DCs to mediate anti-tumour immunosurveillance and immunity was explored by Baker et al. [70]. IgG antibodies with tunable FcRn affinities loaded on FcRn-expressing DCs could tailor CD8+ T-cell immune responses against a defined tumour antigen that offers potential for the development of more potent anti-tumour immunotherapies.

4. Therapeutic exploitation of FcRn expression levels in cancer

4.1. FcRn expression and catabolism in cancer growth

Metabolic changes are characteristics of cancerous tissues and the regulation of energy metabolism is today considered a hallmark in the establishment of cancer [73]. The phenomenon by which cancer cells preferentially utilise glucose by aerobic glycolysis to increase cell growth known as the Warburg effect was first described by Otto Warburg almost a century ago [74]. Since then, our understanding of the reprogrammed metabolic network in cancer cells has rapidly expanded [75]. Glucose and glutamine are two major nutrient sources utilised to sustain tumour growth and progression used for glycolysis and the tricarboxylic acid cycle, respectively [76]. In addition to a primary protein source, amino acids can function as metabolites to activate important pathways such as mammalian target of rapamycin complex 1 (mTORC1), autophagy or as neurotransmitters [77]. Other alternative nutrient sources for ATP acquisition and biomass synthesis during tumour growth are lactate [78], acetate [79], ketone bodies [80], ammonia [81] and exogenous proteins [82]. The deregulated metabolism driving cancer biology is reflected in the altered homeostatic control of energy balance in cancer patients [83]. Approximately half of all cancer patients exhibit cachexia, characterized by extreme weight loss and muscle wasting [84]. Pro-cachectic cytokines have shown to play a critical role in cancer development [85] and anti-cytokine treatment is being investigated as a therapy in cancer patients exhibiting cachexia [86]. Cancer cachexia is further characterized by

hypoalbuminemia even though HSA synthesis rates remain mostly unaffected [87] or mildly increase [88], that supports HSA accumulation and catabolism in solid tumours. Direct evidence for HSA catabolism as an underlying cause for hypoalbuminemia was provided from an elegant study by Davidson et al. to track the breakdown products of labelled albumin in mice exhibiting spontaneous KRAS-mutated pancreatic ductal adenocarcinoma (PDAC) [6]. Higher concentrations of labelled albumin peptides detected in tumour-derived tissue compared to disease-free pancreas tissue, suggests albumin consumption may serve as an important source of amino acids to fuel high metabolic requirements. The oncogenic RAS mutations frequently occur in human tumours of which KRAS is the predominant mutated isoform in PDAC [89] that drives the initiation, development and maintenance of tumour growth in PDAC patients [90]. Macropinocytosis was the mechanism attributed to HSA uptake and degradation in KRAS mutated cells to enable transport extracellular proteins into the cell [5,91]. HSA is normally protected from lysosomal degradation through FcRn-mediated endosomal cellular recycling [20] but Liu et al. proposed down-regulation of FcRn in KRAS mutated tumours leading to reduced HSA recycling and increased lysosomal degradation [91]. In a different study, FcRn expression in a majority of human tumour cell lines expressing wild type RAS tested showed low or undetectable levels [92]. FcRn knockdown in tumour cell lines with detectable FcRn expression resulted in increased intracellular HSA levels, conversely, increased FcRn levels exhibited lower intracellular HSA levels. The authors evaluated the effect of FcRn expression on tumour growth of implanted breast and prostate cancer cells following FcRn knockdown or overexpression in mice. Tumour growth rates increased in mice xenografts lacking FcRn expression, compared to corresponding xenografts expressing FcRn. Decreased serum albumin levels were detected in mice implanted with tumours lacking FcRn expression, compared to mice implanted with FcRn-expressing tumour cells that supports elevated albumin consumption to stimulate tumour growth [92].

In another study, high-throughput gene profiling of human breast

cancer biopsies found downregulation of the *FCGRT* gene in progressive breast carcinomas and, hence, *FCGRT* was proposed as a potential prognostic biomarker for breast cancer treatment [93]. It was, however, not specified whether *FCGRT* downregulation was found in the breast cancer cells or the infiltrating immune cells. The altered *FCGRT* expression, therefore, might reflect the reduced anti-tumour immuno-surveillance functions of FcRn rather than tumour epithelial expression effects in this cohort of cancer patients, as FcRn downregulation in tumour infiltrating immune cells has been shown to impair anti-tumour immune responses [70]. Decreased FcRn mRNA and protein levels were also found in hepatocellular carcinoma biopsies [94] and non-small cell lung carcinoma biopsies [95] and were associated with poor cancer prognosis.

4.2. Therapeutic exploitation of FcRn downregulation

An increase in HSA accumulation as result of decreased FcRn expression could be utilised for delivery of cytotoxic drug cargos to cancer cells requiring high metabolic intake. Cytotoxic drugs conjugated to HSA could be preferentially taken up by macropinocytosis and trafficked to lysosomes in RAS-transformed cancer cells and released following HSA breakdown (Fig. 3). This approach was explored with a HSA-doxorubicin (DOX) conjugate against PDAC in a study by Liu et al. [91]. FcRn expression levels were first determined in human pancreatic cancer cell lines with or without the oncogenic KRAS mutation. KRAS-mutated cell lines exhibited very low FcRn protein expression, compared to the wild-type RAS-expressing cell line or a non-cancerous cell line control. Modulation of FcRn expression in PDAC cell lines by FcRn-specific siRNA suppressed recycling of the albumin-conjugated drug and increased degradation *in vitro*. Significantly, FcRn-reduced recycling and concomitant increased HSA catabolism made PDAC cells more susceptible to albumin-conjugated drugs, but not to free drug. PDAC xenografts with or without KRAS mutation and different FcRn levels were implanted subcutaneously in mice to confirm preferential uptake of albumin-conjugated drugs by PDAC cells *in vivo*. Tumour growth was significantly inhibited in mice bearing KRAS mutated low FcRn-expressing tumours by albumin-conjugated drugs proposed as a consequence of reduced recycling and enhanced macropinocytosis.

In different work by Wang et al., a bifunctional delivery system was used to exploit enhanced macropinocytosis and susceptibility of PDAC to albumin-conjugated drugs [96]. The bifunctional recombinant protein, termed Fv-LDP-D3, was comprised of the following; an anti-EGFR antibody fragment (Fv), HSA domain III (D3), and the enediyne-associated anti-tumour antibiotic compound apoprotein lidamycin (LDP). The assembled recombinant protein could be further enhanced

with an enediyne chromophore derived cytotoxic compound (AE). PDAC cell viability was inhibited by the recombinant proteins Fv-LDP and Fv-LDP-D3, regardless if KRAS-mutated or wild type RAS. It was concluded that the inhibition of cell proliferation was predominantly mediated by EGFR signalling inhibition, although the exact mechanism responsible for the susceptibility of PDAC to albumin-conjugated anti-cancer drugs was not reported. The therapeutic efficacy of recombinant proteins Fv-LDP, Fv-LDP-D3 and Fv-LDP-D3-AE was evaluated in mice subcutaneously implanted with KRAS-mutated PDAC xenografts. Significant smaller tumour volumes were observed in mice treated with recombinant protein Fv-LDP (58% reduction), Fv-LDP-D3 (81% reduction) and Fv-LDP-D3-AE (81% reduction). No direct evidence, however, was given to confirm the mechanism proposed by Wang et al. or if FcRn expression was low and influenced protein uptake and PDAC susceptibility to albumin-conjugated drugs.

It could be relevant to use HSA engineered with different FcRn affinities [97] to further elucidate the role of FcRn in the susceptibility of PDAC cells to internalise albumin-drug conjugates. Increased cancer cell uptake of albumin-drugs may compromise the effect of drugs dependent on extracellular target engagement. The mAb, bevacizumab, binds growth factor VEGF-A to block VEGFR activation and signalling in tumour cells. Work has shown that glioblastoma cells become resistant to the anti-angiogenic mAb, bevacizumab, through macropinocytotic uptake and subsequent trafficking to the lysosome [98].

4.3. FcRn expression and anabolism in cancer growth

The metabolic demands of cancer cells are high due to an increased proliferation rate [99]. Numerous studies have attributed HSA accumulation in cancer cells [31,92,100] as a nutrient resource [6,101,102]. Mechanisms that prevent nutritional consumption of extracellular proteins, however, have been described [103]. The kinase mTORC1 is a protein complex that coordinates cellular nutrient levels and when required, stimulate anabolic metabolism and growth. Even in KRAS mutated cells, mTORC1 suppresses degradation of the internalised proteins *in vitro* [103]. The authors showed inhibition of mTORC1 led to elevated lysosomal catabolism of extracellular proteins and promotes KRAS mutated cell proliferation in poorly vascularized tumour regions in mice. This suggests that extracellular protein catabolism is not triggered if nutrient demands of either healthy or malignant cells are met and this is influenced by the state of disease progression. It could be speculated that conservation of serum HSA levels is beneficial in maintaining HSA-mediated transport of ligand cargos such as fatty acids used in cell growth. FcRn on the vascular endothelial cell membrane is involved in tissue uptake of HSA bound fatty acids [104]. Following

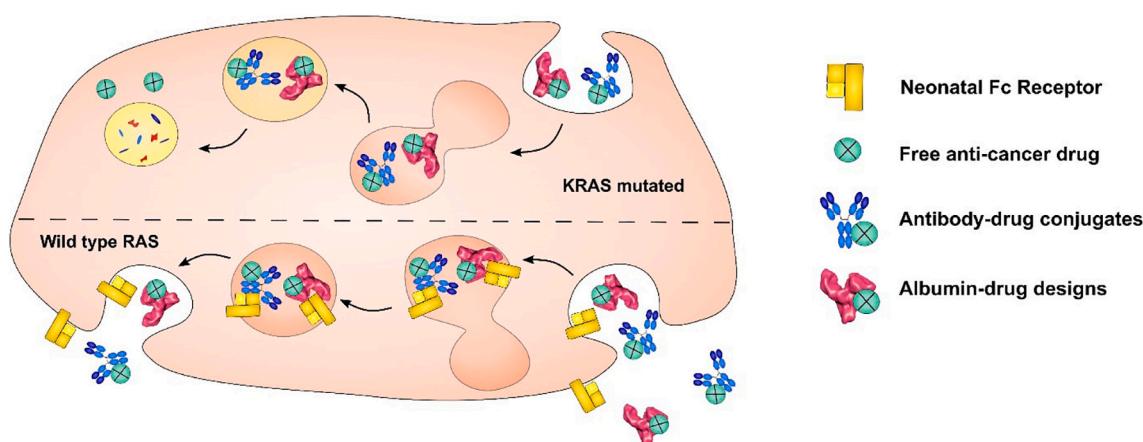


Fig. 3. Therapeutic exploitation of FcRn downregulation in cancer. Enhanced macropinocytosis due to FcRn downregulation increases the susceptibility of KRAS mutated cancer cells to antibody-drug conjugates or albumin-drug designs (top). Wild type RAS cells expressing FcRn recycle antibody-drug conjugates or albumin-drug designs (bottom).

HSA-fatty acid complex entry across the apical vascular membrane, the complex dissociates and the fatty acid interacts with the lipid bilayer membrane, then translocates into the cytosol to be used for energy production [105]. Intracellular fatty acids bind to fatty acid binding proteins, forming acyl-CoA, used for the acylation of diacylglycerol, protein and signal transduction. Furthermore, acyl-CoA is a fuel for the citric acid cycle upon β -oxidation in mitochondria [106]. It is feasible that HSA-mediated delivery of nutrient cargos such as fatty acids to the TME [102] could be driven by FcRn upregulation. The presence of FcRn in various histologic types of human breast carcinoma and lymph node metastases [107] and colorectal and breast cancer cell lines commonly used in xenograft studies [108] promotes a role of maintained FcRn expression in tumour progression.

Recent work from our laboratory [109] supports a role of FcRn expression in cancer. An extensive human biopsy immunohistochemical screen ($N = 310$) revealed significant FcRn upregulation in eight different cancer types. Lower metabolic rates were observed in the human colorectal cancer cell line HT-29 when FcRn expression was ablated by CRISPR/Cas9 gene editing. Reduced tumour size of HT-29 FcRn knock out (HT-29 hFcRn KO) cell xenografts in mice compared to wild type HT-29 (HT-29 WT) cell xenografts suggests a supportive role of FcRn in tumour growth. A panel of fluorescently labelled recombinant HSA engineered with different FcRn binding affinities (null-binder: NB, wild-type: WT and high-binder: HB) were used as a tool-set to investigate FcRn-driven cellular recycling and tumour accumulation. The amount of *in vitro* recycling correlated with FcRn binding affinities; HB albumin exhibiting more than a two-fold increase in recycling compared to WT albumin and NB albumin in HT-29 WT cells. Loss of FcRn expression in HT-29 hFcRn KO cells resulted in impeded albumin recycling for all HSA variants, which supports an FcRn-dependent albumin recycling process exists in cancer epithelial cells. The circulatory half-life of the fluorescently labelled recombinant HSA variants was determined in HT-29 WT tumour-bearing mice and confirmed a concomitant increase in half-life with increase in FcRn binding affinity. The co-localization of the fluorescent-labelled HSA variants in bioluminescent cancer xenografts in mice, greater with HB albumin, supports a role of FcRn in albumin recruitment, however, evidence of concomitant delivery of nutrient cargos was not investigated in this work. Nutrient cargo release during HSA cellular recycling is expected to be dependent on the cellular transport mechanisms of the particular nutrient. For example, fatty acids can bind membrane proteins or diffuse through the extracellular membrane [110,111], which could permit release from albumin prior to FcRn

engagement within endosomes.

4.4. Therapeutic exploitation of FcRn upregulation

There is evidence for FcRn-driven transcytosis across polarised epithelium exploited in mucosal drug delivery [112,113]. In the work of Pridgen et al. [113] FcRn-mediated transcytosis was exploited for the oral delivery of insulin using Fc-modified polymeric nanoparticles. In a study by Bern et al. pulmonary uptake of coagulation factor VII HSA fusion was shown after intranasal delivery in human FcRn transgenic mice lacking endogenous albumin [114]. Targeting FcRn at epithelial barriers is seemingly a viable strategy for treatment of mucosal tumours or transmucosal delivery to systemic sites. FcRn-driven cellular recycling in non-polarised cells, however, could be exploited for targeted cancer therapy (Fig. 4). Release of drug payload prior or during an FcRn-driven endosomal recycling sorting process is a requirement for this approach. For covalent drug conjugates, this may necessitate stimuli-responsive spacers for intracellular delivery [115] or triggered release by tumour-associated factors such as peptides or enzymes in the TME employed by antibody-drug conjugates [45]. Extracellular acting drugs circumvent this requirement and simplifies the design criteria. Extracellular bispecific T-cell engagers have emerged as a potent weapon against cancer by redirecting T-cells against tumour-associated antigens. Bispecific antibodies are engineered without the Fc component to circumvent Fc γ or C1q-mediated immune overstimulation [116,117] at the expense of loss of FcRn-driven half-life extension. Recombinant HSA variants engineered with different FcRn binding affinities offer tunable half-life extension without off-target immune stimulation. Work from our laboratory has demonstrated the programmable *in vivo* half-life and anti-tumour effects of bispecific T-cell engager-albumin fusions [118]. The bispecific T-cell engager antibody termed *light T-cell engager* (LiTE) consisted of an anti-EGFR single-domain V_{HH} nanobody binding EGFR on the cancer cell surface and an anti-CD3 scFv domain binding simultaneously to the CD3 on T-cells [117]. LiTE was fused with recombinant HSA variants (termed Albu-LiTE) engineered with different FcRn affinity as a method to tune the circulatory half-life [118]. T-cell activation upon exposure to FcRn-expressing HT-29 cells was enhanced by LiTE and Albu-LiTE constructs, demonstrated by CD69 upregulation and IL-2 secretion of T-cells *in vitro*. Furthermore, antibody-mediated T-cell cytotoxicity for LiTE and Albu-LiTE constructs was EGFR-specific in a dose-dependent manner and did not occur in the absence of EGFR expression *in vitro*. A humanised double transgenic (hFcRn^{+/+}, hAlb^{+/+})

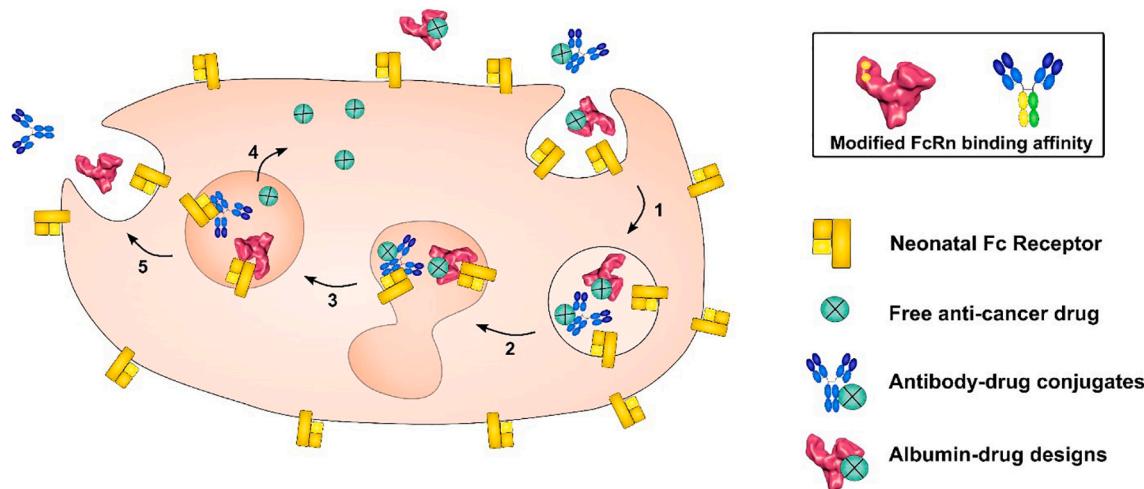


Fig. 4. Therapeutic exploitation of FcRn upregulation in cancer. Enhanced endosomal uptake of antibody-drug conjugates or albumin-drug designs due to FcRn upregulation in solid tumours. Uptake of antibody-drug conjugates or albumin-drug designs (1). Endosomal sorting (2). Stimuli-responsive drug release (3) and diffusion (4). Antibody and/or albumin is recycled to the cell surface (5). Insert depicts albumin and antibody variants with tunable FcRn affinities to modulate the uptake and cellular recycling.

mouse [119] was genetically modified to generate an immunocompromised strain depleted of B and T-cells. Tumour growth of subcutaneously implanted HT-29 cells in combination with co-injected PBMCs were more effectively inhibited following a single intraperitoneal injection of Albu-LiTE, compared to LiTE or the EGFR-specific mAb cetuximab. Moreover, serum half-life of Albu-LiTE was successfully extended and could be detected even 16 days post-injection, in contrast to LiTE cleared from the body within 24 h.

5. Conclusion and perspectives

FcRn was first associated with intestinal transepithelial and transplacental IgG transport [7,120]. Subsequent identification in adults and various cell types has redefined and expanded the FcRn range of functions that paves the way for therapeutic exploitation. The prominent role of FcRn-driven endothelial recycling prolonging serum levels of IgG and HSA is already utilised in design of long-acting cancer therapeutics. A role of FcRn in immuno-surveillance detection of a developing tumour and anti-tumour immunity could be exploited to target FcRn expressing immune cells for more potent cancer immunotherapy.

In contrast to a ligand-activated receptor such as EGFR, FcRn is not expected to be a direct target for therapeutic intervention, but offers the advantage of using a target to increase cellular drug delivery. Folate-drug and GalNac-siRNA conjugates designed to enter cells by receptor-mediated endocytosis and release cargo during receptor recycling [121,122] supports an FcRn-mediated drug delivery approach with a similarly recycled receptor. Such strategy necessitates covalent partner drug dissociation before recycling to the cell surface, likely requiring stimuli-responsive linkers built into the conjugate design [123–125]. Whilst, likely not a requirement for non-covalent drug associates, temporal control of drug release in such systems would still offer a challenge. Design criteria should consider site-selective conjugation of the partner drug to maintain engagement of IgG and albumin with FcRn. The available single free thiol at Cys34 in albumin domain I (DI), distant from the main binding interface in DIII, has been a focus of albumin-drug conjugation. We found that the FcRn binding affinity, however, is compromised to some degree most likely due to a contributory binding interface in DI, however, this can be restored using high binding albumin variants [126,127]. This review focuses on potential therapeutic exploitation of FcRn expression in cancer by its cognate ligands, IgG and HSA, but the FcRn-targeted strategy could be applied to drug delivery systems. FcRn-binding peptides such as short terminal peptide sequences could be an alternative strategy to improve protein pharmacokinetics and delivery of nanoparticles. FcRn-binding peptides are genetic fusions of a short FcRn-binding peptide (FcBP) sequence to peptides to mimic FcRn-IgG interactions [128]. Nanoparticles decorated with these FcRn-binding ligands have been shown to capture therapeutic antibodies on the surface to target cancer cells [129]. In other work, increase protein delivery across FcRn-expressing epithelial barriers has been shown with Fc-targeted nanoparticles [112,113] promoting FcRn targeting with nanoparticle delivery systems. Controlled display of targeting ligands on the surface of nanoparticles, however, remains a challenge in the field. Exploitation of FcRn-driven transcytosis of IgG and HSA across mucosal epithelium circumvents any FcRn-mediated drug recycling concerns but is limited to polarised barriers. An active targeting strategy is still dependent, however, on display of receptor at the cell surface. Continuous exchange between a mobile pool of FcRn on the surface and inside the cell has been reported, but at low surface expression levels in both endothelial cells and the basolateral membrane of epithelial cells [130,131]. Clinical trials investigating FcRn blockers for the treatment of antibody-mediated autoimmune diseases show evidence of cell surface engagement, that supports an FcRn-targeted approach. The TME of many solid tumours is slightly acidic [132,133] that could be exploited for high FcRn engagement by antibody or albumin-drug designs due to demonstrated higher affinity with the receptor at low pH [20]. More investigation into the surface display

pattern of FcRn in epithelial cancer tissue is still required, however, to support the application of FcRn for active cellular targeting.

Metabolic reprogramming of cancer and FcRn dysregulation implicates involvement of FcRn in cancer progression [5,91,92,109]. The nutritional demand driving metabolic reprogramming depends on factors such as tissue origin [134], cancer stage [135] and cachexia status [136] that could explain different FcRn expression levels reported in the literature. FcRn expression levels in cancer tissue could be linked to the heterogeneous TME immune landscape shown to vary between cancer patients [137]. Pro-inflammatory NF- κ B present in the TME has been reported to stimulate FcRn upregulation in human cancer cells and primary monocytes [138] that may influence FcRn expression levels. Patient screening for FcRn expression could be used as a stratification method for tailoring the treatment approach according to FcRn levels. Increased HSA uptake by macropinocytosis is documented in KRAS mutated cancer cells [5,6,92], but evidence of corresponding low FcRn expression in these cancer cells is limited. Intracellular delivery of albumin-based cancer therapeutics in KRAS mutated cancer, however, is an exciting approach. As an alternative, drug designs engineered for high or low FcRn affinity could be used to maximise FcRn engagement or divert drug from cellular recycling, respectively, in FcRn expressing cells.

FcRn-mediated half-life extension has been utilised in the design of marketed cancer therapeutics but observed altered FcRn profiles in cancer and FcRn-mediated anti-tumour immuno-surveillance offers new emerging therapeutic opportunities. Exploitation is dependent on a greater understanding of the mechanistic basis and FcRn expression levels in cancer for tailoring cancer drug designs.

Funding

This research was funded by the Novo Nordisk Foundation, Grant; CEMBID (Center for Multifunctional Biomolecular Drug Design, Grant Number: NNF17OC0028070).

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

We would like to thank Amalie Arnoldsen Juhl and Diego Pilati for assistance with the figures.

References

- [1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA Cancer J. Clin.* 68 (2018) 394–424.
- [2] D. Rosenblum, N. Joshi, W. Tao, J.M. Karp, D. Peer, Progress and challenges towards targeted delivery of cancer therapeutics, *Nat. Commun.* 9 (2018) 1410.
- [3] M.T. Manzari, Y. Shamay, H. Kiguchi, N. Rosen, M. Scaltriti, D.A. Heller, Targeted drug delivery strategies for precision medicines, *Nat. Rev. Mater.* 6 (2021) 351–370.
- [4] G. Gu, D. Dustin, S.A. Fuqua, Targeted therapy for breast cancer and molecular mechanisms of resistance to treatment, *Curr. Opin. Pharmacol.* 31 (2016) 97–103.
- [5] C. Commissio, S.M. Davidson, R.G. Soydane-Azeloglu, S.J. Parker, J. Kamphorst, S. Hackett, E. Grabocka, M. Nofal, J.A. Drebin, C.B. Thompson, J. D. Rabinowitz, C.M. Metallo, M.G. Vander Heiden, D. Bar-Sagi, Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells, *Nature* 497 (2013) 633–637.
- [6] S.M. Davidson, O. Jonas, M.A. Keibler, H.W. Hou, A. Luengo, J.R. Mayers, J. Wyckoff, A.M. Del Rosario, M. Whitman, C.R. Chin, K.J. Condon, A. Lammers, K.A. Kellersberger, B.K. Stall, G. Stephanopoulos, D. Bar-Sagi, J. Han, J. D. Rabinowitz, M.J. Cima, R. Langer, M.G. Vander Heiden, Direct evidence for cancer-cell-autonomous extracellular protein catabolism in pancreatic tumors, *Nat. Med.* 23 (2017) 235–241.
- [7] N.E. Simister, A.R. Rees, Isolation and characterization of an fc receptor from neonatal rat small intestine, *Eur. J. Immunol.* 15 (1985) 733–738.

- [8] S. Latvala, B. Jacobsen, M.B. Otteneder, A. Herrmann, S. Kronenberg, Distribution of FcRn across species and tissues, *J. Histochem. Cytochem.* 65 (2017) 321–333.
- [9] A.P. West Jr., P.J. Bjorkman, Crystal structure and immunoglobulin G binding properties of the human major histocompatibility complex-related Fc receptor(,), *Biochemistry* 39 (2000) 9698–9708.
- [10] C. Chaudhury, S. Mehnaz, J.M. Robinson, W.L. Hayton, D.K. Pearl, D. C. Roopenian, C.L. Anderson, The major histocompatibility complex-related Fc receptor for IgG (FcRn) binds albumin and prolongs its lifespan, *J. Exp. Med.* 197 (2003) 315–322.
- [11] N.E. Simister, K.E. Mostov, An fc receptor structurally related to MHC class I antigens, *Nature* 337 (1989) 184–187.
- [12] W.P. Burmeister, L.N. Gastinel, N.E. Simister, M.L. Blum, P.J. Bjorkman, Crystal structure at 2.2 a resolution of the MHC-related neonatal Fc receptor, *Nature* 372 (1994) 336–343.
- [13] M. Raghavan, L.N. Gastinel, P.J. Bjorkman, The class I major histocompatibility complex related fc receptor shows pH-dependent stability differences correlating with immunoglobulin binding and release, *Biochemistry* 32 (1993) 8654–8660.
- [14] V. Oganesyan, M.M. Damschroder, K.E. Cook, Q. Li, C. Gao, H. Wu, W. F. Dall'Acqua, Structural insights into neonatal Fc receptor-based recycling mechanisms, *J. Biol. Chem.* 289 (2014) 7812–7824.
- [15] M. Raghavan, V.R. Bonagura, S.L. Morrison, P.J. Bjorkman, Analysis of the pH dependence of the neonatal Fc receptor/immunoglobulin G interaction using antibody and receptor variants, *Biochemistry* 34 (1995) 14649–14657.
- [16] C. Chaudhury, C.L. Brooks, D.C. Carter, J.M. Robinson, C.L. Anderson, Albumin binding to FcRn: distinct from the FcRn-IgG interaction, *Biochemistry* 45 (2006) 4983–4990.
- [17] M.T. Larsen, M. Kuhlmann, M.L. Hvam, K.A. Howard, Albumin-based drug delivery: harnessing nature to cure disease, *Mol. Cell Ther.* 4 (2016) 3.
- [18] D. Pilati, K.A. Howard, Albumin-based drug designs for pharmacokinetic modulation, *Expert Opin. Drug Metab. Toxicol.* 16 (2020) 783–795.
- [19] G. Vidarsson, G. Dekkers, T. Rispens, IgG subclasses and allotypes: from structure to effector functions, *Front. Immunol.* 5 (2014) 520.
- [20] E.G.W. Schmidt, M.L. Hvam, F. Antunes, J. Cameron, D. Viuff, B. Andersen, N. N. Kristensen, K.A. Howard, Direct demonstration of a neonatal Fc receptor (FcRn)-driven endosomal sorting pathway for cellular recycling of albumin, *J. Biol. Chem.* 292 (2017) 13312–13322.
- [21] T. Peters, All About Albumin : Biochemistry, Genetics, and Medical Applications, Academic Press, San Diego, 1996.
- [22] A. Morell, W.D. Terry, T.A. Waldmann, Metabolic properties of IgG subclasses in man, *J. Clin. Invest.* 49 (1970) 673–680.
- [23] P.J. Hornby, P.R. Cooper, C. Kliwinski, E. Ragwan, J.R. Mabus, B. Harman, S. Thompson, A.L. Kauffman, Z. Yan, S.H. Tam, H. Dorai, G.D. Powers, J. Giles-Komar, Human and non-human primate intestinal FcRn expression and immunoglobulin G transcytosis, *Pharm. Res.* 31 (2014) 908–922.
- [24] N.A. Lozano, A. Lozano, V. Marini, R.J. Saranz, R.S. Blumberg, K. Baker, M. F. Agresta, M.F. Ponzio, Expression of FcRn receptor in placental tissue and its relationship with IgG levels in term and preterm newborns, *Am. J. Reprod. Immunol.* 80 (2018), e12972.
- [25] S. Heidl, I. Ellinger, V. Niederberger, E.E. Waltl, R. Fuchs, Localization of the human neonatal Fc receptor (FcRn) in human nasal epithelium, *Protoplasma* 253 (2016) 1557–1564.
- [26] Z. Li, S. Palaniyandi, R. Zeng, W. Tuo, D.C. Roopenian, X. Zhu, Transfer of IgG in the female genital tract by MHC class I-related neonatal Fc receptor (FcRn) confers protective immunity to vaginal infection, *Proc. Natl. Acad. Sci. U. S. A.* 108 (2011) 4388–4393.
- [27] J.P. Haymann, J.P. Levrault, S. Bouet, V. Kappes, J. Hagege, G. Nguyen, Y. Xu, E. Rondeau, J.D. Sraer, Characterization and localization of the neonatal Fc receptor in adult human kidney, *J. Am. Soc. Nephrol.* 11 (2000) 632–639.
- [28] M. Yoshida, S.M. Claypool, J.S. Wagner, E. Mizoguchi, A. Mizoguchi, D. C. Roopenian, W.I. Lencer, R.S. Blumberg, Human neonatal Fc receptor mediates transport of IgG into luminal secretions for delivery of antigens to mucosal dendritic cells, *Immunity* 20 (2004) 769–783.
- [29] M. Pyzik, T. Rath, T.T. Kuo, S. Win, K. Baker, J.J. Hubbard, R. Grenha, A. Gandhi, T.D. Kramer, A.R. Mezo, Z.S. Taylor, K. McDonnell, V. Nienaber, J.T. Andersen, A. Mizoguchi, R. Blumberg, S. Purohit, S.D. Jones, G. Christianson, W.I. Lencer, I. Sandlie, N. Kaplowitz, D.C. Roopenian, R.S. Blumberg, Hepatic FcRn regulates albumin homeostasis and susceptibility to liver injury, *Proc. Natl. Acad. Sci. U. S. A.* 114 (2017) E2862–E2871.
- [30] V. Tenten, S. Menzel, U. Kunter, E.M. Sicking, C.R. van Roeyen, S.K. Sanden, M. Kaldenbach, P. Boor, A. Fuss, S. Uhlig, R. Lanzmich, B. Willemse, H. Dijkman, M. Grepl, K. Wild, W. Kriz, B. Smeets, J. Floege, M.J. Moeller, Albumin is recycled from the primary urine by tubular transcytosis, *J. Am. Soc. Nephrol.* 24 (2013) 1966–1980.
- [31] Y. Matsumura, H. Maeda, A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumorotropic accumulation of proteins and the antitumor agent smancs, *Cancer Res.* 46 (1986) 6387–6392.
- [32] L.D. Crammer, Spotlight on aldoxorubicin (INNO-206) and its potential in the treatment of soft tissue sarcomas: evidence to date, *Onco Targets Ther.* 12 (2019) 2047–2062.
- [33] R. Graeser, D.E. Chung, N. Esser, S. Moor, C. Schachtele, C. Unger, F. Kratz, Synthesis and biological evaluation of an albumin-binding prodrug of doxorubicin that is cleaved by prostate-specific antigen (PSA) in a PSA-positive orthotopic prostate carcinoma model (LNCaP), *Int. J. Cancer* 122 (2008) 1145–1154.
- [34] G. Compain, N. Oumata, J. Clarhaut, E. Peraudeau, B. Renoux, H. Galons, S. Papot, A beta-glucuronidase-responsive albumin-binding prodrug for potential selective kinase inhibitor-based cancer chemotherapy, *Eur. J. Med. Chem.* 158 (2018) 1–6.
- [35] B. Renoux, F. Raes, T. Legigan, E. Peraudeau, B. Eddhif, P. Poinot, I. Tranoy-Opalinski, J. Alsarraff, O. Koniev, S. Kolodoch, S. Lerondel, A. Le Pape, J. Clarhaut, S. Papot, Targeting the tumour microenvironment with an enzyme-responsive drug delivery system for the efficient therapy of breast and pancreatic cancers, *Chem. Sci.* 8 (2017) 3427–3433.
- [36] J.T. Isaacs, S.L. Dalrymple, D.M. Rosen, H. Hammers, A. Olsson, T. Leanderson, Anti-cancer potency of tasquinimod is enhanced via albumin-binding facilitating increased uptake in the tumor microenvironment, *Oncotarget* 5 (2014) 8093–8106.
- [37] V. Brower, Tasquinimod treatment for prostate cancer, *Lancet Oncol.* 17 (2016), e322.
- [38] R. Pili, M. Haggman, W.M. Stadler, J.R. Gingrich, V.J. Assikis, A. Bjork, O. Nordle, G. Forsberg, M.A. Carducci, A.J. Armstrong, Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer, *J. Clin. Oncol.* 29 (2011) 4022–4028.
- [39] A.J. Armstrong, M. Haggman, W.M. Stadler, J.R. Gingrich, V. Assikis, J. Polikoff, J.E. Damber, L. Belkoff, O. Nordle, G. Forsberg, M.A. Carducci, R. Pili, Long-term survival and biomarker correlates of tasquinimod efficacy in a multicenter randomized study of men with minimally symptomatic metastatic castration-resistant prostate cancer, *Clin. Cancer Res.* 19 (2013) 6891–6901.
- [40] M.S. Hassan, N. Awasthi, J. Li, F. Williams, M.A. Schwarz, R.E. Schwarz, U. von Holzen, Superior therapeutic efficacy of nanoparticle albumin bound paclitaxel over cremophor-bound paclitaxel in experimental esophageal adenocarcinoma, *Transl. Oncol.* 11 (2018) 426–435.
- [41] K.C. Mantripragada, H. Safran, Optimizing initial chemotherapy for metastatic pancreatic cancer, *Future Oncol.* 12 (2016) 1125–1133.
- [42] T. Yun, H.T. Kim, J.Y. Han, S.J. Yoon, H.Y. Kim, B.H. Nam, J.S. Lee, A phase II study of weekly paclitaxel plus gemcitabine as a second-line therapy in patients with metastatic or recurrent small cell lung cancer, *Cancer Res.* 48 (2016) 465–472.
- [43] T. Kazemi, V. Younesi, F. Jadidi-Niaragh, M. Yousefi, Immunotherapeutic approaches for cancer therapy: an updated review, *Artif. Cells. Nanomed. Biotechnol.* 44 (2016) 769–779.
- [44] W.Q. Cai, L.S. Zeng, L.F. Wang, Y.Y. Wang, J.T. Cheng, Y. Zhang, Z.W. Han, Y. Zhou, S.L. Huang, X.W. Wang, X.C. Peng, Y. Xiang, Z. Ma, S.Z. Cui, H.W. Xin, The latest battles between EGFR monoclonal antibodies and resistant tumor cells, *Front. Oncol.* 10 (2020) 1249.
- [45] J.Z. Drago, S. Modi, S. Chandrarapathy, Unlocking the potential of antibody-drug conjugates for cancer therapy, *Nat. Rev. Clin. Oncol.* 18 (2021) 327–344.
- [46] A. Papachristos, N. Pippa, C. Demetzos, G. Sivilapenko, Antibody-drug conjugates: a mini-review. The synopsis of two approved medicines, *Drug Deliv.* 23 (2016) 1662–1666.
- [47] H.I. Park, H.W. Yoon, S.T. Jung, The highly evolvable antibody fc domain, *Trends Biotechnol.* 34 (2016) 895–908.
- [48] T.H. Kang, S.T. Jung, Boosting therapeutic potency of antibodies by taming Fc domain functions, *Exp. Mol. Med.* 51 (2019) 1–9.
- [49] G. Sadeghnezhad, E. Romao, R. Bernedo-Navarro, S. Massa, K. Khajeh, S. Muylldermans, S. Hassania, Identification of new DR5 agonistic nanobodies and generation of multivalent nanobody constructs for cancer treatment, *Int. J. Mol. Sci.* 20 (2019).
- [50] H. Xu, I.N. Buhtoiarov, H. Guo, N.V. Cheung, A novel multimeric IL15/IL15Ralpha-Fc complex to enhance cancer immunotherapy, *Oncoimmunology* 10 (2021) 1893500.
- [51] K.T. Xenaki, S. Oliveira, P.M.P. van Bergen En Henegouwen, Antibody or antibody fragments: implications for molecular imaging and targeted therapy of solid tumors, *Front. Immunol.* 8 (2017) 1287.
- [52] G. Martinelli, N. Boissel, P. Chevallier, O. Ottmann, N. Gokbuget, M.S. Topp, A. K. Fielding, A. Rambaldi, E.K. Ritchie, C. Papayannidis, L.R. Sterling, J. Benjamin, A. Stein, Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study, *J. Clin. Oncol.* 35 (2017) 1795–1802.
- [53] C. Kellner, A. Otte, E. Cappuzzello, K. Klausz, M. Peipp, Modulating cytotoxic effector functions by Fc engineering to improve cancer therapy, *Transfus. Med. Hemother.* 44 (2017) 327–336.
- [54] T. Schlothauer, S. Herter, C.F. Koller, S. Grau-Richards, V. Steinhart, C. Spick, M. Kubbies, C. Klein, P. Umana, E. Mossner, Novel human IgG1 and IgG4 Fc-engineered antibodies with completely abolished immune effector functions, *Protein Eng. Des. Sel.* 29 (2016) 457–466.
- [55] J. Zalevsky, A.K. Chamberlain, H.M. Horton, S. Karki, I.W. Leung, T.J. Sproule, G. A. Lazar, D.C. Roopenian, J.R. Desjardins, Enhanced antibody half-life improves in vivo activity, *Nat. Biotechnol.* 28 (2010) 157–159.
- [56] S. Meyer, M. Nederend, J.H. Jansen, K.R. Reiding, S.R. Jacobino, J. Meeldijk, N. Bovenschen, M. Wuhrer, T. Valerius, R. Ubink, P. Boross, G. Rouwendal, J. H. Leusen, Improved in vivo anti-tumor effects of IgA-Her2 antibodies through half-life extension and serum exposure enhancement by FcRn targeting, *MAbs* 8 (2016) 87–98.
- [57] R.M. Stern, N.T. Connell, Ravulizumab: a novel C5 inhibitor for the treatment of paroxysmal nocturnal hemoglobinuria, *Ther. Adv. Hematol.* 10 (2019), 2040620719874728.

- [58] H.P. Montoyo, C. Vaccaro, M. Hafner, R.J. Ober, W. Mueller, E.S. Ward, Conditional deletion of the MHC class I-related receptor FcRn reveals the sites of IgG homeostasis in mice, *Proc. Natl. Acad. Sci. U. S. A.* 106 (2009) 2788–2793.
- [59] W.H. Toh, J. Louber, I.S. Mahmoud, J. Chia, G.T. Bass, S.K. Dower, A. M. Verhagen, P.A. Gleeson, FcRn mediates fast recycling of endocytosed albumin and IgG from early macropinosomes in primary macrophages, *J. Cell Sci.* (2020) 133.
- [60] D.K. Challa, X. Wang, H.P. Montoyo, R. Velmurugan, R.J. Ober, E.S. Ward, Neonatal Fc receptor expression in macrophages is indispensable for IgG homeostasis, *Mabs* 11 (2019) 848–860.
- [61] C. Vaccaro, J. Zhou, R.J. Ober, E.S. Ward, Engineering the fc region of immunoglobulin G to modulate in vivo antibody levels, *Nat. Biotechnol.* 23 (2005) 1283–1288.
- [62] L. Blumberg, J. Humphries, K. Lasseter, R. Blumberg, SYNT001: a humanized IgG4 monoclonal antibody that disrupts the interaction of FcRn and IgG for the treatment of IgG-mediated autoimmune diseases, *Blood* 130 (2017) 3483.
- [63] A.C. Newland, B. Sanchez-Gonzalez, L. Rejto, M. Egyed, N. Romanyuk, M. Godar, K. Verschueren, D. Gandini, P. Ulrichs, J. Beauchamp, T. Dreier, E.S. Ward, M. Michel, H.A. Liebman, H. de Haard, N. Leupin, D.J. Kuter, Phase 2 study of efgartigimod, a novel FcRn antagonist, in adult patients with primary immune thrombocytopenia, *Am. J. Hematol.* 95 (2020) 178–187.
- [64] L.E. Ling, J.L. Hillson, R.G. Tiessen, T. Bosje, M.P. van Iersel, D.J. Nix, L. Markowitz, N.A. Cilfone, J. Duffner, J.B. Streisand, A.M. Manning, S. Arroyo, M281, an anti-FcRn antibody: pharmacodynamics, pharmacokinetics, and safety across the full range of IgG reduction in a first-in-human study, *Clin. Pharmacol. Ther.* 105 (2019) 1031–1039.
- [65] X.P. Zhu, G. Meng, B.L. Dickinson, X.T. Li, E. Mizoguchi, L.L. Miao, Y.S. Wang, C. Robert, B.Y. Wu, P.D. Smith, W.I. Lencer, R.S. Blumberg, MHC class I-related neonatal Fc receptor for IgG is functionally expressed in monocytes, intestinal macrophages, and dendritic cells, *J. Immunol.* 166 (2001) 3266–3276.
- [66] S.W. Qiao, K. Kobayashi, F.E. Johansen, L.M. Solid, J.T. Andersen, E. Milford, D. C. Roopenian, W.I. Lencer, R.S. Blumberg, Dependence of antibody-mediated presentation of antigen on FcRn, *P. Natl. Acad. Sci. USA* 105 (2008) 9337–9342.
- [67] K. Baker, S.W. Qiao, T.T. Kuo, V.G. Aveson, B. Platzter, J.T. Andersen, I. Sandlie, Z.G. Chen, C. de Haar, W.I. Lencer, E. Fiebiger, R.S. Blumberg, Neonatal Fc receptor for IgG (FcRn) regulates cross-presentation of IgG immune complexes by CD8(−)CD11b(+) dendritic cells, *P. Natl. Acad. Sci. USA* 108 (2011) 9927–9932.
- [68] J.J. Hubbard, M. Pyzik, T. Rath, L.K. Kozicky, K.M.K. Sand, A.K. Gandhi, A. Grevys, S. Foss, S.C. Menzies, J.N. Glickman, E. Fiebiger, D.C. Roopenian, I. Sandlie, J.T. Andersen, L.M. Sly, K. Baker, R.S. Blumberg, FcRn is a CD32a co-receptor that determines susceptibility to IgG immune complex-driven autoimmunity, *J. Exp. Med.* (2020) 217.
- [69] G.V. Sharonov, E.O. Serebrovskaya, D.V. Yuzhakova, O.V. Britanova, D. M. Chudakov, B cells, plasma cells and antibody repertoires in the tumour microenvironment, *Nat. Rev. Immunol.* 20 (2020) 294–307.
- [70] K. Baker, T. Rath, M.B. Flak, J.C. Arthur, Z. Chen, J.N. Glickman, I. Zlobec, E. Karamitopoulou, M.D. Stachler, R.D. Odze, W.I. Lencer, C. Jobin, R. S. Blumberg, Neonatal Fc receptor expression in dendritic cells mediates protective immunity against colorectal cancer, *Immunity* 39 (2013) 1095–1107.
- [71] D.C. Castaneda, C. Dhomme, T. Baranek, E. Dalloneau, L. Lajoie, A. Valayer, C. Arnoult, M.V. Demattei, D. Fouquenet, C. Parent, N. Heuze-Vourc'h, V. Gouilleux-Gruart, Lack of FcRn impairs natural killer cell development and functions in the tumor microenvironment, *Front. Immunol.* 9 (2018) 2259.
- [72] F. Pages, A. Berger, M. Camus, F. Sanchez-Cabo, A. Costes, R. Molidor, B. Mlecnik, A. Kirilovsky, M. Nilsson, D. Damotte, T. Meatchi, P. Bruneval, P. H. Cugnenc, Z. Trajanoski, W.H. Fridman, J. Galon, Effector memory T cells, early metastasis, and survival in colorectal cancer, *N. Engl. J. Med.* 353 (2005) 2654–2666.
- [73] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, *Cell* 144 (2011) 646–674.
- [74] O. Warburg, F. Wind, E. Negelein, The metabolism of tumors in the body, *J. Gen. Physiol.* 8 (1927) 519–530.
- [75] R.J. DeBerardinis, N.S. Chandel, Fundamentals of cancer metabolism, *Sci. Adv.* 2 (2016), e1600200.
- [76] M.G. Vander Heiden, L.C. Cantley, C.B. Thompson, Understanding the Warburg effect: the metabolic requirements of cell proliferation, *Science* 324 (2009) 1029–1033.
- [77] Z. Wei, X. Liu, C. Cheng, W. Yu, P. Yi, Metabolism of amino acids in cancer, *Front. Cell. Dev. Biol.* 8 (2020) 603837.
- [78] B. Faubert, K.Y. Li, L. Cai, C.T. Hensley, J. Kim, L.G. Zacharias, C. Yang, Q.N. Do, S. Doucette, D. Burguete, H. Li, G. Huet, Q. Yuan, T. Wigal, Y. Butt, M. Ni, J. Torrealba, D. Oliver, R.E. Lenkinski, C.R. Malloy, J.W. Wachsmann, J.D. Young, K. Kernstine, R.J. DeBerardinis, Lactate metabolism in human lung tumors, *Cell* 171 (2017) 358–371 (e359).
- [79] Z.T. Schug, B. Peck, D.T. Jones, Q. Zhang, S. Grosskurth, I.S. Alam, L.M. Goodwin, E. Smethurst, S. Mason, K. Blyth, L. McGarry, D. James, E. Shanks, G. Kalna, R. E. Saunders, M. Jiang, M. Howell, F. Lassailly, M.Z. Thin, B. Spencer-Dene, G. Stamp, N.J. van den Broek, G. Mackay, V. Bulusu, J.J. Kamphorst, S. Tardito, D. Strachan, A.L. Harris, E.O. Aboagye, S.E. Critchlow, M.J. Wakelam, A. Schulze, E. Gottlieb, Acetyl-CoA synthetase 2 promotes acetate utilization and maintains cancer cell growth under metabolic stress, *Cancer Cell* 27 (2015) 57–71.
- [80] T. Li Huang, L. Wang, L. Zhang, R. Yan, K. Li, S. Xing, G. Wu, L. Hu, W. Jia, S. C. Lin, C.V. Dang, L. Song, P. Gao, H. Zhang, Hepatocellular carcinoma redirects to ketolysis for progression under nutrition deprivation stress, *Cell Res.* 26 (2016) 1112–1130.
- [81] J.B. Spinelli, H. Yoon, A.E. Ringel, S. Jeanfavre, C.B. Clish, M.C. Haigis, Metabolic recycling of ammonia via glutamate dehydrogenase supports breast cancer biomass, *Science* 358 (2017) 941–946.
- [82] A. Stolzing, T. Grune, Neuronal apoptotic bodies: phagocytosis and degradation by primary microglial cells, *FASEB J.* 18 (2004) 743–745.
- [83] S.A. Purcell, S.A. Elliott, V.E. Baracos, Q.S. Chu, C.M. Prado, Key determinants of energy expenditure in cancer and implications for clinical practice, *Eur. J. Clin. Nutr.* 70 (2016) 1230–1238.
- [84] H. Suzuki, A. Asakawa, H. Amitani, N. Nakamura, A. Inui, Cancer cachexia-pathophysiology and management, *J. Gastroenterol.* 48 (2013) 574–594.
- [85] M.J. Tisdale, Cachexia in cancer patients, *Nat. Rev. Cancer* 2 (2002) 862–871.
- [86] B.L. Prado, Y. Qian, Anti-cytokines in the treatment of cancer cachexia, *Ann. Palliat. Med.* 8 (2019) 67–79.
- [87] K.C. Fearon, J.S. Falconer, C. Slater, D.C. McMillan, J.A. Ross, T. Preston, Albumin synthesis rates are not decreased in hypoalbuminemic cachectic cancer patients with an ongoing acute-phase protein response, *Ann. Surg.* 227 (1998) 249–254.
- [88] P.B. Soeters, R.R. Wolfe, A. Shenkin, Hypoalbuminemia: pathogenesis and clinical significance, *JPEN J. Parenter. Enteral Nutr.* 43 (2019) 181–193.
- [89] A.M. Waters, C.J. Der, KRAS: the critical driver and therapeutic target for pancreatic cancer, *Cold Spring Harb. Perspect. Med.* (2018) 8.
- [90] A.A. Khan, X. Liu, X. Yan, M. Tahir, S. Ali, H. Huang, An overview of genetic mutations and epigenetic signatures in the course of pancreatic cancer progression, *Cancer Metastasis Rev.* 40 (2021) 245–272.
- [91] H. Liu, M. Sun, Z. Liu, C. Kong, W. Kong, J. Ye, J. Gong, D.C.S. Huang, F. Qian, KRAS-enhanced macropinocytosis and reduced FcRn-mediated recycling sensitize pancreatic cancer to albumin-conjugated drugs, *J. Control. Release* 296 (2019) 40–53.
- [92] R. Swiercz, M. Mo, P. Khare, Z. Schneider, R.J. Ober, E.S. Ward, Loss of expression of the recycling receptor, FcRn, promotes tumor cell growth by increasing albumin consumption, *Oncotarget* 8 (2017) 3528–3541.
- [93] M.P. Jansen, J.A. Foekens, I.L. van Staveren, M.M. Dirkzwager-Kiel, K. Ritstier, M.P. Look, M.E. Meijer-van Gelder, A.M. Sieuwerts, H. Portengen, L.C. Dorssers, J.G. Klijn, E.M. Berns, Molecular classification of tamoxifen-resistant breast carcinomas by gene expression profiling, *J. Clin. Oncol.* 23 (2005) 732–740.
- [94] L. Shi, W. Zhang, F. Zou, L. Mei, G. Wu, Y. Teng, KLHL21, a novel gene that contributes to the progression of hepatocellular carcinoma, *BMC Cancer* 16 (2016) 815.
- [95] E. Dalloneau, N. Baroukh, K. Mavridis, A. Maillet, F. Gueugnon, Y. Courty, A. Petit, T. Kryza, M. Del Rio, S. Guyetant, D.C. Cadena Castaneda, C. Dhomme, C. Arnoult, A. Scorrias, V. Gouilleux-Gruart, N. Heuze-Vourc'h, Downregulation of the neonatal Fc receptor expression in non-small cell lung cancer tissue is associated with a poor prognosis, *Oncotarget* 7 (2016) 54415–54429.
- [96] X. Wang, W. Sheng, Y. Wang, L. Li, Y. Li, S. Zhang, X. Liu, S. Chen, Y. Zhen, A macropinocytosis-intensifying albumin domain-based scFv antibody and its conjugate directed against K-Ras mutant pancreatic cancer, *Mol. Pharm.* 15 (2018) 2403–2412.
- [97] J.T. Andersen, B. Dalhus, J. Cameron, M.B. Daba, A. Plumridge, L. Evans, S. O. Brennan, K.S. Gunnarsen, M. Bjoras, D. Sleep, I. Sandlie, Structure-based mutagenesis reveals the albumin-binding site of the neonatal Fc receptor, *Nat. Commun.* 3 (2012) 610.
- [98] G. Muller-Greven, C.R. Carlin, M.E. Burgett, M.S. Ahluwalia, A. Lauko, A. S. Nowacki, C.J. Herting, M.A. Qadan, M. Bredel, S.A. Toms, J.D. Lathia, D. Hambardzumyan, J.N. Sarkaria, P. Hamerlik, C.L. Gladson, Macropinocytosis of bevacizumab by glioblastoma cells in the perivascular niche affects their survival, *Clin. Cancer Res.* 23 (2017) 7059–7071.
- [99] P.P. Hsu, D.M. Sabatini, Cancer cell metabolism: Warburg and beyond, *Cell* 134 (2008) 703–707.
- [100] E.N. Hoogenboezem, C.L. Duvall, Harnessing albumin as a carrier for cancer therapies, *Adv. Drug Deliv. Rev.* 130 (2018) 73–89.
- [101] J.J. Kamphorst, M. Nofal, C. Commissio, S.R. Hackett, W. Lu, E. Grabocka, M. G. Vander Heiden, G. Miller, J.A. Drebins, D. Bar-Sagi, C.B. Thompson, J. D. Rabinowitz, Human pancreatic cancer tumors are nutrient poor and tumor cells actively scavenge extracellular protein, *Cancer Res.* 75 (2015) 544–553.
- [102] B.T. Finicle, V. Jayashankar, A.L. Edinger, Nutrient scavenging in cancer, *Nat. Rev. Cancer* 18 (2018) 619–633.
- [103] W. Palm, Y. Park, K. Wright, N.N. Pavlova, D.A. Tuveson, C.B. Thompson, The utilization of extracellular proteins as nutrients is suppressed by mTORC1, *Cell* 162 (2015) 259–270.
- [104] K. Nishi, K. Yamasaki, M. Otagiri, Serum albumin, lipid and drug binding, *Subcell. Biochem.* 94 (2020) 383–397.
- [105] W. Stremmel, L. Pohl, A. Ring, T. Herrmann, A new concept of cellular uptake and intracellular trafficking of long-chain fatty acids, *Lipids* 36 (2001) 981–989.
- [106] G.J. van der Vusse, M. van Bilsen, J.F. Glatz, D.M. Hasselbalck, J.J. Luijken, Critical steps in cellular fatty acid uptake and utilization, *Mol. Cell. Biochem.* 239 (2002) 9–15.
- [107] P. Cianga, C. Cianga, L. Cozma, E.S. Ward, E. Carasevici, The MHC class I related Fc receptor, FcRn, is expressed in the epithelial cells of the human mammary gland, *Hum. Immunol.* 64 (2003) 1152–1159.
- [108] E. Palma, B. Randlev, P. Wen, S. Ulufatu, K. Howell, C.A. Boswell, L. Khawli, H. Koeppen, G. Meng, S. Scales, J. Tibbitts, Abstract A138: evaluation of neonatal Fc receptor (FcRn) expression and function in tumor cell lines and their potential effect on IgG disposition in solid tumors, *Mol. Cancer Ther.* 10 (2011) A138.
- [109] M.T. Larsen, O.A. Mandrup, K.K. Schelde, Y. Luo, K.D. Sorensen, F. Dagnæs-Hansen, J. Cameron, M. Stougaard, T. Steiniche, K.A. Howard, FcRn overexpression in human cancer drives albumin recycling and cell growth; a

- mechanistic basis for exploitation in targeted albumin-drug designs, *J. Control. Release* 322 (2020) 53–63.
- [110] W. Stremmel, Transmembrane transport of fatty acids in the heart, *Mol. Cell. Biochem.* 88 (1989) 23–29.
- [111] G.J. van der Vusse, M. van Bilsen, J.F. Glatz, Cardiac fatty acid uptake and transport in health and disease, *Cardiovasc. Res.* 45 (2000) 279–293.
- [112] D. Vilasalju, C. Alexander, M. Garnett, M. Eaton, S. Stolnik, Fc-mediated transport of nanoparticles across airway epithelial cell layers, *J. Control. Release* 158 (2012) 479–486.
- [113] E.M. Pridgen, F. Alexis, T.T. Kuo, E. Levy-Nissenbaum, R. Karnik, R.S. Blumberg, R. Langer, O.C. Farokhzad, Transepithelial transport of Fc-targeted nanoparticles by the neonatal fc receptor for oral delivery, *Sci. Transl. Med.* 5 (2013), 213ra167.
- [114] M. Bern, J. Nilsen, M. Ferrarese, K.M.K. Sand, T.T. Gjolberg, H.E. Lode, R. J. Davidson, R.M. Camire, E.S. Baekkevold, S. Foss, A. Greveys, B. Dahlus, J. Wilson, L.S. Hoydahl, G.J. Christianson, D.C. Roopenian, T. Schlothauer, T. E. Michaelson, M.C. Moe, S. Lombardi, M. Pinotti, I. Sandlie, A. Branchini, J. T. Andersen, An engineered human albumin enhances half-life and transmucosal delivery when fused to protein-based biologics, *Sci. Transl. Med.* (2020) 12.
- [115] N. Joubert, C. Denevaud-Sabourin, F. Bryden, M.C. Viaud-Massuard, Towards antibody-drug conjugates and prodrug strategies with extracellular stimuli-responsive drug delivery in the tumor microenvironment for cancer therapy, *Eur. J. Med. Chem.* 142 (2017) 393–415.
- [116] S.L. Harwood, A. Alvarez-Cienfuegos, N. Nunez-Prado, M. Compte, S. Hernandez-Perez, N. Merino, J. Bonet, R. Navarro, P.M.P. Van Bergen En Henegouwen, S. Lykkenmark, K. Mikkelsen, K. Molgaard, F. Jabs, L. Sanz, F.J. Blanco, P. Roda-Navarro, L. Alvarez-Vallina, ATTACK, a novel bispecific T cell-recruiting antibody with trivalent EGFR binding and monovalent CD3 binding for cancer immunotherapy, *Oncoimmunology* 7 (2017) e1377874.
- [117] K. Molgaard, S.L. Harwood, M. Compte, N. Merino, J. Bonet, A. Alvarez-Cienfuegos, K. Mikkelsen, N. Nunez-Prado, A. Alvarez-Mendez, L. Sanz, F. J. Blanco, L. Alvarez-Vallina, Bispecific light T-cell engagers for gene-based immunotherapy of epidermal growth factor receptor (EGFR)-positive malignancies, *Cancer Immunol. Immunother.* 67 (2018) 1251–1260.
- [118] O.A. Mandrup, S.C. Ong, S. Lykkenmark, A. Dinesen, I. Rudnik-Jansen, N. F. Dagnæs-Hansen, J.T. Andersen, L. Alvarez-Vallina, K.A. Howard, Programmable half-life and anti-tumour effects of bispecific T-cell engager-albumin fusions with tuned FcRn affinity, *Commun. Biol.* 4 (2021) 310.
- [119] D. Viuff, F. Antunes, L. Evans, J. Cameron, H. Dyrnesli, B. Thue Ravn, M. Stougaard, K. Thiam, B. Andersen, S. Kjaerulff, K.A. Howard, Generation of a double transgenic humanized neonatal Fc receptor (FcRn)/albumin mouse to study the pharmacokinetics of albumin-linked drugs, *J. Control. Release* 223 (2016) 22–30.
- [120] J.L. Leach, D.D. Sedmak, J.M. Osborne, B. Rahill, M.D. Lairmore, C.L. Anderson, Isolation from human placenta of the IgG transporter, FcRn, and localization to the syncytiotrophoblast: implications for maternal-fetal antibody transport, *J. Immunol.* 157 (1996) 3317–3322.
- [121] M. Scaranti, E. Cojocaru, S. Banerjee, U. Banerji, Exploiting the folate receptor alpha in oncology, *Nat. Rev. Clin. Oncol.* 17 (2020) 349–359.
- [122] C.R. Brown, S. Gupta, J. Qin, T. Racie, G. He, S. Lentini, R. Malone, M. Yu, S. Matsuda, S. Shulga-Morskaya, A.V. Nair, C.S. Theile, K. Schmidt, A. Shahraz, V. Goel, R.G. Parmar, I. Zlatev, M.K. Schlegel, J.K. Nair, M. Jayaraman, M. Manoharan, D. Brown, M.A. Maier, V. JadHAV, Investigating the pharmacodynamic durability of GalNAc-siRNA conjugates, *Nucleic Acids Res.* 48 (2020) 11827–11844.
- [123] K.A. Howard, M. Dong, D. Oupicky, H.S. Bisht, C. Buss, F. Besenbacher, J. Kjems, Nanocarrier stimuli-activated gene delivery, *Small* 3 (2007) 54–57.
- [124] U.L. Rahbek, K.A. Howard, D. Oupicky, D.S. Manickam, M. Dong, A.F. Nielsen, T. B. Hansen, F. Besenbacher, J. Kjems, Intracellular siRNA and precursor miRNA trafficking using bioresponsive copolymer peptides, *J. Gene Med.* 10 (2008) 81–93.
- [125] T. Luhmann, L. Meinel, Nanotransporters for drug delivery, *Curr. Opin. Biotechnol.* 39 (2016) 35–40.
- [126] S.S. Petersen, E. Klaning, M.F. Ebbesen, B. Andersen, J. Cameron, E.S. Sorensen, K.A. Howard, Neonatal Fc receptor binding tolerance toward the covalent conjugation of payloads to cysteine 34 of human albumin variants, *Mol. Pharm.* 13 (2016) 677–682.
- [127] J. Schmoker, A. Voldum, G. Tsakiridou, M. Kuhlmann, J. Cameron, E.S. Sorensen, J. Wengel, K.A. Howard, Site-selective conjugation of an anticoagulant aptamer to recombinant albumins and maintenance of neonatal Fc receptor binding, *Nanotechnology* 28 (2017) 204004.
- [128] J.T. Sockolosky, M.R. Tiffany, F.C. Szoka, Engineering neonatal Fc receptor-mediated recycling and transcytosis in recombinant proteins by short terminal peptide extensions, *Proc. Natl. Acad. Sci. U. S. A.* 109 (2012) 16095–16100.
- [129] H.J. Kang, Y.J. Kang, Y.M. Lee, H.H. Shin, S.J. Chung, S. Kang, Developing an antibody-binding protein cage as a molecular recognition drug modular nanoplatform, *Biomaterials* 33 (2012) 5423–5430.
- [130] L. D'Hooghe, A.D. Chalmers, S. Heywood, P. Whitley, Cell surface dynamics and cellular distribution of endogenous FcRn, *PLoS One* 12 (2017), e0182695.
- [131] W.I. Lencer, R.S. Blumberg, A passionate kiss, then run: exocytosis and recycling of IgG by FcRn, *Trends Cell Biol.* 15 (2005) 5–9.
- [132] V. Estrella, T. Chen, M. Lloyd, J. Wojtkowiak, H.H. Cornell, A. Ibrahim-Hashim, K. Bailey, Y. Balagurunathan, J.M. Rothberg, B.F. Sloane, J. Johnson, R. A. Gatenby, R.J. Gillies, Acidity generated by the tumor microenvironment drives local invasion, *Cancer Res.* 73 (2013) 1524–1535.
- [133] E. Boedtkjer, S.F. Pedersen, The acidic tumor microenvironment as a driver of cancer, *Annu. Rev. Physiol.* 82 (2020) 103–126.
- [134] M.R. Sullivan, M.G. Vander Heiden, Determinants of nutrient limitation in cancer, *Crit. Rev. Biochem. Mol. Biol.* 54 (2019) 193–207.
- [135] H.S. Lai, J.C. Lee, P.H. Lee, S.T. Wang, W.J. Chen, Plasma free amino acid profile in cancer patients, *Semin. Cancer Biol.* 15 (2005) 267–276.
- [136] V.E. Baracos, L. Martin, M. Korc, D.C. Guttridge, K.C.H. Fearon, Cancer-associated cachexia, *Nat. Rev. Dis. Prim.* 4 (2018) 17105.
- [137] N.M. Anderson, M.C. Simon, The tumor microenvironment, *Curr. Biol.* 30 (2020) R921–R925.
- [138] X. Liu, L. Ye, G.J. Christianson, J.Q. Yang, D.C. Roopenian, X. Zhu, NF-kappaB signaling regulates functional expression of the MHC class I-related neonatal Fc receptor for IgG via intronic binding sequences, *J. Immunol.* 179 (2007) 2999–3011.