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狂犬病新型基因工程疫苗研究进展

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摘要　狂犬病是由狂犬病病毒感染中枢神经系统引起的一种古老的人兽共患传染病,人和动物感染后一旦出现临床症状,死亡率几乎 100%,至今仍无有效的治疗方法。当前,接种疫苗是预防狂犬病最为有效的途径。因此,狂犬病疫苗研发一直是狂犬病研究领域的热点之一,进而不断涌现出新型疫苗。本文对近期狂犬病新型灭活疫苗、弱毒疫苗、核酸疫苗、亚单位疫苗、病毒样颗粒疫苗、口服疫苗等基因工程疫苗研究进展进行系统梳理,以期把握狂犬病疫苗研究现状,为研发更为有效的狂犬病新型疫苗提供新思路。

关键词　狂犬病;狂犬病病毒;灭活疫苗;弱毒疫苗;核酸疫苗;亚单位疫苗;病毒样颗粒疫苗;口服疫苗;基因工程

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狂犬病(rabies)是由狂犬病病毒(rabies virus,RABV)感染引起的一种高度致死性的人兽共患传染病。RABV 共编码 5 个结构蛋白,分别是核蛋白(nucleoprotein,N)、磷蛋白(phosphoprotein,P)、基质蛋白(matrix protein,M)、糖蛋白(glycoprotein,G)以及 RNA 依赖的 RNA 聚合酶大蛋白(RNA-dependent RNA polymerase large protein,L),其中 RABV 糖蛋白(RABV-G)是病毒粒子表面唯一的蛋白,在 RABV 感染宿主后结合细胞表面的受体帮助入侵,同时也能够刺激机体产生保护性中和抗体(virus-induced neutralizing antibody,VNA)。

狂犬病在全球范围内每 15 min 发生 1 例,其中 95% 以上病例发生在亚洲、非洲的一些发展中国家和欠发达地区[1]。人通常是通过已感染 RABV 的动物咬伤、抓伤或舔舐等密切接触方式被感染。狂犬病一旦出现临床症状其死亡率接近 100%,暴露后预防处置(包括伤口清洗、疫苗免疫和抗体注射)是预防狂犬病的唯一有效途径[2]。犬是当前狂犬病传播的主要传染源(占比 95%以上),对家养动物进行广泛免疫(达到 70%以上)是消除人间狂犬病的最有效措施。

世界卫生组织(WHO)提出了 2030 年消灭人间狂犬病的目标[3],而要实现这一目标就需要开发更为廉价、高效的新型狂犬病疫苗。早在 1885 年法国科学家路易斯·巴斯德就首次发明了狂犬病疫苗,并成功应用到人狂犬病的防控[4]。时至今日,狂犬病疫苗的发展历经组织灭活苗、禽培苗、细胞苗、基因工程苗等不同的发展阶段。得益于基因工程技术的飞速发展,近年来狂犬病新型基因工程疫苗研究获得长足进步,本文对该方面的研究进展进行系统综述。

1　狂犬病新型灭活疫苗

灭活疫苗具有非常高的安全性,但狂犬病传统灭活疫苗免疫后效力较低,持续时间较短,需多次免疫,免疫程序相对繁琐。狂犬病新型灭活疫苗则采用反向遗传操作技术对毒株改造后再制备灭活疫苗,从而提高疫苗免疫原性。RABV-G 是 RABV 诱导机体产生中和性抗体的唯一抗原,因此,提高 RABV-G 的表达量是增强灭活疫苗免疫原性的策略之一。如将含有 2 个 RABV-G 基因(将另外 1 个拷贝的 G 基因插入在 G/L 间)的重组病毒株 rHEP-dG 制备的灭活疫苗免疫小鼠和比格犬后,较亲本毒制成的灭活疫苗能诱导产生更高水平的

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VNA[5]。此外密码子优化也是提高 RABV-G 表达量的策略之一，如在 G/L 间额外插入 1 个 RABV-G，并对 2 个 RABV-G 均进行鼠源密码子优化的重组 RABV 灭活后免疫小鼠能产生更高水平的 VNA[6]，是优良的狂犬病灭活疫苗候选株。而另一项研究表明，表达 2 个 RABV-G 的重组 RABV 灭活后进行的小鼠免疫试验显示将额外的 1 个 G 基因插入到 G/L 间较 P/M 间能更好地诱导机体产生 VNA[7]，这表明诱导机体产生 VNA 不仅和 RABV-G 的表达量有关(RABV 复制过程中蛋白表达量按 N-P-M-G-L 的顺序依次递减)，还存在其他未知影响因素。除了增加 RABV-G 表达量外，与 RABV-G 偶联表达外源免疫激活因子也同样可以增加疫苗免疫原性。例如，与 RABV-G 融合表达 B 细胞激活因子(B cell activating factor，BAFF)并展示在病毒粒子表面的重组 RABV 灭活疫苗能刺激小鼠短时间内产生高滴度 VNA[8]，可开发为暴露后免疫疫苗。

此外，以 RABV 为载体来表达其他病原保护性抗原而开发的重组二联灭活疫苗也是新型灭活疫苗的发展方向之一。如基于 RABV-G 的蛋白三维结构，设计构建的 RABV 和莫科拉病毒(mokola virus，MOKV)嵌合 G 蛋白重组灭活疫苗候选株免疫后能为机体提供对 RABV 和狂犬病病毒属的多种病毒在内的免疫保护[9]，极大地拓宽了狂犬病疫苗的应用范围。而表达犬瘟热病毒(canine distemper virus，CDV)H(CDV-H)或 F 蛋白(CDV-F)的重组狂犬病灭活疫苗在提供 RABV 免疫保护的同时也能提供 CDV 免疫保护[10]；采用汽化保存的 RABV-埃博拉病毒(ebola virus，EBOV)重组灭活疫苗比冷藏保存的灭活疫苗具有更好的热稳定性，能同时保护机体免受 RABV 和 EBOV 的攻击[11]；表达 SARS-CoV-2 S1 与 RABV-G 嵌合体的 RABV-COVID-19 重组灭活疫苗 CORAVAX™免疫小鼠 56 d 后，仍能诱导机体同时产生针对以上 2 种病毒的高水平 VNA[12]。

2 狂犬病新型弱毒疫苗

RABV 反向遗传操作系统的建立和发展为 RABV 弱毒活疫苗的开发提供了便利的工具[13]。利用反向遗传操作技术可将与 RABV 致病性相关的关键氨基酸位点突变，进而构建获得高度弱化的狂犬病活疫苗候选株。如将 RABV-G 和 M 基因位置交换且 G 蛋白 333 位氨基酸突变(R333E)而高度致弱的 RABV 活疫苗(ERAg3m 株)单次肌肉注射 3 周后能在致死剂量的 RABV 街毒(MD5951 株)攻击下为仓鼠和小鼠提供 100%保护，比灭活疫苗具有更高的免疫保护率，可作为暴露后免疫候选疫苗株[14]。另一项研究表明，RABV ERA 株 N 基因和 G 基因同时突变(N273/394-G333)而高度致弱毒株具有更高的安全性[15]；基因改造(G 基因 N194S 和 R333E 同时突变)的 RABV ERAGS 株用作疫苗免疫后能诱导小鼠、貉、猪、犬和牛等产生保护性免疫力[16-18]。此外，串联表达 3 个拷贝 G 蛋白的重组 RABV(SPBAANGAS-GAS-GAS)弱毒在小鼠体内几乎无致病性且免疫原性强，可作为暴露前和暴露后免疫预防疫苗候选株[19]。

为了进一步提高疫苗安全性，通过反向遗传操作系统开发的 M 基因缺失的复制缺陷型狂犬病疫苗(RABV-ΔM)由于仅能在宿主体内复制 1 轮，因此具有极高的安全性，同时也能为犬提供较长时间免疫保护[20]。类似开发的 RABV-P 基因缺失并表达 MERS-S1 的复制缺陷型狂犬病疫苗(RABVΔP-MERS/S1)同样也具有较高的安全性，并能同时提供对中东呼吸道综合征冠状病毒(middle east respiratory syndrome coronavirus，MERS-CoV)和 RABV 的免疫保护[21]。

值得关注的是，能够表达免疫增强因子或调节因子的重组狂犬病疫苗近年来也相继涌现，其策略是利用反向遗传操作系统将促进免疫反应的细胞因子或趋化因子插入病毒基因组，使其随病毒复制而表达，进而增强疫苗的体液免疫效果(图 1)。目前主要有 2 种增强宿主体液免疫反应的策略：一种是激活宿主的抗原递呈细胞，主要是树突状细胞(dendritic cell，DC)，如表达优化的高迁移率群组框 1(high-mobility group box 1，HMGB1)的重组 RABV 能通过激活 DC 而增加 RABV 免疫原性，从而激活更多的体液免疫[22]；融合表达靶向树突状细胞小肽(DCBp)的重组 RABV 可促进 DC 的成熟，进而促进下游体液免疫的产生[23]；而表达 Fms 样络氨酸激酶 3 配体(Fms-like tyrosine kinase 3 ligand，Flt3L)的重组 RABV 小鼠免疫试验显示能招募并激活 DC，进而促进机体产生高水平 VNA[24]。另外一种策略是激活产生抗体的主要部位-生发中心(germinal center，GC)，促进生发中心 B 细胞的生成。如表达 C-X-C 基序趋化因子 13(C-X-C motif chemokine，CXCL13)的重组 RABV 能促进引流

淋巴结生发中心的形成，小鼠免疫试验显示其诱导产生更多的 GC B 细胞并激活更多的浆细胞从而产生更多的 VNA[25]；表达细胞内黏附分子 1（intracellular adhesion molecule-1，ICAM-1）的重组 RABV 也能激活更多的 B 细胞，在低剂量免疫下即能迅速诱导 VNA 产生[26]，有作为 RABV 暴露后免疫预防疫苗的潜力；表达 BAFF 的重组狂犬病疫苗能快速激活滤泡外 B 细胞，并在短期内产生高水平 VNA，可作为暴露后预防疫苗[27]；表达共刺激因子 OX40 配体（costimulatory factor OX40-ligand，OX40L）的重组 RABV 免疫小鼠后可产生大量的滤泡辅助性 T 细胞（T follicular helper cells，Tfh）、GC B 细胞和浆细胞，从而持续产生高水平 VNA[28]。此外，一些表达白介素如 IL-6[29]、IL-7[30]、IL-15[31]、IL-18[32]、IL-21[33] 的重组 RABV 都能不同程度地增强疫苗的体液免疫，显著提高 VNA 滴度，其中 IL-7 还可以促进记忆 B 细胞的产生，增强长效免疫应答。

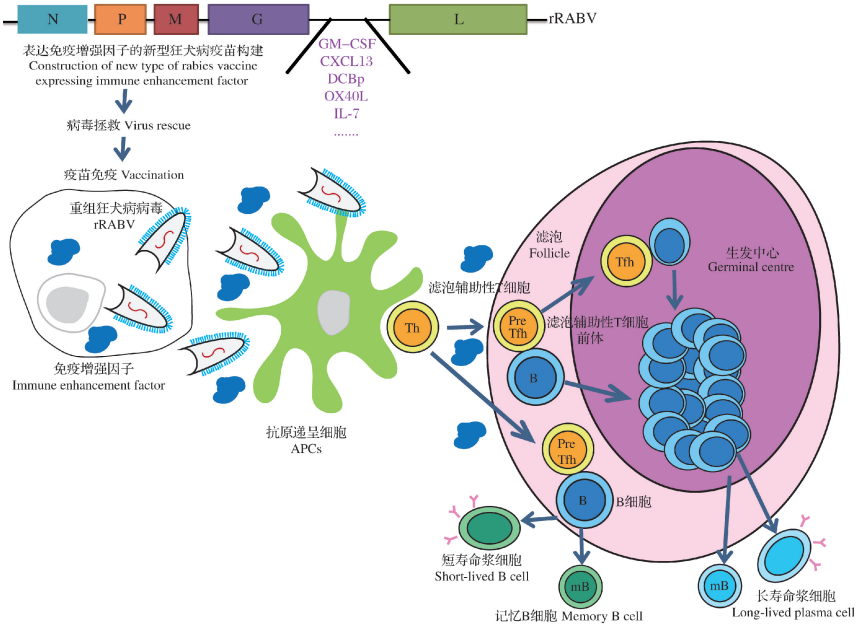

图 1　表达免疫增强因子的狂犬病新型弱毒疫苗示意图

Fig.1　Schematic diagram of new attenuated rabies vaccine expressing immune enhancement factor

通过表达细胞因子或趋化因子来提高疫苗的免疫原性可以有效提高狂犬病疫苗的免疫效力，但是在动物或人体内过表达这些细胞因子是否会存在一定的副作用或有其他安全性隐患还需进一步评估。

3　狂犬病新型活载体疫苗

利用其他病毒载体表达 RABV-G 也是狂犬病新型疫苗研究的热点之一。痘病毒（vaccinia virus）在 1982 年就被开发成表达外源基因的载体，随后开发了表达 RABV-G 的重组痘病毒载体疫苗（V-RG）并作为野生动物口服活载体疫苗在北美洲使用多年[34-36]，该重组病毒具有较好的热稳定性，但免疫效果在部分野生动物中不是很理想。而金丝雀痘病毒（canarypox）载体重组狂犬病疫苗（PUREVAX® Feline Rabies and PUREVAX® Rabies，Merial）可为猫提供长达 3 a 的免疫保护[37]，具有很高的应用价值。腺病毒载体也是狂犬病疫苗开发的优良载体，ONRAB® 就是基于人腺病毒 5 型（human adenovirus 5，AdHu5）载体开发的野生动物用口服狂犬病疫苗[38-42]，在消除野生动物狂犬病方面具有较好的应用前景。也有研究表明将分别表达 RABV-G 和 RABV-N 的重组腺病毒组合免疫小鼠能提供更好免疫保护[43]；而同时表达 RABV-G 和 CDV-H 的重组腺病毒二联苗（rAd5-G-H）能为小鼠和狐狸同时提供针对 RABV 和 CDV 的免疫保护[44]；同时表达重症热性血小板减少症候群病毒（severe fever with thrombocytopenia syndrome virus，SFTSV）Gn 和 RABV-G 的重组腺病毒 Ad5-G-Gn 免疫小鼠也能诱导产生针对以上 2 种病毒的 VNA，可作为犬、猫候选疫苗[45]。值得关注的是近年来非人灵长类腺病毒载体疫苗也发展迅速，如基于复制缺陷型黑猩猩腺病毒载体开发的狂犬病疫苗（ChAd155-

RG)被认为是下一代人用狂犬病疫苗候选株[46]。黑猩猩腺病毒载体狂犬病疫苗(ChAd68-Gp)能为比格犬提供致死剂量的RABV(CVS-11)攻击保护[47];此外,猴腺病毒载体狂犬病疫苗(ChAdOx2 RabG)也可被开发为廉价的犬用狂犬病疫苗[48]。

除常用的痘病毒和腺病毒载体外还有许多其他病毒载体也被用来研究作为狂犬病疫苗载体的可行性。如表达RABV-G的副痘病毒(Orf virus,ORFV)能为小鼠、猫、犬和家畜提供免疫保护[49-50];而猫疱疹病毒1(feline herpesvirus 1,FHV-1)载体开发的猫用狂犬病疫苗对消除猫狂犬病和猫-人传播途径至关重要[51]。此外,表达RABV-G的重组杆状病毒(baculoviridae)疫苗可为小鼠提供致死剂量RABV(CVS-24)的攻击保护[52];重组腺相关病毒(adeno-associated virus,AAV)表达的RABV-G能在小鼠体内诱导长达1 a以上的体液免疫反应,保护小鼠免受RABV(CVS-24)的致死性攻击[53]。而基于西尼罗病毒(west nile virus,WNV)载体开发的表达RABV-G的复制子(RepliVax®)疫苗也能为小鼠、犬和猪提供免疫保护[54];重组SFV病毒(semliki forest virus,SFV)载体疫苗可以在哺乳动物细胞大量表达RABV-G[55],从而可开发为狂犬病疫苗。另外,还有采用犬腺病毒-2(canine adenovirus type 2,CAV-2)[56]、新城疫病毒(newcastle disease virus,NDV)[57-58]、副流感病毒5型(parainfluenza virus 5,PIV5)[59]、犬瘟热病毒[60]等病毒载体开发的兽用狂犬病疫苗。这些病毒载体狂犬病疫苗有些已用于野生动物,有些只开展了临床前研究,但对开发动物用甚至人用狂犬病疫苗都具有重要的价值,具备开发成廉价、高效的下一代狂犬病疫苗的潜力。

4 狂犬病新型核酸疫苗

狂犬病核酸疫苗包括DNA疫苗和RNA疫苗。狂犬病DNA疫苗主要通过将编码RABV-G的编码框构建到真核表达载体上,免疫后利用宿主细胞翻译表达RABV-G从而刺激机体产生VNA。传统DNA疫苗免疫效果不够理想,持续时间短,狂犬病新型DNA疫苗多通过添加佐剂提高免疫效果。如添加了C3d-P28佐剂的编码G5线性多肽的狂犬病DNA疫苗(pVaxF1)克服了DNA疫苗免疫剂量大、效果差的弱点,能够持续刺激机体产生RABV特异性VNA[61];添加铝佐剂的pgp.LAMP-1狂犬病DNA疫苗也能提供针对RABV的免疫保护[62];通过共表达TLR通路中重要接头分子MyD88的狂犬病DNA疫苗也能有效提高其免疫效果[63]。此外,由壳聚糖[64]、泊洛沙姆[65]、聚醚亚胺(PETIM)高分子树脂[66]等纳米颗粒包裹的DNA疫苗都能有效提高狂犬病DNA疫苗的传递效率,从而提高疫苗免疫效果[67]。

狂犬病RNA疫苗则是将RABV-G的编码框构建成能独立翻译RABV-G的mRNA作为免疫原而开发的新型疫苗(图2)。如编码RABV-G的非复制且耐高温狂犬病mRNA疫苗能对小鼠、新生和成年猪产生免疫保护[68-69];人用预防性狂犬病mRNA疫苗(CV7201)是由编码RABV-G的mRNA和鱼精蛋白组合冻干的热稳定型mRNA疫苗,是第一个在健康人群中开展概念验证研究的mRNA疫苗,其临床试验也显示出较好的安全性和免疫原性[70-71]。此外,基于甲病毒(alphavirus)基因组构建并由阳离子纳米乳剂(cationic nanoemulsion,CNE)传递的狂犬病自我复制mRNA(self-amplifying mRNA)疫苗在小鼠中具有较好的免疫效果和安全性[72];而将编码RABV-G的cDNA进行体外转录后转染BHK-21细胞,包装成能表达RABV-G的重组SFV-RABV-G的mRNA疫苗也能在小鼠体内激发有效的免疫反应[73]。

5 狂犬病新型亚单位疫苗和病毒样颗粒疫苗

直接将人工表达的RABV-G作为免疫原而开发的疫苗称为狂犬病亚单位疫苗。传统RABV-G表达采用原核表达系统或昆虫细胞表达系统[74],而采用黑腹果蝇S2(schneider 2)细胞表达的RABV-G也具有较好的免疫效果[73,75]。而采用哺乳动物细胞HEK-293T表达的嵌合有GCN4-pⅡ三聚化功能域的RABV-G胞外域嵌合体蛋白可以三聚体形式存在,因而更接近天然的RABV-G从而具有更好的免疫原性,能为小鼠提供更好的免疫保护[76]。此外,添加犬热休克蛋白Gp96佐剂的狂犬病多肽疫苗免疫试验和攻毒保护试验结果显示能为小鼠和比格犬提供免疫保护[77],表明合成肽也具有发展狂犬病疫苗的应用前景。

RABV病毒样颗粒(virus-like particle,VLP)可由RABV-G形成(需RABV-M辅助形成),因不具有感染和复制能力,且能很好地展示抗原表位而具有良好的疫苗发展潜力。传统的VLP多用昆虫

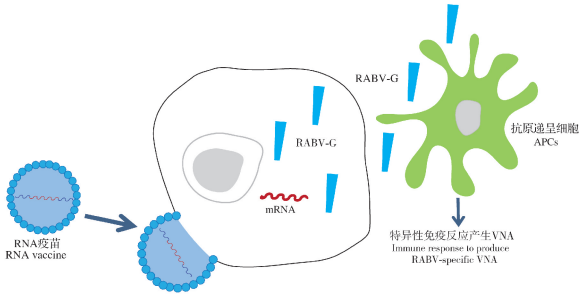

图 2　狂犬病新型 mRNA 疫苗示意图

Fig.2　Schematic diagram of new mRNA vaccine for rabies

细胞表达系统来实现，而采用哺乳动物细胞 HEK-293 表达的 RABV-VLP 同样具有较好的免疫原性[78-79]。此外，将 GM-CSF 嵌合在 RABV-VLP 表面则可以激活更多的树突状细胞，从而增强 RABV 体液免疫反应[80]；含有膜锚定鞭毛蛋白（EVLP-F）或大肠杆菌热不稳定肠毒素 B 亚单位（EVLP-L）分子佐剂的 2 个嵌合病毒样颗粒（cRVLPs）能在小鼠和犬模型中诱导更高水平的 RABV 特异性免疫反应[81]。值得关注的是，表达 RABV-G 的委内瑞拉马脑炎病毒（venezuelan equine encephalitis virus，VEEV）载体复制子疫苗（VEEV-RABV-G），能够形成仅包含 RABV-G 单一蛋白的类病毒粒子，并且可以在 BHK-21 细胞中连续传代，VEEV-RABV-G 在乳鼠和小鼠脑内直接注射均展现出极高的安全性，并且能够提供与狂犬病弱毒疫苗相当的免疫保护，可以作为下一代安全、高效的疫苗候选株[82]（图 3）。

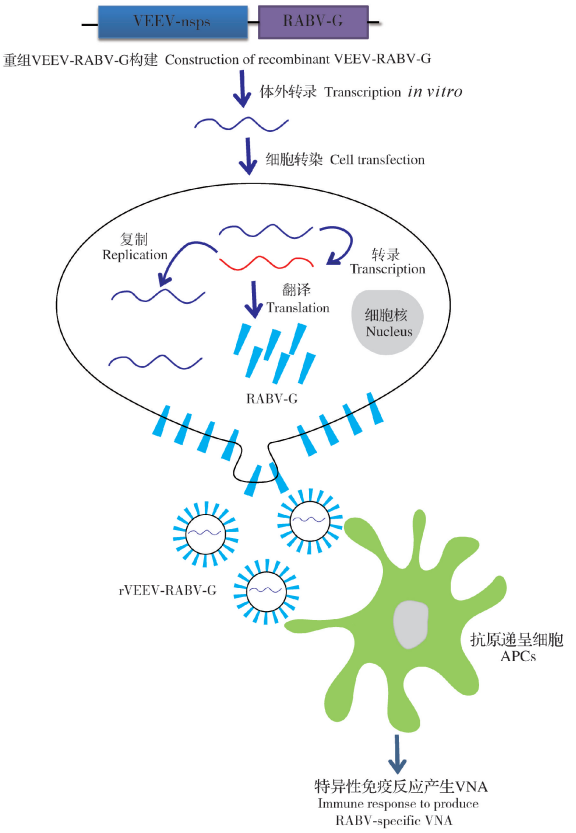

图 3　新型狂犬病病毒样颗粒疫苗 VEEV-RABV-G 示意图

Fig.3　Schematic diagram of the new rabies virus-like particle vaccine VEEV-RABV-G

6　狂犬病口服疫苗

由于使用的便利性，口服疫苗对消除流浪犬、猫和野生动物中的狂犬病从而降低人间狂犬病具有重大的意义[83-86]。因此上述狂犬病疫苗若能开发成口服疫苗则对狂犬病防控和消除意义重大[87]，令人欣喜的是已有相关探索和应用研究，如 SAG2 是由 RABV 疫苗株 SAD-Bern 经突变筛选的高度致弱的狂犬病口服疫苗，在犬及其他野生动物试验中显示较好的安全性和有效性[88-89]；而由 SAD-L16 派生出的口服疫苗 SPBN-GASGAS 可为狐狸[90-91]、浣熊[90]和犬[92]提供有效的狂犬病保护。此外，基于人腺病毒载体的狂犬病口服疫苗ONRAB® 已在北美洲的野生动物中应用多年[42]；痘病毒载体狂犬病口服疫苗 V-RG 也在北美洲野生动物狂犬病控制中发挥了重要的作用[36]。RABV ERA 株 G 蛋白 R333E 突变致弱的狂犬病口服疫苗在犬试验中是安全的，且能提供长时间的免疫保护[93]。而表达犬粒细胞-巨噬细胞集落刺激因子（granulocyte-macrophage colony-stimulating factor，GM-CSF）的重组 RABV 口服疫苗，能募集和激活更多的树突状细胞，诱导犬产生更高水平的 VNA[94]。而以犬腺病毒 2 型为载体的狂犬病疫苗（CAV-2-E3Δ-RGP）经口服也可为犬提供长效免疫保护，但也有研究表明犬体内已有的针对犬腺病毒的抗体可能会影响免疫效果[95]。

除了病毒载体，利用可食用转基因植物表达保护性抗原从而免疫人群和动物也是提高群体免疫的有效途径[96]。而据此开发的表达 RABV-G 的转基因玉米口服绵羊后能诱导机体产生针对 RABV 的保护性免疫应答[97]。此外，在番茄毛状根中表达 RABV-G 也可被开发为动物用口服疫苗[98]。

7　展　望

要实现 WHO 倡议的在 2030 年消除人间狂犬

病的目标依然任重道远。2007年我国因狂犬病死亡的人数约3 300人，位居全球第二，仅次于印度。近年来，随着狂犬病疫苗在家养动物中的广泛应用，我国每年死于狂犬病的人数已逐年下降至2020年的300例以下。疫苗免疫是消除人间狂犬病最有效的措施，针对3个主要的免疫群体——人、宠物和野生动物，需要根据不同需求开发更为有效的新型疫苗。由于人用疫苗将安全性置于首位，目前人用狂犬病疫苗均为灭活疫苗，需多次免疫(4～5针)后才能产生有效的VNA，免疫程序繁琐，且费用较高，因此研发安全性高、只需1针免疫、长效的狂犬病疫苗是人用狂犬病疫苗的发展方向，而mRNA疫苗和类病毒粒子疫苗是未来人用狂犬疫苗的发展重点。当前狂犬病的主要传染源为犬，尤其是农村犬和流浪犬，而只有在犬、猫中实现70%以上的免疫覆盖率才能有效降低人间狂犬病的发病率，因此，迫切需要开发廉价、高效的兽用狂犬病疫苗，经过密码子优化的灭活疫苗和类病毒粒子疫苗具有较好的应用前景。鉴于RABV储存宿主是野生动物，要消除狂犬病终究要实现野生动物的广泛免疫。因此，广泛应用基于RABV弱毒或者其他活病毒载体开发的安全、有效的狂犬病口服疫苗来提高野生动物的免疫率则是未来最终消除狂犬病的关键举措。

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Recent progress of novel genetic engineering rabies vaccines

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Abstract Rabies is an ancient zoonosis caused by rabies virus, which infects the central nervous system, causing almost 100% mortality once the clinical symptoms appear. There is no effective treatment available so far. Currently, vaccination is still the most effective way to prevent rabies, so developing rabies vaccines is one of the hot spots in the field of rabies research. With the rapid development of biotechnology, novel rabies vaccines for different uses have been continuously emerged. In this report, the research progress of latest genetic engineering rabies vaccines including inactivated vaccine, attenuated vaccine, nucleic acid vaccine, subunit vaccine, virus-like particle vaccine, oral vaccine etc. is reviewed to grasp the current trend of rabies vaccine and lay the foundation for developing next generation of rabies vaccines.

Keywords rabies; rabies virus; inactivated vaccine; attenuated vaccine; nucleic acid vaccine; subunit vaccine; virus-like particle vaccine; oral vaccine; genetic engineering

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