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·综　述·

新生儿Fc受体基础研究和临床应用进展

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[**摘　要**] 新生儿Fc受体(FcRn)是免疫球蛋白G(IgG)和白蛋白的特异性受体,通过酸碱度依赖的方式与两者结合,使IgG和白蛋白免于被溶酶体降解而拥有较长的血浆半衰期。FcRn具有实现IgG和白蛋白的跨膜转运及促进抗原提呈的作用。在自身免疫病中,抗FcRn抗体可以通过竞争性结合FcRn,促进致病性IgG的降解;在传染性疾病中,通过增加治疗抗体与FcRn的亲和力,可以延长药物半衰期,而将病毒抗原与IgG的Fc片段结合可以引起黏膜的局部免疫反应,用于疾病防治;在癌症中,FcRn的配体白蛋白作为抗癌药物的载体,可以实现高效给药,而FcRn本身或许可以作为肿瘤患者预后的预测指标。本文综述了FcRn的功能、相关药物研发机制及其在自身免疫病、传染性疾病和癌症中的作用,以期为FcRn的药物研发和临床应用提供参考。

[**关键词**] 新生儿Fc受体;免疫球蛋白G;白蛋白;自身免疫病;传染病;癌症;综述
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Research progress on neonatal Fc receptor and its application

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[**Abstract**] Neonatal Fc receptor (FcRn) is a specific receptor for immunoglobulin G (IgG) and albumin, which binds to them in a pH-dependent manner and prevents them from lysosomal degradation to keep a long plasma half-life. In addition, FcRn plays an

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important role in transmembrane transport of IgG and albumin and in antigen presentation. In autoimmune diseases, anti-FcRn antibody can promote the degradation of pathogenic IgG by competitive binding to FcRn. In infectious diseases, the half-life of drugs can be prolonged by increasing the affinity between therapeutic antibody and FcRn, while the combination of viral antigen and Fc fragment of IgG can cause local immune response of mucosa for disease prevention and treatment. In cancer, albumin as a carrier of anticancer drugs can achieve efficient drug delivery, and FcRn itself may be used as a predictor of the prognosis of cancer patients. This review details the functions of FcRn, highlights its role in autoimmune diseases, infectious diseases and cancer, as well as the mechanism of drug development based on FcRn, to provide a reference for the clinical application and drug development of FcRn.

[**Key words**] Neonatal Fc receptor; Immunoglobulin G; Albumin; Autoimmune disease; Infectious disease; Cancer; Review

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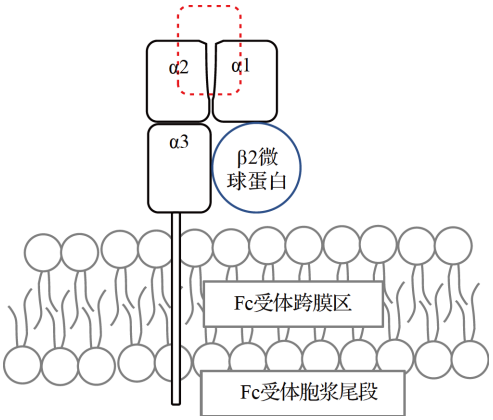
[**缩略语**] 新生儿Fc受体(neonatal Fc receptor,FcRn);免疫球蛋白G(immunoglobulin G,IgG);主要组织相容性复合体(major histocompatibility complex,MHC)

FcRn是IgG和白蛋白的特异性受体,由MHC Ⅰ类相关分子和β2微球蛋白组成[1]。FcRn通过酸碱度依赖的方式与IgG和白蛋白结合,维持IgG和白蛋白在血浆中的浓度,实现两者的跨膜转运[2]。此外,FcRn可以结合并促进IgG-抗原复合物多聚体的降解,增强抗原提呈细胞的抗原提呈作用[3]。以FcRn为靶点的药物在临床上有巨大潜力,如在自身免疫病的治疗中,抗FcRn抗体通过阻断FcRn介导的细胞内IgG再循环途径精准靶向致病性抗体[4]。近年来,抗FcRn抗体成为各大制药公司的开发热点及并购目标。2020年10月,美国Johnson & Johnson公司宣布将以65亿美元收购美国Momenta Pharmaceuticals公司,后者的核心产品就是抗FcRn单抗药物Nipocalimab[5]。本文综述了FcRn的功能及其临床药物的设计机制,并介绍了FcRn在自身免疫病、传染性疾病及癌症中的作用,以期为药物研发和临床应用提供参考。

1　FcRn的功能

1.1　介导抗体再循环

FcRn是由一条重链和一条轻链非共价结合组成的异二聚体[6]。重链的结构类似MHC Ⅰ类分子,具有一个胞浆尾段、一个跨膜区以及α1、α2、α3三个胞外功能段。三个胞外功能段与轻链(β2微球蛋白)共同成为FcRn与IgG的作用位点[7-10](图1)。FcRn与IgG的结合呈酸碱度依赖性,这是FcRn实现IgG的跨膜转运及维持血浆IgG水平稳态的基础。在弱酸性(酸碱度5.0~6.5)环境中,IgG-Fc段CH_2-CH_3铰链区域中的氨基酸残基His310和His435发生质子化,易与FcRn的酸性氨基酸残基(Glu115和Asp130)结合,显示出IgG与



虚线方框所选结构对应主要组织相容性复合体Ⅰ类分子的α1-α2所形成的抗原提呈槽,在Fc受体中,该处为封闭状态.

图1　新生儿Fc受体结构示意图

Figure 1　Structure of the neonatal Fc receptor

FcRn的高亲和力;而在中性或碱性条件下,IgG与FcRn的亲和力因为His310和His435的去质子化而大大降低[2,7,11]。血管内皮是FcRn介导IgG再循环的主要部位,包含IgG在内的细胞外液被细胞非特异性胞饮后,与含有FcRn的酸性内体融合,暴露于酸性环境中的IgG与FcRn结合形成复合物,随后出芽形成不含其他蛋白质的微泡并返回细胞膜,接触弱碱性的血浆时,IgG从FcRn上释放进入血液循环[12-14](图2),因此IgG比其他类型的抗体具有更长的半衰期[15]。

1.2 介导IgG跨膜转运

血管内皮中的FcRn不仅可以参与IgG的循环,还可以介导IgG从细胞顶端到基底外侧表面的转运过程(图2),这一过程也在上皮细胞中得到体现。作为唯一可通过胎盘屏障的抗体,来自母体的IgG对于胎儿初期的免疫至关重要,而这依赖于合胞体滋养层细胞囊泡中存在的FcRn[16-17]。被胞饮的IgG与内体中的FcRn结合后被转运至合胞体滋养层基底侧,近中性的酸碱度使IgG从FcRn上解离进入胎儿的血液循环。此外,FcRn还在呼吸道、肠、肾、中枢神经系统的脑微血管内皮和脉络丛上皮中表达,介导IgG的转运[18-21]。

1.3 增强抗原提呈

FcRn的重链类似MHC Ⅰ类分子,然而其抗原提呈槽为封闭状态(图1),不能直接向T细胞和自然杀伤细胞提呈抗原肽[22]。Qiao等[3]发现,不同于IgG单体和小的IgG-抗原复合物,IgG-抗原形成的多聚体将由FcRn转运至溶酶体中进行抗原的降解及抗原肽向MHC Ⅱ类分子、MHC Ⅰ类分子上的装载(图2)。之后该团队用右旋糖酐硫酸钠进行小鼠结肠炎的造模,发现与FcRn缺失的小鼠模型相比,野生型小鼠在给予右旋糖酐硫酸钠后表现出更严重的结肠炎[23]。研究者推测这与FcRn通过增强抗原提呈激活T细胞相关。该团队还发现在Fcγ受体介导IgG-抗原复合物摄取后,FcRn的细胞内途径对于$CD8^{-}CD11b^{+}$树突细胞交叉呈递极低浓度的IgG复合抗原是必要的[24]。

虽然白蛋白与FcRn的结合位点与IgG不相同[25-26],但FcRn也通过依赖于酸碱度的结合方式介导白蛋白的跨膜转运和长半衰期的维持。

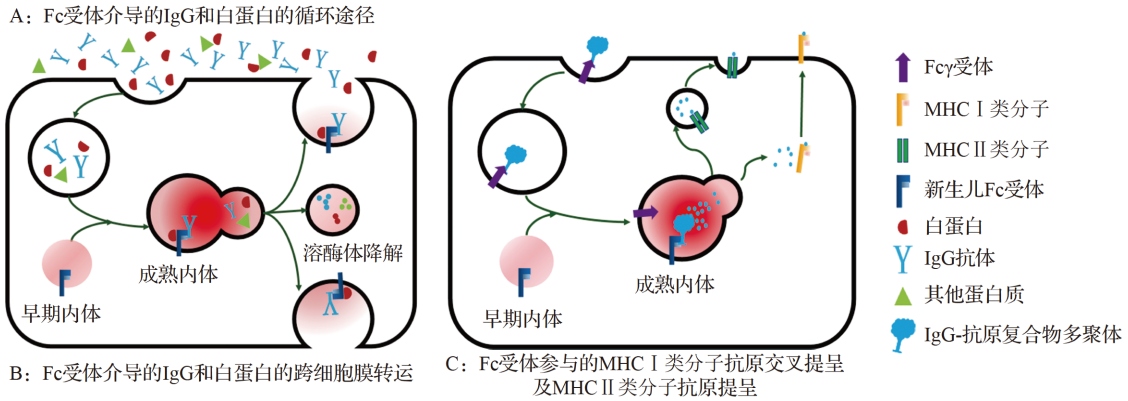
2 基于FcRn功能开发的药物设计机制

2.1 增加单克隆抗体与FcRn在酸性环境中的亲和力以延长抗体半衰期

IgG上Thr250、Met252、Ser254、Thr256、Thr307、Glu380、Met428、His433和Asn434位置的各种突变可以改变IgG与FcRn的亲和力,且其中一些突变的组合可以产生协同作用,进一步提高与FcRn的亲和力[27]。该机制最重要的是提高IgG与FcRn在酸性环境中的结合,而不影响两者在中性和弱碱性环境中的解离。

2.2 增加IgG在中性环境中与FcRn的亲和力以增加抗原抗体复合物的摄取

抗原抗体复合物被细胞内吞后通过FcRn保



A:细胞通过胞吞作用摄取细胞外的免疫球蛋白G(IgG)抗体、白蛋白及其他蛋白质,形成的囊泡与含有Fc受体的早期内体融合后,IgG及白蛋白可以通过与细胞膜上的Fc受体结合而避免被溶酶体降解;B:在肠道、呼吸道、胎盘等部位的Fc受体可以进一步将与之结合的IgG和白蛋白转运至细胞基底侧,实现跨膜转运;C:IgG-抗原复合物多聚体与抗原提呈细胞上的Fcγ受体结合后被胞吞形成囊泡,当与含有Fc受体的早期内体融合后,随着所处环境酸碱度的下降, IgG-抗原复合物多聚体与Fcγ受体分离而与Fc受体结合,并被转运至溶酶体进一步分解成抗原肽,最后由主要组织相容性复合体(MHC)Ⅰ类分子及MHC Ⅱ类分子提呈至细胞表面.

图 2 新生儿Fc受体的功能示意图

Figure 2 The function of the neonatal Fc receptor

护途径再循环到血液中,而抗原抗体复合物相比抗原相对分子质量较大,不易被肾脏滤过,易造成血浆抗原积聚[28]。通过改造抗体可变区得到的酸碱度依赖性抗原结合再循环抗体和钙离子依赖性抗原结合再循环抗体,可以分别在内体的酸性环境和低钙离子浓度条件下与抗原解离,抗原在溶酶体中被降解的同时,抗体则被FcRn介导至循环中继续发挥作用[29-31]。清道夫抗体则是再循环抗体的进一步变体,经过Fc段改造后其与FcRn在中性环境中(如细胞外)的亲和力大大增加。增强的亲和力将抗体锚定在细胞表面的FcRn上,作为“内吞受体”结合细胞外的抗原,加强抗体-抗原复合物的摄取及抗原的清除[32]。

2.3 减弱致病性IgG或白蛋白与FcRn的亲和力以加速其清除

通过设计与FcRn亲和力更高的药物与IgG或白蛋白竞争性结合位点,去除多余或异常的IgG和蛋白质,目前这一机制在自身免疫病的研究中最深入。或改变目标抗体与FcRn结合相关的Fc区,以此缩短抗体半衰期,如在利用放射性标记的抗体进行放射成像时,抗体的半衰期过长会干扰成像及损伤机体,而与FcRn亲和力低的放射性标记的抗体半衰期短,不良反应减少[33]。

2.4 搭载药物于IgG和白蛋白上以实现药物跨膜转运

Bern等[34]在白蛋白羧基末端结构域Ⅲ引入E505Q、T527M和K573P突变,得到与FcRn亲和力增加的白蛋白变体E505Q/T527M/K573P(QMP)。搭载于QMP上的重组凝血因子Ⅷ不仅保留了治疗特性,半衰期也大大延长。Azevedo等[35]则将包载胰岛素的纳米微粒与蛋白变体结合,达到口服经肠黏膜高效给药的目的。该蛋白变体包含一个增加FcRn结合的K573P定点突变及一个防止与其他受体结合的K500A/H464Q定点突变[36-37]。当搭载的“药物”为抗原时,则可以借助FcRn跨膜转运含有抗原的IgG,在黏膜固有层将抗原递呈给抗原提呈细胞,引起如肠黏膜、呼吸道黏膜等处的局部免疫反应,应用于疫苗的开发设计。

3 基于FcRn功能开发的药物临床应用

3.1 应用于自身免疫病

自身免疫病的致病机制主要是机体对自身抗原发生免疫反应,产生致病性抗体[38-39],而抗FcRn治疗正是通过阻断FcRn介导的细胞内IgG再循环途径来加速致病性IgG分解代谢,从而达到治疗的目的。目前,用于自身免疫病治疗的FcRn相关药物主要分为Fc片段和抗FcRn单克隆抗体两类。

Efgartigimod(ARGX-113)是起源于IgG1的Fc片段,其5个氨基酸残基经由荷兰arGEN-X公司的ABDEG技术诱导突变,在中性及酸性环境中与FcRn的亲和力大大增强[4]。临床研究(NCT03457649)显示,Efgartigimod单次给药后可将IgG水平降低50%,而多次给药后IgG水平可进一步降低至25%,且IgG水平恢复到基线水平的时间可持续至最后一次给药后的8周[4]。随后开展的将Efgartigimod用于治疗重症肌无力患者的临床Ⅱ期、Ⅲ期试验不仅证实了这一结果,更是通过一系列量表评分的变化展现了Efgartigimod为患者带来的直接临床效益[40-41]。除了重症肌无力,Efgartigimod还被用于治疗由致病性IgG介导的多种严重自身免疫病,如免疫性血小板减少性紫癜、寻常型天疱疮、慢性炎性脱髓鞘性多发性神经病[42]。目前,Efgartigimod已被欧盟委员会批准作为治疗重症肌无力患者的罕用药。

Nipocalimab (M281)是一种靶向FcRn的人源化IgG1单克隆抗体,可以在细胞内(酸碱度为6)及细胞外(酸碱度为7.6)与FcRn高亲和力结合[43]。在人类胎盘灌注模型中,应用Nipocalimab后的4~6 h内,IgG从母体循环到胎儿循环的转移受到抑制,而Nipocalimab由母体循环向胎儿循环的转移不显著,表明FcRn起效快且母体服用Nipocalimab可降低胎儿和新生儿药物暴露的风险[44]。目前正在进行的Nipocalimab相关临床试验主要围绕重症肌无力(NCT03772587)、胎儿和新生儿溶血病(NCT03755128)和温抗体型自身免疫性溶血性贫血(NCT04119050)的治疗。其他抗FcRn单克隆抗体还包括SYNT001(ALXN1830)[45-46]、Rozanolixizumab(UCB7665)[47-49]、Batoclimab(HBM9161)[50]、ABY-039[51]等,已有的临床试验结果表明,抗FcRn单克隆抗体具有良好的疗效和耐受性。此外,Cines等[52]在用SYNT001进行试验时发现,加入SYNT001实验组的凝血因子X的活性与对照组相比降低了62.8%,从而提出FcRn可放大IgG免疫复合物对组织因子活性的诱导的设想,并发现利用FcRn靶向治疗自身免疫病时带来的另一个益处——降低静脉血栓栓塞的风险。

Liu等[53]最近发现,人巨细胞病毒的US11蛋白可以通过Derlin-1/TMEM129介导的内质网相关降解途径降解FcRn,导致肠或胎盘上皮细胞的IgG转运减少以及血管内皮细胞中IgG抗体的降解增多,从而使病毒逃避免疫系统的攻击。该团队据此提出可通过人巨细胞病毒的US11蛋白阻断FcRn功能和促进自身反应性IgG的破坏来治疗自身免疫病的设想。

3.2 应用于传染性疾病

3.2.1 预防传染性疾病 黏膜是病毒入侵人体的第一道防线,有效的黏膜局部免疫反应对于人体预防感染至关重要,而这依赖于黏膜存在有效的抗体浓度[54]。Yoshida等[55]发现,肠道细胞表达的FcRn可以介导IgG穿过肠黏膜屏障至肠腔内侧,当IgG与抗原充分接触形成免疫复合物后,FcRn再将该复合物从肠腔侧转运到基底侧,并通过树突细胞的提取诱导黏膜形成局部的免疫反应。Lu等[56]将人获得性免疫缺陷病毒的Gag(p24)蛋白融合到IgG的Fc上,用Gag-Fc加佐剂对小鼠进行鼻内免疫,小鼠不仅在肺部产生免疫反应,而且在阴道黏膜等部位也发现了免疫细胞的应答。而Zhang等[57]则将呼吸道合胞病毒的F蛋白与IgG的Fc片段融合得到F-Fc滴鼻免疫,通过FcRn传递,在小鼠肺部产生了高效价抗体。上述研究结果提示,利用嵌合免疫原通过FcRn引起黏膜局部免疫反应的现象可能是用来设计预防性病毒疫苗的一种有效方法。

3.2.2 治疗传染性疾病 通过增强抗病毒抗体与FcRn的亲和力可以延长抗体半衰期,增加抗体的作用时间和效力。Ko等[58]利用定点突变的方法修饰VRC01(一种针对HIV-1包膜糖蛋白CD4结合位点的广泛中和性单克隆抗体)以获得与FcRn亲和力更强的抗体VRC01-LS。在小鼠模型中发现VRC01-LS可以在未明显改变与Fcγ受体Ⅲa结合的能力以及抗体依赖性细胞介导的细胞毒性活性的前提下,显著延长抗体在血清中的半衰期。在Ⅰ期临床试验(NCT02599896)中,VRC01-LS在血清中的半衰期比VRC01增加了近4倍[59]。

研究发现,改造呼吸道合胞病毒单克隆抗体(MEDI-524)[60]和乙型肝炎病毒单克隆抗体(huE6F6)[61]的Fc片段,可增加与FcRn的亲和性,延长两种治疗性抗体的半衰期。在2019冠状病毒病治疗中,美国Vir Biotechnology公司与Xencor公司合作,希望借助其独有的Xtend XmAb Fc技术延长抗2019冠状病毒病病原体——严重急性呼吸综合征冠状病毒2的中和抗体在血液中的半衰期,而这一技术的关键在于改造抗体的Fc,以提高与FcRn受体的亲和力[62]。

Zhao等[63]通过CRISPR/Cas 9文库筛选发现FcRn是介导大部分肠道病毒脱壳的受体。用埃可病毒6型感染FcRn缺失的细胞无法观测到细胞感染的阳性信号和病毒繁殖的信号,说明FcRn的存在增加了细胞对于埃可病毒6型的易感性[63]。这一发现为将来抗肠道病毒药物的研发提供了新思路。

3.3 应用于癌症

3.3.1 预测肿瘤患者转归 肺癌、结直肠癌、乳腺癌、前列腺癌、肝癌相关临床研究数据显示,FcRn表达水平下调可能与疾病的不良预后相关[64-67]。但也有研究发现,与接受*FcRn*基因敲除的细胞移植物相比,接受FcRn高表达人结直肠癌细胞异种移植物的小鼠的肿瘤在28 d内生长加速[68],表明FcRn介导肿瘤的生长效应。此外,与野生型白蛋白相比,乳腺癌异种移植物中荧光标记的高结合FcRn型白蛋白的积累增加了两倍[68],推测可能是高表达的FcRn促进了白蛋白在肿瘤内的聚集,为肿瘤生长提供了营养来源。FcRn表达的上调和下调都可能引起患者预后的改变,因此其作为预后标志是否具有组织特异性、疾病进展阶段相关性仍须进一步探讨。

3.3.2 抗肿瘤治疗 Castaneda等[69]发现,FcRn表达缺陷小鼠的自然杀伤细胞形态幼稚,功能也更不成熟,主要表现为产生γ干扰素的能力下降,提示FcRn可以通过促进自然杀伤细胞的成熟进行抗肿瘤治疗。在FcRn低表达的癌症患者中,FcRn介导的白蛋白循环减弱,使白蛋白在肿瘤细胞内的降解增加,因此可以将抗癌药物搭载于白蛋白上,促进抗癌药物靶向病灶,如阿霉素偶联白蛋白在胰腺癌中显示出更好的肿瘤抑制作用[70]。而在FcRn过表达的癌症患者中,携带荧光的靶向FcRn的单克隆抗体有助于癌症的定位成像及诊断。

4 结 语

FcRn可维持IgG和白蛋白血浆水平稳态和双

向跨膜转运以及促进抗原提呈细胞的抗原提呈，基于FcRn设计的药物在自身免疫病、传染性疾病和癌症的预防和治疗中可能蕴含着巨大的潜力，而以FcRn的配体(IgG和白蛋白)作为药物载体可以延长药物的作用时间，提高药物的吸收效率，优化给药方式。尽管从FcRn概念的提出到如今的临床应用，FcRn研究已经有了长足的进步，但仍存在很大的探索空间，如Hubbard等[71]发现FcRn是决定机体对IgG免疫复合物驱动的自身免疫易感性的Fcγ受体Ⅱa(CD32a)的共受体，提示FcRn可能与Fcγ受体介导的经典免疫反应有关。相信随着研究的深入及药物改造技术的成熟，FcRn将在药物递送、抗体工程、自身免疫、癌症等诸多领域的药物研发和临床应用中发挥更大的作用。

利益冲突 所有作者均声明不存在利益冲突

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