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单克隆抗体在抗病毒感染中的研究进展 *

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摘要：单克隆抗体（monoclonal antibody, mAb），指同一种抗原决定簇的细胞克隆所产生的均一性抗体。mAb 已成功应用以诊疗各种疾病，尤其是癌症和免疫性疾病。近些年来，mAb 逐渐用于治疗病毒性疾病，针对急性和慢性病毒感染研发的抗病毒 mAb 数量逐渐增长。mAb 的组合疗法可同时靶向病毒多个表位，从而克服病毒免疫逃逸的问题，多价 mAb 的设计开发能够更加有效的作用于病毒。本文比较了不同 mAb 制备方法的优缺点，总结了 mAb 近期在抗病毒感染领域的研究进展，并讨论了 mAb 作为治疗病毒性疾病药物的前景。

关键词：单克隆抗体；抗病毒；作用机制

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Research Progress of Monoclonal Antibody in Viral Infection*

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ABSTRACT: Monoclonal antibody refers to the homogenous antibody produced by the cell clone of the same antigen determinant. MAb has been successfully used in the treatment of various diseases, especially cancer and immune diseases. However, in recent years, monoclonal antibody has gradually been used to treat viral infections. The number of anti-viral monoclonal antibody developed for acute and chronic viruses has gradually increased. The combination therapy of mAb can target multiple epitopes of virus at the same time, so as to overcome the problem of virus immune escape. The design and development of multivalent monoclonal antibody can act on virus more effectively. In this paper, the advantages and disadvantages of different preparation methods of mAb were compared, and the recent research progress of mAb in the field of antiviral was summarized. The prospect of mAb as a drug for treating viral diseases was discussed.

Key words: Monoclonal antibody; Antivirus; Mechanism of action

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前言

抗病毒 mAb 疗法的作用机制是 mAb 快速靶向病毒或感染细胞，从而减弱病毒感染。在 mAb 减少病毒传播方面，一是取决于 mAb 与抗原结合的活性，二是取决于 mAb Fc 片段所携带的效应功能。到目前为止，大多数抗病毒 mAb 通过识别病毒表面抗原进而中和病毒，其直接作用机制是影响病毒增殖。但是近几年来在各种动物模型进行的抗病毒 mAb 治疗中获得的证据表明，抗病毒 mAb 在与免疫系统的不同组分相互作用时也可以通过间接机制进行作用，即诱导受感染个体的内源性免疫系统以激活持久的抗病毒免疫。基于这种作用机制，抗病毒 mAb 的免疫疗法对患者和临床医疗体系都将会具有非常大的益处。

1 单克隆抗体的开发

19 世纪 90 年代，Emil von Behring 等[1]第一次使用已免疫的血清来治疗白喉，成功后，血清疗法被广泛应用于病毒性疾病的预防和治疗。20 世纪 70 年代，Kohler 等[2]开发了杂交瘤技术。单克隆抗体（monoclonal antibody, mAb）开始进入人们的视线，然而这些 mAb 的应用产生了人抗鼠抗体反应（HAMA reaction）。只有使得 mAb 变得更加趋近人源化，或者开发全人源单克隆抗体（fully human monoclonal antibody），才可以避免 HAMA 反应。近几年来，全人源单克隆抗体的制备技术不断发展，已被用于治疗各种疾病，包括癌症、自身免疫性疾病和传染

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病[3,4]。抗体开发的发展历史及特点汇总于表 1。

表 1 单克隆抗体的发展历史及特点

Table 1 Development history and characteristics of monoclonal antibody

Method	Year of development	Advantages	Disadvantages
Serum therapy[1]	1890s	① Easily produces large amounts of antibody ② Compared with antibiotics, serotherapy is effective in treating viral infections	① Security issue ② The quality of antibody produced by different batches of serum is different. ③ Dose cannot be determined ④ Antibody are ineffective
Hybridoma technology[2, 5]	1970s	Easily produces high-affinity antibody	HAMA reaction
Humanized mouse[6-8]	1980s	Easily produces high-affinity antibody	① High cost ② The experiment takes a long time. ③ Potential safety issues need to be confirmed
Phage display[9, 10]	1980s	① To facilitate screening ② low cost ③ Exceptionally large antibody libraries (10^8-10^{10}) ④ Produces fully human antibody	① The antibodies obtained are not all monoclonal antibody against an antigen ② Nonnative heavy and light chain pairs
Ribosome display[11]	1990s	① Large antibody libraries (10^{11}) ② Antibody specificity ③ High affinity ④ Produces fully human antibody	① mRNA is easy to degrade ② A protein - ribosome - mRNA forms a ternary complex, which is unstable
Yeast display[12, 13]	1990s	① To facilitate screening ② Low cost ③ Produces fully human antibody ④ Large antibody libraries (10^7-10^9) ⑤ Quantitative screening using flow cytometry ⑥ Fully human antibody	Nonnative heavy and light chain pairs
Single B-cell isolation[14, 15]	21st century	① Produces fully human antibody ② Produces fully human antibody ③ Genetic diversity	① High cost ② The experiment takes a long time ③ Requires B cells from infected or vaccinated individuals ④ Low-throughput screening (10^3-10^5)

2 抗病毒单克隆抗体

2.1 病毒免疫逃逸单克隆抗体治疗

RNA 病毒的 RNA 聚合酶在病毒复制的过程中不具备校对和修复的能力,当出现选择性压力时,病毒就可能出现病毒突变体[20,21]。当给予抗病毒 mAb 治疗时,这就有可能使病毒在抗病毒 mAb 治疗过程中出现病毒突变体。病毒突变体可不受抗病毒 mAb 的作用,即出现病毒免疫逃逸。例如,感染了呼吸道合胞病毒的婴儿在接受帕利珠单抗治疗后,病情不断加重并发展为急性下呼吸道感染。对婴儿体内分离出的病毒进行核苷酸序列分析后发现在部分呼吸道合胞病毒表面的融合蛋白发生了突变,这样一来使呼吸道合胞病毒出现了病毒免疫逃逸的现象[22]。

病毒免疫逃逸的出现以及病毒的适应性改变,这些都可能影响病毒在宿主内的作用。病毒的突变体可能会对特定的抗病毒 mAb 产生抗性,但是病毒突变之后,其感染性及毒力也可能会随之改变[23]。

2.2 单克隆抗体组合疗法

为了避免出现病毒免疫逃逸反应,所以在设计 mAb 时,应参照以下两个原则,一是能够覆盖多个病毒靶抗原表位,二是能够预防病毒的免疫逃逸。现如今,已经开发出了多种 mAb 组合(见表 2),并且基于组合中不同 mAb 的特异性和功能性,使它们在覆盖度和特异性方面相互补充。

由于 mAb 与病毒抗原表位的结合是具有特异性的,因此在特定情况下就需要应用多种 mAb 进行组合治疗。以狂犬病病毒为例,不同的狂犬病病毒种靶抗原表位有所差别。当感染狂犬病病毒之后,应当及时施用不同的狂犬病免疫球蛋白组合,如狂犬病免疫球蛋白(HRIG)和马抗狂犬病血清(ERIG)联合使用,这样才能彻底的抑制病毒[24]。因此,mAb 组合应该能够覆盖广泛的病毒靶抗原表位,并且在抗原抗体结合时不应存在竞争关系;其次,病毒因其中一种 mAb 作用而产生病毒免疫逃逸时,组合中另外一种 mAb 能够作用于病毒免疫逃逸株,反之亦然[25,26]。这样一来,病毒免疫逃逸的问题就可以通过多种 mAb 的组合来克服。

目前，已经有很多 mAb 组合研发成功并应用。例如，针对甲型流感病毒 H5N1 的两种 mAb 组合，组合中的这些 mAb 分别结合不同的病毒抗原表位，并且已证明能够抑制病毒免疫逃逸[27]。

表 2 多种单克隆抗体组合

Table 2 Monoclonal antibody cocktails

Target	No. of mAb included
SARS-CoV[28, 29]	2 or 3 mAb
Ebola virus[19, 30]	2 or 3 mAb
Influenza virus[27]	2 mAb
Rabies virus[24-26]	2 or 3 mAb
Hepatitis B virus[31]	3 mAb

2.3 多特异性单克隆抗体

当我们评价抗病毒 mAb 的生物学效能时，抗体效价就是其中一个重要的因素。抗体结合抗原表位的个数称为抗原结合价，如单个抗体有 2 个抗原结合位点时，这个抗体称为双价抗体[18]。在 mAb 中和病毒的过程中，单价 mAb 有时会出现交联反应，这种交联反应会使中和反应的效率大大降低。但二价 mAb 可以抑制这种交联反应，提升中和反应效率[32]。例如在单纯疱疹病毒中，使用单价 mAb 时就会严重影响该抗体对病毒的中和作用，当使用二价 mAb 时，就能够很好地抑制病毒增殖[33]。另外，二价抗体能够更有效地中和那些包膜有着丰富棘突的病毒，如呼吸道合胞病毒和流感病毒[34, 35]。但是，一些病毒如 HIV 病毒的表面棘突密度非常低，棘突彼此之间相距太远，二价 mAb 就难以通过桥接的方式结合病毒[36-38]，然而，理论上来说多价 mAb 是可以通过改变抗体的几何结构来达到结合病毒的目的，例如二聚形式的 mAb 2G12 已经被证明能够大幅提升中和效率。聚合了 IgA 的多价 mAb 2F5 和聚合了 IgM 的多克隆抗体 2G12，它们也已被证实相比于最初的 mAb，其中和效率均有明显提升[39]。

3 单克隆抗体抗病毒感染的作用机制

3.1 直接作用机制

迄今为止研究的大多数抗病毒 mAb 是免疫球蛋白 G（IgG），病毒或感染细胞与免疫球蛋白 G 结合形成抗原 - 抗体复合物，抗原 - 抗体复合物可结合杀伤细胞（NK 细胞、巨噬细胞等）表面的 Fcγ 受体（FcγRs），介导杀伤细胞直接靶向结合抗原，进而杀灭病毒或感染细胞。这种杀灭病毒的方式被称为抗体依赖性细胞介导的细胞毒作用（ADCC）[17]。

这种抗原 - 抗体复合物还可以激活补体，被激活的补体可以使得病毒颗粒裂解失活，这种激活补体经典模式进而杀伤病毒的方式，被称为补体依赖性细胞毒作用（complement-dependent cytotoxicity，CDC），被激活的补体还可以发挥吞噬作用来清除病毒或感染细胞，这种杀灭病毒的方式被称为抗体依赖性细胞吞噬作用（antibody-dependent cellular phagocytosis，ADCP）[40-43]。因此，在免疫疗法中，mAb 可以通过各种直接机制作用于病毒。

3.2 间接作用机制

越来越多的证据表明，mAb 的抗病毒作用也可以通过间接机制来执行。即参与宿主免疫反应，其作用效果远远超出中和作用[44-47]。这类似于疫苗样效应，mAb 在进行中和作用的同时激活内源性体液免疫和细胞免疫，具体来说，mAb 通过抗体依赖性细胞介导的细胞毒作用（ADCC）诱导病毒或感染细胞的裂解，这样一来，提供了一个有利于诱导内源性抗病毒免疫应答的炎症环境[17]。此外与仅仅被病毒感染的细胞相比，mAb 与病毒或感染细胞结合构成的免疫复合物更容易被树突状细胞捕获，使得具有更强功能性的树突状细胞被激活，进而激活抗病毒细胞毒性 T 淋巴细胞反应（CTL），加快了内源性免疫应答的效率[48]。其次，在免疫反应中调节性 T 细胞（Treg）表达会抑制自身抗病毒免疫应答，而 mAb 能够抑制 Treg 的表达，这对诱导体液免疫和细胞免疫是十分关键的[49]。最后，在免疫治疗过程中自身免疫系统产生的内源性抗体可以作用于病毒，当 mAb 从治疗过程中去除，且机体再次感染病毒时，记忆 T 细胞将被激活，从而分泌抗体中和病毒[48]。另外，在最近的一项研究中发现中性粒细胞在抗病毒 mAb 诱导的免疫保护中也发挥着不可替代的关键作用。中性粒细胞是天然免疫效应细胞，在机体受病原体感染后可由 NK 细胞介导进而清除病原体，它们在抗病毒 mAb 诊疗过程中的免疫调节作用未被研究过，但该报道指出，由于中性粒细胞在抗病毒 mAb 的治疗过程中与 B 细胞的活化有一定的联系，能够诱导有效地体液免疫反应，是诱导宿主抗病毒体液免疫应答的必要因素[50]。最近在各种动物模型实验中获得的证据也都表明 mAb 的抗病毒疗法是可以诱导自身内源性免疫反应[51-55]。然而，一些问题仍然无法确定如参与这些免疫反应的细胞分子机制仍未完全明确。

尽管抗病毒 mAb 的间接作用机制如此重要，但是十分遗憾的是在以往的研究中都忽视了这一点，直到最近才开始对其进行研究，这可能与下述的这几个原因有关。首先，大多数抗病毒 mAb 最初是根据它们对病毒繁殖的抑制作用来选择应用的。其次，在进行模拟病毒感染的实验动物中，由于主要考虑的是被动免疫效果，没有进一步对内源性免疫应答进行深入分析[51-55]。第三，在部分实验中，用以产生、分泌 mAb 的物种与使用该抗体进行体内实验时的物种是不同的，因此与 Fc 相关的效应功能存在缺陷，限制了进一步进行内源性免疫的研究[56]。最后，由于道德、技术和经济原因，以及正在进行的临床试验数量较少等各种主观及客观因素，都对内源性免疫应答的深入研究起了一定的阻碍作用。

4 小结与展望

综上所述，过去的几十年里，mAb 在制备技术上取得了较大的进展。越来越多的证据表明，mAb 可激活病毒感染机体的内源性免疫系统，发挥抗病毒作用。mAb 越来越多地被认为是诊疗严重病毒性疾病的首选药物[16]。针对 H5N1 流感病毒、人类免疫缺陷病毒、单纯疱疹病毒、巨细胞病毒、丙型肝炎病毒、埃博拉病毒、马尔堡病毒、严重急性呼吸综合征冠状病毒、登革热病毒、狂犬病病毒、亨德拉病毒、尼帕病毒、黄热病病毒和西尼罗河病毒等，相应的抗病毒 mAb 已在过去的几年中逐渐开始应用[17]。目前，一些 mAb 正在进行临床试验，包括一些多价

的 mAb 和 mAb 的组合疗法[18, 19]。相信在不久的未来，mAb 将会作为一种有效的手段用于病毒感染性疾病的诊疗和预防。

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