2026, 66(1): 18-33
CSTR: 32112.14.j.AMS.20250479
DOI: 10.13343/j.cnki.wsxb.20250479

微生物学报
*Acta Microbiologica Sinica*
http://journals.im.ac.cn/actamicrocn

Review 综述

# 抗体可结晶片段效应功能及其在疫苗免疫学检测中的应用进展

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王亚伟, 谭文杰. 抗体可结晶片段效应功能及其在疫苗免疫学检测中的应用进展[J]. 微生物学报, 2026, 66(1): 18-33.
WANG Yawei, TAN Wenjie. Progress in crystallizable fragment effector functions and its application in the evaluation of vaccines[J]. Acta Microbiologica Sinica, 2026, 66(1): 18-33.

**摘　要：**抗体是疫苗发挥保护作用的核心效应分子。传统观点认为抗体主要通过中和作用实现保护，即抗体的抗原结合片段(antigen-binding fragment, Fab)结构域能够阻断病毒与宿主细胞表面受体结合，从而抑制感染。近年来研究发现，抗体的可结晶片段(crystallizable fragment, Fc)结构域在调节免疫应答中同样发挥着关键作用。Fc结构域可与效应细胞[如自然杀伤细胞(natural killer cells, NK cells)、巨噬细胞、中性粒细胞和树突状细胞(dendritic cells, DCs)]表面的Fc受体(Fc receptors, FcRs)或补体受体结合，激活多条先天免疫信号通路，并介导多种非中和性抗病毒效应。这些效应功能包括抗体依赖的细胞介导的细胞毒作用(antibody-dependent cellular cytotoxicity, ADCC)、抗体依赖性细胞吞噬作用(antibody-dependent cellular phagocytosis, ADCP)、抗体依赖性补体沉积作用(antibody-dependent complement deposition, ADCD)以及补体依赖性细胞毒作用(complement-dependent cytotoxicity, CDC)等。尽管Fc效应功能的检测相较于中和抗体滴度测定更为复杂，但其在疫苗诱导的保护效应中的重要性日益凸显。本文系统综述了抗体Fc结构域介导的免疫效应机制，探讨了其在病毒性疫苗免疫保护过程中的功能，并总结了当前主流的Fc功能检测方法，为新型病毒性疫苗的研发与免疫效果评价提供理论依据与技术参考。

**关键词：**抗体；可结晶片段效应功能；抗体依赖的细胞介导的细胞毒作用；抗体依赖性细胞吞噬作用；抗体依赖性补体沉积作用；补体依赖性细胞毒作用；疫苗评价

资助项目：国家自然科学基金(82061138008)
This work was supported by the National Natural Science Foundation of China (82061138008).
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Received: 2025-06-19; Accepted: 2025-07-10; Published online: 2025-07-31

# Progress in crystallizable fragment effector functions and its application in the evaluation of vaccines

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**Abstract:** Antibodies serve as critical effector molecules in mediating vaccine-induced protection. While antibody-mediated immunity has traditionally been attributed primarily to neutralization, where the fragment antigen-binding (Fab) domain blocks viral entry by preventing the interaction between viruses and host cells, accumulating evidence underscores the pivotal role of the crystallizable fragment (Fc) domain in orchestrating broader immune responses. By interacting with Fc receptors or complement receptors on effector cells such as natural killer cells, macrophages, neutrophils, and dendritic cells, the Fc domain activates multiple innate immune pathways and elicits a spectrum of non-neutralizing antiviral effector functions. These include antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), antibody-dependent complement deposition (ADCD), and complement-dependent cytotoxicity (CDC). Although the evaluation of Fc-mediated functions is more complex than the measurement of neutralizing antibody titers, the contribution of such functions to vaccine efficacy is increasingly recognized. This review provides a comprehensive overview of Fc-mediated immune effector mechanisms, highlights their critical roles in antiviral vaccine-induced protection, and summarizes recent advances in Fc function assays, with the aim of supporting the rational design and immunogenicity evaluation of next-generation viral vaccines.

**Keywords:** antibody; Fc effector functions; antibody-dependent cellular cytotoxicity (ADCC); antibody-dependent cellular phagocytosis (ADCP); antibody-dependent complement deposition (ADCD); complement-dependent cytotoxicity (CDC); vaccine evaluation

疫苗接种是人类公共卫生史上最具成本效益的干预手段之一，在天花和脊髓灰质炎等高致死性传染病的防控中发挥了决定性作用。据世界卫生组织统计，全球每年通过疫苗接种可预防 200 万–300 万例死亡[1]。在病毒性疫苗诱导的免疫应答中，抗体产生是介导保护作用的核心机制[2-3]。传统疫苗免疫效果评估常以中和抗体滴度作为关键免疫指标。中和抗体通过空间位阻阻止病毒颗粒与宿主细胞表面受体结合，或干扰病毒包膜与宿主细胞膜的融合过程，从而在感染早期构建免疫屏障[4]。麻疹疫苗和脊髓灰质炎疫苗的成功应用证实了中和抗体在预防原发感染中的核心地位[5-6]。

近年研究发现，中和抗体水平不能完全解释某些疫苗[如流感疫苗、人类免疫缺陷病毒(human immunodeficiency virus, HIV)疫苗]的临床保护效果差异[7-9]，这促使研究者重新审视抗体可结晶片段(crystallizable fragment, Fc)介导的非中和功能在抗病毒免疫中的重要性。抗体 Fc 结构域可通过与免疫细胞表面 Fc 受体(Fc

receptors, FcRs)及补体系统相互作用，介导多种效应功能，包括抗体依赖的细胞介导的细胞毒作用(antibody-dependent cellular cytotoxicity, ADCC)、抗体依赖性补体沉积作用(antibody-dependent complement deposition, ADCD)、抗体依赖性细胞吞噬作用(antibody-dependent cellular phagocytosis, ADCP)以及补体依赖性细胞毒性作用(complement-dependent cytotoxicity, CDC)[4,7]。这些 Fc 效应功能已在 HIV[8]、流感[10]、疟疾[11]、结核病[12]、严重急性呼吸综合征冠状病毒 2 型(severe acute respiratory syndrome-coronavirus-2, SARS-CoV-2)[13]以及猴痘病毒(monkeypox virus, MPXV)[14-15]等多种病毒感染模型和疫苗保护效应中得到验证。以流感病毒为例，部分针对血凝素(hemagglutinin, HA)的抗体或疫苗虽然体外缺乏中和活性，但其 Fc 结构域与 FcRs 结合后可有效募集自然杀伤细胞(natural killer cell, NK cell)通过 ADCC 作用抑制病毒感染[10,16]。此外，ADCD 和 ADCP 在流感病毒清除过程中也发挥重要功能[17-18]，提示这些 Fc 效应机制可能通过协同作用提供免疫保护。

疫苗免疫效果评价若仅分析中和抗体水平则难以全面反映“保护性免疫”能力。系统解析抗体 Fc 结构域介导的效应功能，有助于更全面理解疫苗诱导的免疫保护机制，为疫苗设计和免疫策略优化提供新思路。本文旨在系统综述抗体 Fc 结构域在病毒性疫苗免疫中的作用机制，重点介绍主要 Fc 效应功能及其检测方法的最新研究进展，以期为新一代病毒性疫苗的研发与免疫效果评价提供全面的理论基础和技术参考。

## 1 抗体的分子结构与功能多样性

抗体(immunoglobulin, Ig)是由抗原刺激的 B 细胞分化为浆细胞后分泌的一类免疫球蛋白，能够通过特异性结合抗原介导体液免疫应答。经典抗体结构呈“Y”字形，由 2 条相同的轻链(light chain, LC)和 2 条相同的重链(heavy chain, HC)通过二硫键连接而成(图 1A)[19-21]。轻链由一个可变区(variable region of light chain, $V_L$)和一个恒定区(constant region of light chain, $C_L$)组成；重链则包含一个可变区(variable region of heavy chain, $V_H$)和 3 个恒定区(constant regions of heavy chain, $C_H1$−$C_H3$)。根据重链恒定区的差异及其理化性质和功能，人类抗体可分为 IgG、IgA、IgM、IgD 和 IgE 5 类[19-21]。

从功能结构域来看，抗体可分为抗原结合片段(antigen-binding fragment, Fab)和 Fc (图 1A)。Fab 结构域包含 $V_L$、$V_H$、$C_L$ 和 $C_H1$ 区域，其可变区内含互补决定区(complementarity-determining regions, CDRs)，负责抗原特异性识别；Fc 结构域由 $C_H2$ 和 $C_H3$ 构成，能与 FcRs 或补体受体(complement receptors, CRs)结合以激活下游免疫应答[19]。以 IgG 为例，其 Fc 段主要与 Fcγ 受体家族相互作用，包括高亲和力的 CD64(FcγRI)、中低亲和力的 CD32(FcγRII)和 CD16(FcγRIII)；其中，FcγRIIb 因胞内段含免疫受体酪氨酸抑制基序(immunoreceptor tyrosine-based inhibition motif, ITIM)，可抑制其他激活型 FcγR 介导的信号通路(图 1B)[20]。此外，IgG 亚型对 FcγR 的亲和力也存在差异，IgG1 和 IgG3 与 FcγR 的结合能力显著强于 IgG2 和 IgG4 (图 1B)[21]。除 IgG 外，其他抗体类型也通过其特异性 FcRs 介导免疫功能，如 IgA 通过 FcαRI(CD89)、IgE 通过 FcεRI 参与信号转导[22-23]。

抗体介导的 Fc 效应功能的类型受 FcRs 固有特性及其在不同免疫细胞中的表达模式的影响[24-25]。免疫效应细胞根据发育来源与功能特性可分为固有免疫细胞(如吞噬细胞、NK 细胞等)和适应性免疫细胞(如 T 细胞和 B 细胞)。Fc 结构域主要通过与固有免疫细胞表面的 FcRs 结合，激活快速且非特异性的免疫防御反应[25]。不同固有免疫细胞可按介导的效应机制进一步划分为多个功能亚群。例如，吞噬细胞(如巨噬

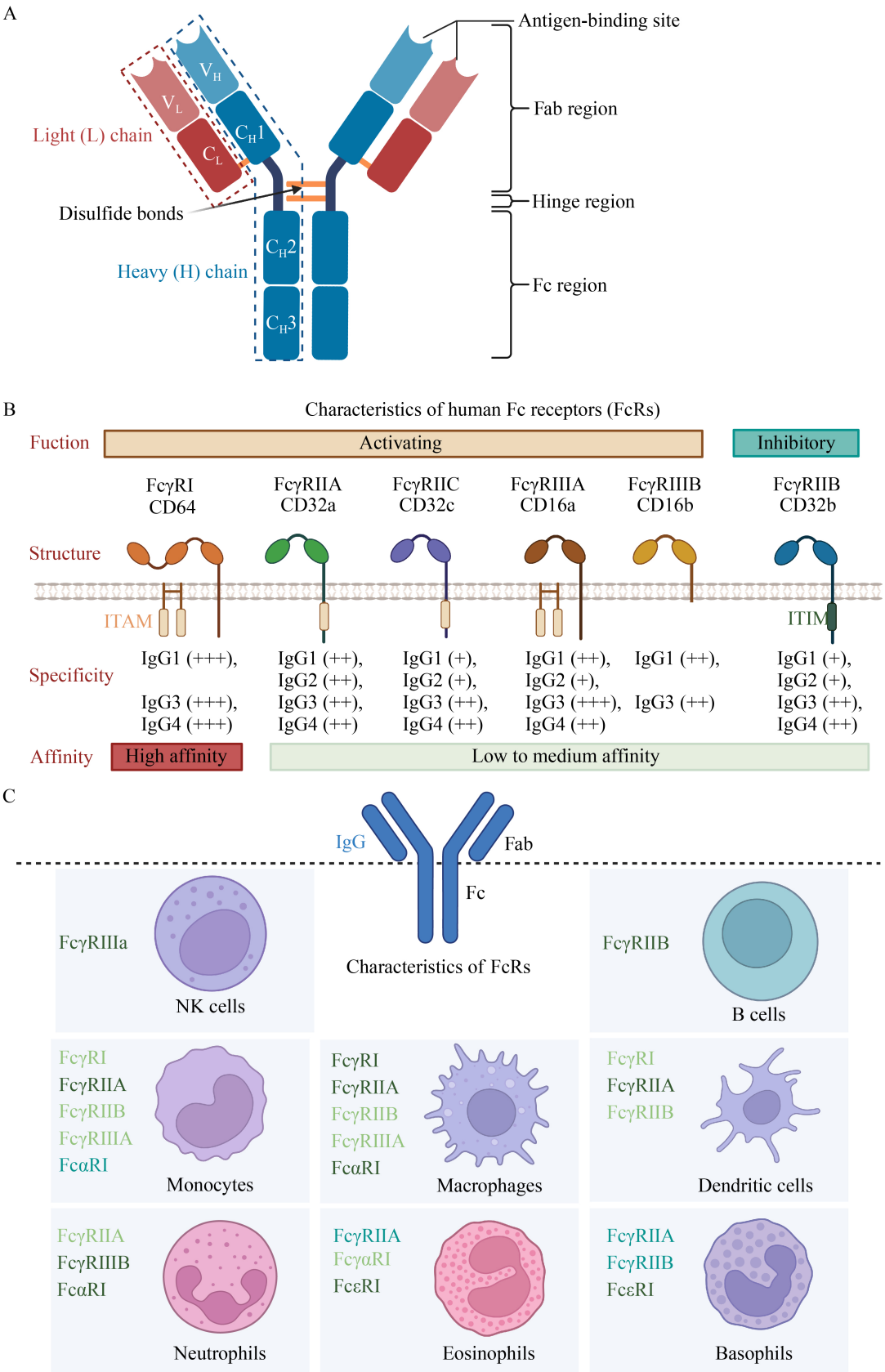
A
Antigen-binding site
Fab region
Hinge region
Fc region
Light (L) chain
Disulfide bonds
Heavy (H) chain
VH
VL
CH1
CL
CH2
CH3
B
Characteristics of human Fc receptors (FcRs)
Fuction
Activating
Inhibitory
FcγRI CD64
FcγRIIA CD32a
FcγRIIC CD32c
FcγRIIIA CD16a
FcγRIIIB CD16b
FcγRIIB CD32b
Structure
ITAM
ITIM
Specificity
IgG1 (+++), IgG3 (+++), IgG4 (+++)
IgG1 (++), IgG2 (++), IgG3 (++), IgG4 (++)
IgG1 (+), IgG2 (+), IgG3 (++), IgG4 (++)
IgG1 (++), IgG2 (+), IgG3 (+++), IgG4 (++)
IgG1 (++), IgG3 (++)
IgG1 (+), IgG2 (+), IgG3 (++), IgG4 (++)
Affinity
High affinity
Low to medium affinity
C
IgG
Fab
Fc
Characteristics of FcRs
FcγRIIIa
NK cells
FcγRIIB
B cells
FcγRI
FcγRIIA
FcγRIIB
FcγRIIIA
FcαRI
Monocytes
FcγRI
FcγRIIA
FcγRIIB
FcγRIIIA
FcαRI
Macrophages
FcγRI
FcγRIIA
FcγRIIB
Dendritic cells
FcγRIIA
FcγRIIIB
FcαRI
Neutrophils
FcγRIIA
FcγαRI
FcεRI
Eosinophils
FcγRIIA
FcγRIIB
FcεRI
Basophils

**图1　人类IgG Fc和Fc受体(FcRs)结构与功能特征。**A：IgG的基本结构($V_L$：轻链可变区；$V_H$：重链可变区；$C_H$：重链恒定区；$C_L$：轻链恒定区)；B：人类IgG Fc受体(FcγRs)的主要特征[包括其功能类型(激活型与抑制型)、结构域组成、IgG 亚型/异构体结合特异性及结合亲和力。不同IgG亚型和FcγRs的亲和力以结合常数Ka表示，+++：$>1\times10^7$ L/mol；++：$1\times10^5$–$1\times10^7$ L/mol；+：$<1\times10^5$ L/mol。ITAM：免疫受体酪氨酸激活基序；ITIM：免疫受体酪氨酸抑制基序]；C：FcRs在不同免疫细胞中的差异性表达(展示了包括自然杀伤细胞、单核细胞、巨噬细胞、树突状细胞、中性粒细胞、嗜酸性粒细胞、嗜碱性粒细胞和B细胞所表达的Fc受体种类)。图片在Biorender.com中完成。

Figure 1　Structural and functional characteristics of human IgG Fc and Fc receptors (FcRs). A: Basic structure of IgG ($V_L$: Variable domain of light chain; $V_H$: Variable domain of heavy chain; $C_H$: Constant domain of heavy chain; $C_L$: Constant domain of light chain); B: Main characteristics of human IgG Fc receptors (FcγRs) [Including their functional types (activating and inhibitory), structural domains, IgG subclass/isotype-binding specificities, and binding affinities. Binding affinities of different IgG subclasses to FcγRs are shown using association constants Ka, +++: $>1\times10^7$ L/mol; ++: $1\times10^5$–$1\times10^7$ L/mol; +: $<1\times10^5$ L/mol. ITAM: immunoreceptor tyrosine-based activation motif, ITIM: immunoreceptor tyrosine-based inhibitory motif]; C: Differential expression of Fc receptors on various immune cells (Showing the type of FcRs on natural killer cells, monocytes, macrophages, dendritic cells, neutrophils, eosinophils, basophils, and B cells). The figures were created using Biorender.com.

细胞和中性粒细胞)主要通过清除病原体发挥免疫防御功能：巨噬细胞高表达 FcγRI(CD64)和 FcγRIIa(CD32a)，可通过 ADCP 清除被抗体包被的病原体，同时分泌白细胞介素(interleukin, IL)-1β、肿瘤坏死因子(tumor necrosis factor, TNF)-α 等促炎因子增强局部免疫应答[26]；中性粒细胞主要表达 FcγRIIIb(CD16b)，通过诱导中性粒细胞胞外诱捕网形成(neutrophil extracellular trap formation, NETosis)释放和产生活性氧(reactive oxygen species, ROS)，在抗真菌免疫中起重要作用[27]。NK 细胞组成性表达 FcγRIIIa(CD16a)能识别被抗体结合的病毒感染细胞，并通过释放穿孔素(perforin)和颗粒酶(granzyme)介导 ADCC[28-29]。树突状细胞依赖 FcγRIIa(CD32a)摄取免疫复合物，通过主要组织相容性复合体(major histocompatibility complex, MHC)-I 和 MHC-II 分子进行抗原交叉提呈，激活 $CD8^+$和 $CD4^+$ T 细胞，并上调 CD80、程序性死亡受体配体 1 (programmed cell death-ligand 1, PD-L1)等共刺激及免疫调节分子，诱导 T 细胞向 Th1 或 Th2 亚群分化[30]。

除 FcRs 外，抗原呈递细胞(antigen-presenting cells, APCs)表面的 CRs 也在免疫效应中发挥关键作用。补体蛋白 C3b 和 C4b 在 C1q 介导下沉积于免疫复合物表面，可与中性粒细胞、单核细胞和 DCs 等细胞表面的 CRs 结合，诱导调理作用并促进抗原呈递，从而增强 T 细胞应答[31]。此外，C3b 及其衍生物 iC3b、C3dg 和 C3d 可与 B 细胞表面的 CRs 结合，促进 B 细胞向生发中心迁移、增强其存活能力，进而促进记忆 B 细胞生成并增强体液免疫应答[32-33]。

FcRs 的多样性使抗体 Fc 结构域具备动态调控免疫应答的能力。Fc 结构域识别病原体后通过与不同 FcRs 结合启动免疫信号级联反应，介导 ADCC、ADCP、ADCD 和 CDC 等多种免疫效应[7,34-35]。这些 Fc 介导的效应功能不仅在抗病毒免疫中发挥关键作用，还参与感染后炎症反应、免疫稳态维持及免疫病理过程的调控。综上所述，FcRs 的结构多样性与组织特异性表达构成了不同抗体亚型协同调控免疫反应的机制基础，决定了 Fc 结构域介导的固有免疫应答的广度与强度。

## 2 抗体 Fc 结构域介导的免疫效应功能及检测方法

抗体在抗病毒免疫中通过多种机制发挥作用。其 Fc 结构域可介导抗体与免疫细胞表面 FcRs 或 CRs 相互作用，启动一系列非中和性抗病毒免疫效应。目前研究已明确的 Fc 效应功能包括 ADCC、CDC、ADCD 以及 ADCP 等。

### 2.1 抗体依赖的细胞介导的细胞毒性作用(ADCC)

ADCC 是指抗体的 Fab 段特异性识别病毒感染细胞表面抗原，并通过其 Fc 段与 NK 细胞、巨噬细胞、中性粒细胞等效应细胞表面的 FcγRIIIa(CD16a)结合，从而激活效应细胞释放穿孔素与颗粒酶等细胞毒性物质，最终导致靶细胞裂解并伴随炎性细胞因子释放的过程[29,36](图 2A)。在 ADCC 效应中，NK 细胞是最主要的效应细胞，其特异性高表达 FcγRIIIa，且胞内富含穿孔素和颗粒酶，具有快速杀伤能力且无须预先致敏的特点[19,25]。在人类抗体亚型中，IgG1 和 IgG3 与 FcγRIIIa 的亲和力最高，是介导 NK 细胞 ADCC 最有效的抗体亚型。近年研究发现，IgA 和 IgE 可分别与其特异性受体 FcαR 和 FcεRI 结合介导免疫细胞发挥 ADCC 等效应功能，该发现在肿瘤免疫治疗领域展现出潜在应用价值[37-38]。

ADCC 在 HIV、流感病毒、SARS-CoV-2 等多种病原体感染的免疫防御中发挥重要作用[39-42]。其作用机制既可通过抗体调理作用间接清除感染细胞，也能直接杀伤某些病原体。多项临床研究证实，HIV 自然控制者体内 ADCC 活性抗体水平显著高于病情进展期患者[43]；流感亚单位疫苗接种者及感染康复者体内 ADCC 活性的抗 HA 抗体水平与病毒清除及症状减轻显著相关[44]。靶向流感病毒 HA 茎部的广谱中和抗体及相关疫苗，其交叉保护机制也主要依赖 ADCC[45-46]。基于上述发现，诱导 ADCC 功能抗体已成为新型疫苗设计的重要策略，特别是对于“广谱”或“通用”疫苗的开

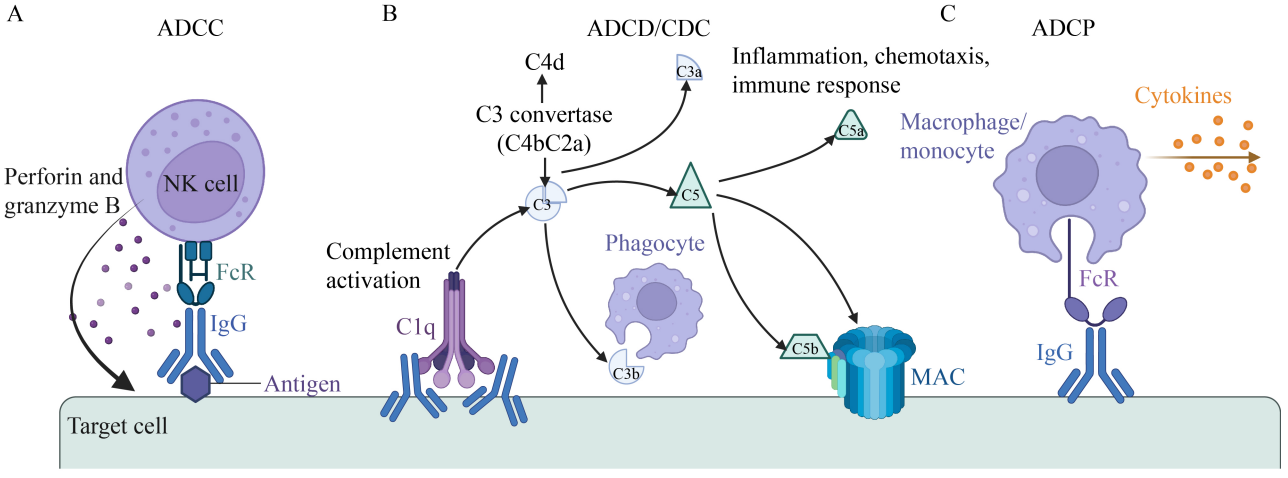


**图2 抗体Fc效应功能。**A：抗体依赖的细胞介导的细胞毒性作用(ADCC)；B：抗体依赖性补体沉积作用(ADCD)和补体依赖性细胞毒作用(CDC)；C：抗体依赖性细胞吞噬作用(ADCP)。图片在Biorender.com中完成。

Figure 2 Antibody Fc effector functions. A: Antibody-dependent cellular cytotoxicity (ADCC); B: Antibody-dependent complement deposition (ADCD) and complement-dependent cytotoxicity (CDC); C: Antibody-dependent cellular phagocytosis (ADCP). The figures were created using Biorender.com.

发[40,45]。RV144 HIV 疫苗试验中，V2 区特异性 IgG3 抗体通过 ADCC 机制使感染风险显著降低[47]。本课题组前期构建了检测甲型流感病毒 M2 蛋白诱导 ADCC 的方法，并验证了 M2 mRNA 疫苗免疫小鼠血清诱发的 ADCC 效应与疫苗保护相关[48]；M2 与 NP 蛋白联用时可产生对流感病毒的交叉保护[49]。

## 2.2 补体依赖性细胞毒作用(CDC)和抗体依赖性补体沉积作用(ADCD)

抗体 Fc 结构域除可通过与先天免疫细胞表面 FcRs 结合介导免疫效应外，还能通过激活补体级联反应参与免疫防御。CDC 是指抗体的 Fab 段与靶细胞膜表面的特异性抗原结合后，Fc 段激活补体经典途径，形成攻膜复合物(membrane attack complex, MAC)，最终导致靶细胞裂解的过程[50]。补体系统由 40 余种可溶性蛋白组成，可通过经典途径、凝集素途径和替代途径 3 种方式激活[32]。其中，IgM、IgG3 和 IgG1 等抗体亚型可有效激活经典补体途径[20]。在经典途径中，IgM 或 IgG 六聚体与 C1q 结合触发补体级联反应，生成 C3 转化酶(C4bC2a)，进一步将 C3 裂解为 C3a 与 C3b[50-51]。C3b 可沉积于靶细胞表面，一方面参与 MAC 的组装，介导 CDC 效应导致病原体或感染细胞的裂解[52]；另一方面 C3b 和 C4b 等补体裂解产物可作为“补体标记”共价结合于靶细胞表面，介导 ADCD 作用，增强巨噬细胞和树突状细胞等通过 CRs 介导的吞噬作用[53]。此外，补体激活产物 C3a 和 C5a 作为重要的炎症介质，不仅能促进免疫复合物沉积并增强吞噬细胞对病原体的摄取能力，还可通过与 T 细胞和 APCs 表面的 CRs 相互作用调节适应性免疫应答[53]。在感染早期，低亲和力的 IgM 抗体能够高效募集 C1q，快速启动补体级联反应清除病原体，构成抗病毒初期的重要防线[54]。

补体系统通过 ADCD 和 CDC 双重机制在抗病毒免疫中发挥重要作用。研究表明在补体缺陷小鼠模型中，经典、凝集素和替代 3 条补体激活途径对控制西尼罗病毒感染均不可或缺[55]。此外，补体系统还参与痘苗病毒的中和过程，证实了抗体 Fab 结构域介导的中和作用与 Fc 结构域介导的补体激活功能的协同保护效应[56-57]。在恒河猴模型中，基于刺突(spike, S)蛋白的 DNA 疫苗诱导的保护效果与 ADCD 及 ADCP 功能显著相关[58]。类似地，采用 Ad26 载体表达 S 蛋白变异体的疫苗，其保护效力与 ADCD 水平及抗体 Fc 段与 FcγRIIa 的结合能力密切相关[59]。这些发现为开发通过增强补体激活的新型疫苗提供了理论依据。

## 2.3 抗体依赖性细胞吞噬作用(ADCP)

抗体依赖性细胞吞噬作用(ADCP)是指巨噬细胞、单核细胞、DC 和中性粒细胞等吞噬细胞通过 FcRs 识别抗原-抗体复合物或病毒感染细胞后介导的吞噬过程[60-61]。该机制依赖于抗体 Fc 段与吞噬细胞表面 FcRs 的特异性结合，从而促进抗体包被的病毒颗粒或感染细胞的吞噬与清除(图 2C)。ADCP 不仅可直接清除病毒及感染细胞，还能通过增强抗原呈递和炎症因子释放进一步激活下游的适应性免疫反应[33]。ADCP 效应功能在不同吞噬细胞中表现出多样性。中性粒细胞可通过 FcγRIIa、FcγRIIIb 及 FcαRI 等受体对抗体复合物作出快速反应，执行病原体降解、NETosis 以及抗原交叉呈递等功能[27]。树突状细胞则借助 FcRn 依赖的 pH 机制摄取免疫复合物，并通过 MHC I/II 通路进行抗原呈递以诱导体液与细胞免疫应答[19]。不同抗体同种型与 FcRs 结合可引发多种免疫效应，IgA 与 FcαRI 结合可高效诱导 NETosis[62]，而 IgG 活化中性粒细胞常导致脱颗粒反应及炎性细胞因子的释放。

尽管 ADCP 在细菌感染防御中的作用已被广泛研究[61,63]，但其在抗病毒感染中的作用机制尚未完全阐明。近年研究发现，ADCP 在流感病毒、HIV 等多种病毒感染及疫苗诱导保护中起关键作用[61]。例如，在 2019 冠状病毒病(coronavirus disease 2019, COVID-19)住院患者

中，S 蛋白特异性抗体介导的 ADCP 水平与生存率呈正相关；急性期患者血清可诱导中性粒细胞 NETosis 反应[64-65]；RV144 HIV 疫苗人体临床试验显示，尽管疫苗诱导的 V1/V2 区 IgG 抗体不具中和活性，但其水平与感染风险下降显著相关，提示其可能通过 ADCP 机制发挥保护作用[8,66-67]。Huber 等[68]通过小鼠疫苗免疫联合病毒攻击模型证实 ADCP 在流感病毒防护中的关键作用，其研究发现缺乏 Fc 受体 γ 链的基因敲除小鼠因无法介导 ADCP 而对流感病毒高度易感，且该过程与 NK 细胞介导的 ADCC 作用无关。此外，ADCP 也可能参与人类重症流感感染后的恢复过程[17,69]。

## 2.4 抗体 Fc 效应功能检测方法

抗体 Fc 结构域介导的免疫效应功能是疫苗研发和抗体药物评价中的重要指标。针对这些功能，研究人员已建立多种体外检测方法，通常涉及三大要素：靶细胞、效应细胞(或补体)以及特异性抗体。根据检测机制的差异，这些方法可大致分为 2 类：一类以靶细胞的损伤或裂解为核心指标，另一类则聚焦于效应细胞的激活状态或功能响应。

在 Fc 效应功能的体外评估中，靶细胞与效应细胞的选择对实验结果的生理相关性和可重复性具有关键影响。靶细胞一般为可稳定表达目标抗原的细胞系，应尽可能贴近疾病模型或临床应用场景，并便于表征与标记。抗体结合靶细胞后，其 Fc 结构域介导与效应细胞或补体的相互作用，进而诱导下游免疫效应的激活。不同 Fc 功能依赖的效应细胞类型有所不同。例如，ADCC 主要依赖表达 FcγRIIIa 的 NK 细胞[48]，而 ADCP 则多采用单核-巨噬细胞系[如人单核细胞白血病细胞系(THP-1)、人组织细胞淋巴瘤细胞系(U937)]或外周血单核细胞(peripheral blood mononuclear cell, PBMC)来源的原代巨噬细胞。效应细胞的来源大致可分为 3 类：(1) 原代细胞，如外周血中分离的 NK 细胞和巨噬细胞等，其受体表达谱与功能状态更贴近体内环境，适用于疫苗或治疗性抗体的体内功能评估，但其获取难度大、个体差异显著，操作相对复杂；(2) 永生化细胞系，如 NK-92 和 THP-1 等，具备良好的操作稳定性和实验重复性，适用于机制研究和高通量筛选，但其 Fc 受体表达可能与原生细胞不同，且功能有限；(3) 工程化报告细胞，如表达特定 Fcγ 受体和荧光素酶的 Jurkat 报告系统[70-71]，适用于标准化和定量化的功能检测，但缺乏完整的免疫效应功能，如吞噬和脱颗粒能力。不同细胞模型在 Fcγ 受体表达谱、信号转导能力以及对不同抗体亚类的响应方面存在差异。因此，应根据具体的研究目标与检测需求，合理选择适用的效应细胞类型。

以 ADCC 检测为例，其体外模型通常由靶细胞、效应细胞与待测抗体共同组成。常见方法包括以靶细胞为核心的检测策略，如 $^{51}$Cr 释放法、乳酸脱氢酶(lactate dehydrogenase, LDH)释放法、荧光素酶报告法和流式细胞术活/死染色，以及以效应细胞激活为核心的功能检测方法，如检测 CD107a 表达或胞内细胞因子的产生等[39]。CDC 的功能评估主要基于靶细胞死亡率或存活率的量化，常用方法包括荧光染料标记、LDH 或三磷酸腺苷(adenosine triphosphate, ATP)释放检测等；此外，还可通过流式细胞术或酶联免疫吸附测定(enzyme-linked immunosorbent assay, ELISA)检测 C5b-9 复合物的表达以间接反映 MAC 导致的细胞裂解水平。ADCD 的检测通常采用荧光微珠、带抗原病毒颗粒或靶细胞为载体，结合流式细胞术、ELISA 和免疫荧光染色技术测定表面 C3b、C4b 等补体成分的沉积程度。ADCP 的评估则侧重于吞噬细胞对抗原的内化效率，主要采用流式细胞术或荧光成像等技术分析巨噬细胞对荧光标记抗原的摄取能力。表 1 从检测原理、应用场景、优缺点等方面系统总结了 ADCC、CDC、ADCD 和 ADCP 的体外检测策略。

**表1　Fc效应功能检测方法**

Table 1　Detection methods for Fc effector functions

| Fc effector function | Method | Detection principle | Application scenario | Advantages and limitations | References |
|---|---|---|---|---|---|
| ADCC | Cytoplasmic-content release assay (e.g., $^{51}$Cr, LDH, or glucose-6-phosphate dehydrogenase) | Assessment of ADCC activity by measuring intracellular components released upon target-cell lysis | High-throughput screening and historically validated method | High sensitivity and wide adoption; radioactive contamination or cumbersome labeling, with background interference | [48,72-74] |
| | Cell viability assay | Live/dead dye-based flow cytometry to determine the fraction of apoptotic/necrotic target cells | Clinical-sample analysis and antibody functional profiling | Radio-free and simple; dye non-specific binding and cell-type variability | [75-77] |
| | Luciferase reporter gene assay | FcγRIIIa signaling in Jurkat-NFAT-Luc-CD16 reporter cells drives luciferase expression | High-throughput functional screening for vaccine or antibody evaluation | High specificity and automation-ready; relies on specific cell line and reports FcγR signaling rather than lysis | [70-71] |
| | Effector cell activation method | Quantify NK-cell activation markers (e.g., CD107a, IFN-γ, MIP-1β) | Clinical immune monitoring and functional validation | Enables functional profiling of effector-cell subsets; indirect ADCC readout, limited assessment of target-cell lysis | [78-80] |
| CDC | Cytoplasmic content release assay | Quantify released intracellular contents (e.g., $^{51}$Cr, LDH) after target-cell lysis | Functional assessment of vaccine- or antibody-elicited antibodies | Well-established and quantifiable; cannot distinguish lysis mechanism, serum background interference | [72,81] |
| | Cell viability assay | Live/dead dye staining followed by flow cytometric quantification of target-cell apoptosis/necrosis | Cell-line-level CDC evaluation | Radio-free and convenient; slightly lower sensitivity, dye selection requires optimization | [82] |
| | C5b-9 assay | Quantify membrane attack complex (MAC) deposition on target cells as a surrogate of CDC activity | Mechanistic studies | High specificity and clinical-sample compatibility; does not directly report cell lysis | [83] |
| ADCD | Bead-based fluorescence assay | Detect C3/C4 deposition on antigen-coated microbeads after complement activation | Functional assessment of vaccine- or antibody-elicited antibodies | High-throughput and highly reproducible; reports complement binding | [84] |
| | Virus-based assay | Quantify C3/C4b deposition on antigen-displaying viral particles after complement activation | Viral vaccine functional evaluation | Closer to authentic viral structure; experimentally complex | [85] |

(待续)

(续表1)

| Fc effector function | Method | Detection principle | Application scenario | Advantages and limitations | References |
|---|---|---|---|---|---|
| ADCP | Bead-based fluorescence assay | Antigen-antibody-coated beads co-cultured with macrophages; phagocytic uptake quantified by fluorescence intensity | Functional assessment of vaccine- or antibody-elicited antibodies | Quantitative, easy to standardize, high-throughput capable; requires optimization of bead-conjugated antigen quality | [86-87] |
| | Sensitive fluorescent dye labeling assay | pH-sensitive dye-labeled antigen; fluorescence activated after lysosomal uptake | Mechanistic studies | Real-time imaging of phagocytic events, high-content screening; true endocytosis reflected, intuitive imaging; costly dyes, instrument-demanding, low throughput | [88-89] |

## 3 讨论

在疫苗诱导的免疫保护过程中，抗体不仅能够通过中和作用阻断病毒入侵，还可借助其Fc结构域与FcRs或CRs结合，激活先天免疫系统，进而发挥多种抗病毒效应。Fc介导的效应功能涵盖ADCC、ADCD、CDC及ADCP等，这些功能不仅可直接清除病毒或杀伤感染细胞，还能通过调节炎症微环境、增强抗原呈递能力以及促进T细胞活化间接参与免疫调控。

然而，Fc结构域的免疫功能具有双重性。在介导抗病毒反应的同时，它也可能诱发抗体依赖性增强(antibody-dependent enhancement, ADE)等免疫病理效应。ADE是指在非中和或亚中和抗体水平下，抗体未能有效中和病毒，反而通过FcRs与免疫细胞结合，形成抗体-病毒复合物并介导病毒内化与扩散，甚至诱导强烈的炎症反应，导致病毒感染增强并加重疾病的现象[45,90-91]。该机制在登革热病毒(dengue virus, DENV)感染中已得到证实[92-93]。在DENV感染中，病毒通过Fc介导通路感染FcRs阳性但不表达病毒天然受体的细胞，形成一种特殊的致病机制[93-94]。具有既往感染史或疫苗接种史的人群因体内存在循环抗体，更易发生ADE。因此，疫苗研发与抗体疗法需评估相关风险。此外，补体系统在病毒感染时若被过度激活也可能加重疾病。例如，在DENV和HIV感染者血清中观察到补体激活水平与疾病严重程度呈正相关[95-96]；SARS-CoV-2感染个体的IgG可通过经典或替代途径激活补体系统，释放C3a/C5a等炎性效应因子，其水平与COVID-19严重程度密切相关[97]。这些结果表明，Fc介导的免疫反应在抗感染防御与免疫病理损伤之间存在动态平衡。需注意的是，ADE现象与疾病本身的免疫反应高度重叠，且缺乏统一检测标准，使得临床识别与判定存在挑战。尽管在SARS-CoV、中东呼吸综合征冠状病毒(Middle East respiratory syndrome coronavirus, MERS-CoV)和寨卡病毒等多种病毒的体外模型中观察到ADE现象，但体内直接证据不足，分子机制仍需进一步阐明[90]。

抗体Fc功能的激活受多种因素调控，包括抗体识别的表位特征、FcγR亚型与分布、抗体同种型、Fc区糖基化修饰、抗体与FcRs或抗原的亲和力以及免疫复合物稳定性[7,35,98]。研究表明疫苗接种与自然感染所诱导抗体的Fc糖基化模式存在差异，这会影响ADCC、ADCP等效应功能的激活效率。在疫苗应答中，中和与非中和抗体的比例及其动态变化是决定抗体效应偏向保护性还是致病性的关键因素[7]。值得强调的

是，Fc 效应功能不仅在“非中和机制”中发挥作用，其还可调节中和抗体的生成，Fc-FcR 可通过影响抗原呈递效率、激活滤泡辅助 T 细胞及 B 细胞亲和力成熟等途径，促进高亲和力中和抗体的生成[99]。例如，猴痘疫苗 mRNA-1769 在非人类灵长类动物中可诱导与改良安卡拉株疫苗相当甚至更优的保护效果，其在抑制 MPXV 病毒血症的发生及减轻组织病理损伤方面的作用与中和抗体及 Fc 介导的效应功能密切相关[14,100]。进一步分析表明该疫苗免疫后所产生的针对胞外病毒的特异性抗体介导的 Fc 效应功能(ADCC、ADCP、ADCD)与中和活性具有协同效应，二者共同阻断病毒复制并减轻病程。这表明中和抗体与 Fc 效应功能并非相互排斥，而是协同构建体液免疫防线。

目前，Fc 效应功能在多种病毒感染中的保护作用已得到广泛验证，但其在疫苗设计与免疫评估中的应用价值直到近年才受到充分重视。系统评估不同疫苗平台、抗原结构、佐剂类型、递送系统及给药方式对 Fc 功能诱导的影响有助于提升疫苗设计的科学性[35,98]。新一代疫苗研发需深入理解免疫保护机制，统筹中和作用与非中和性 Fc 效应功能在体液免疫中的互补作用。此外，在病毒感染过程中可能会有多种 Fc 效应协同发挥作用，不同的效应功能和检测方法也具有相关性。因此，在疫苗或抗体的功能性评价中，常需综合采用多种检测方法，以全面反映其 Fc 依赖的免疫效应特征。随着技术发展，可通过 Luminex 多因子检测、流式细胞术、荧光素酶报告基因系统等方法，同步评估 IgG 亚型分布与 FcR 结合活性，实现对 Fc 效应功能的多维分析。尽管当前 Fc 功能研究多基于人类临床样本，但小鼠模型仍是机制研究不可替代的工具，由于人类与小鼠在 FcR 表达谱、Fc-FcR 结合亲和力及下游信号通路方面存在显著物种差异[24]，因此动物实验结果解读要充分考虑外推局限。

# 4 结论与展望

综上所述，Fc 结构域介导的效应功能是疫苗诱导免疫应答中不可忽视的关键组成部分，在增强免疫保护、解释疫苗效能差异及预测个体免疫反应等方面具有应用前景。未来疫苗设计应立足于系统免疫机制，整合中和抗体与 Fc 效应功能，探索其调控网络与机制基础。这对于提升疫苗免疫原性与保护效果，尤其是应对新发病毒及变异株具有重要意义。

## 作者贡献声明

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