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特约综述

猪圆环病毒病疫苗研究进展

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摘要:猪圆环病毒病(PCVAD)是危害养猪业的重要疫病之一,可引起免疫抑制和继发感染,已经造成严重经济损失。猪圆环病毒(PCV)有4个种。猪圆环病毒2型(PCV2)有9种基因型,其中PCV2d为我国目前优势流行毒株,免疫接种是防控该病的关键手段。本文系统综述了PCV2疫苗的研究进展,重点介绍了病毒灭活疫苗、基于不同表达系统的亚单位疫苗、合成肽疫苗和基因工程活载体疫苗等的研发与应用现状,梳理了PCV2多基因型联合疫苗及其与其他病原联合疫苗的研发和应用效果,探讨了基于Cap重组蛋白病毒样颗粒纳米展示平台的疫苗设计新策略,指出了目前猪圆环病毒商品疫苗存在的缺陷及未来疫苗研究方向。

关键词:猪圆环病毒病;疫苗;免疫防控

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Advances in the vaccines against porcine circovirus disease

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Abstract: Porcine circovirus-associated disease (PCVAD) is one of the most important infectious diseases, which causing immunosuppression of pigs resulting in multiple secondary infection diseases, and significant economic losses to the global swine industry. Currently, it has been reported that porcine circoviruses have at least four species. And porcine circovirus type 2 (PCV2) has nine genotypes, among which PCV2d is the predominant circulating strain in China. PCV2 vaccination remains the key strategy for controlling this disease. This review systematically summarizes the research progress on PCV2 vaccines, focusing on the development and application of inactivated vaccines, subunit vaccines based on different expression systems, synthetic peptide vaccines, and genetically engineered live vector vaccines. It also outlines the development and efficacy of multigenotype PCV2 vaccines and combined vaccines with other pathogens, including the novel vaccine design strategies based on the Cap recombinant protein virus-like particle nano-display platform. And it also highlights the limitations of the current commercial PCV vaccines and future directions for new vaccine research.

Keywords: porcine circovirus disease; vaccine; immunological control

猪圆环病毒病 (porcine circovirus disease), 又称猪圆环病毒相关病 (porcine circovirus-associated disease, PCVAD), 是由猪圆环病毒 (porcine circovirus, PCV) 引起猪的多种疾病的总称, 包括断奶仔猪多系统衰竭综合征 (postweaning multisystemic wasting syndrome, PMWS)、猪皮炎肾病综合征 (porcine dermatitis and nephropathy syndrome, PDNS)、猪呼吸道病、肠炎、母猪繁殖障碍和仔猪先天震颤等, 并且可以导致猪群产生免疫抑制, 从而容易导致其他病原继发感染, 经济损失巨大。PCV 属于圆环病毒科成员, 至少有4个种, 其中猪圆环病毒2型 (PCV2) 研究最多。该病毒粒子直径 17 nm, 基因组大小 1.76 kb, 含有 12 个

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ORF,编码5种蛋白。PCV2存在基因变异,目前至少有9种基因型,包括PCV2a、PCV2b和PCV2d等^[1-2]。不同时期,PCV2存在基因型转变。目前,PCV2d是我国优势流行毒株。自2016年以来,国内外学者从临床繁殖障碍母猪和皮炎肾病综合征仔猪中发现存在PCV3和PCV4感染。基因测序结果显示,PCV2与PCV3 ORF2基因推导的氨基酸同源性仅约37%,与PCV4 ORF2同源性约为45%^[3-4]。PCV2主要侵袭猪淋巴组织,可导致淋巴细胞耗竭^[5-7]。PCV2感染和免疫可诱导猪体产生中和抗体,也可产生细胞免疫。PCV2衣壳蛋白(Cap)具有重要免疫保护作用,是PCV2亚单位疫苗的核心抗原^[8-9]。目前,PCV2疫苗研究比较多。国外商业化的PCV2单苗至少有5种。我国自主研发的PCV2商品疫苗有28种,包括16种单苗(灭活疫苗、亚单位疫苗和合成肽疫苗)、10种二联疫苗及2种三联疫苗,进口注册疫苗8种,为我国该病防控发挥了重要作用。

1 PCV2全病毒灭活疫苗

疫苗种毒有PCV2和PCV1-2嵌合体毒株。2006年梅里亚公司(法国)研发的Circovac PCV2疫苗为世界第一款PCV2疫苗,疫苗种毒属于PCV2a。母猪和仔猪免疫接种,可有效降低病毒血症、病毒组织载量,减少排毒和传播,并促进新生仔猪生长。FosteraPCV是全球第二款PCV2灭活疫苗,疫苗种毒为PCV1-2a嵌合体。实验室条件下,2种疫苗可交叉保护猪免受PCV2d攻击^[10-11]。2010年我国首次研制成功PCV2灭活疫苗,疫苗种毒为PCV2 SH株和LG株,分别属于PCV2b亚型和PCV2a亚型。此后,多个单位相继研发成功PCV2灭活疫苗,疫苗种毒有DBN-SX07、WH、ZJ/C、SD和YZ株,属于PCV2a或PCV2b^[12]。病毒滴度是影响PCV2灭活疫苗质量的关键因素。PCV2在复制过程中依赖于有丝分裂S期表达的蛋白,在PK-15细胞培养过程中加入氨基葡萄糖可刺激细胞分裂,从而促进PCV2复制。Hirai等^[13]发现猪肝原代细胞比猪肾细胞更适合PCV2的增殖。陈念劬等^[14]筛选出PK15-B1克隆细胞,PCV2滴度可提高100倍以上。

2 PCV2亚单位疫苗

21世纪初国内外学者采用大肠杆菌、杆状病毒、酵母、伪狂犬病毒和腺病毒等表达系统,成功表达了PCV2 Cap重组蛋白,亚单位疫苗研究取得重要进展^[15-19]。目前,我国自主研发的商品化PCV2亚单位疫苗有7种,其中2种采用重组杆状病毒系统表达,5种疫苗抗原采用大肠杆菌系统表达。

2.1 重组杆状病毒亚单位疫苗

杆状病毒表达系统可以采用糖基化和磷酸化等方式修饰外源蛋白,使表达的重组蛋白具有与天然病毒蛋白类似的结构和活性,且有利于形成稳定的VLPs。2005—2009年国外采用杆状病毒表达系统,研发成功了3种商品化的PCV2亚单位疫苗(CircoFLEX、Circumvent和PorcilisPCV)。疫苗接种能诱导高水平PCV2中和抗体,减少猪体PCV2含量,降低PCV2病毒血症、鼻腔和粪便排毒,有效防控病毒传播^[19-22]。此后,我国学者也研制成功了PCV2b亚单位疫苗(CP株)和PCV2d亚单位疫苗(重组杆状病毒OKM株)2种亚单位疫苗,对猪圆环病毒病的预防和控制发挥了重要作用。除昆虫细胞表达杆状病毒外源蛋白外,一些学者将家蚕用于表达杆状病毒Cap蛋白,并证明其可以形成病毒样颗粒(virus-like particles, VLP)^[23]。

2.2 大肠杆菌表达系统亚单位疫苗

PCV2 Cap蛋白的N端具有核定位信号(NLS)。NLS富含精氨酸残基和多种稀有密码子,影响其高效表达。我国学者通过密码子优化、重组蛋白SUMO修饰或使用含稀有tRNA基因的大肠杆菌宿主菌株等策略,提高Cap蛋白表达水平,并且形成VLP^[24-26],研制成功5种商品化的PCV2a或PCV2b亚单位疫苗。此外,Li等^[27-28]设计了一种类弹性蛋白多肽(elastin-like polypeptides, ELP)作为纯化标签,采用大肠杆菌系统表达了ELP与PCV2b Cap融合蛋白,通过可逆相转换循环(inverse transition cycling, ITC)技术纯化制备了ELP-Cap融合蛋白,可组装形成Cap蛋白VLP,其免疫效果高于PCV2灭活疫苗(DBN-SX07株)和CircoFLEX PCV2亚单位疫苗。大肠杆菌系统表达的Cap蛋白VLP稳定性与其缓冲液密切相关。Zhang等^[29]通过密码子优化采用大肠杆菌系统高效表达了全长的PCV2d Cap基因,表达量 $75\text{ mg}\cdot\text{mL}^{-1}$,采用含精氨酸、 β -巯基乙醇、甘油、聚乙二醇和谷胱甘肽等成分的缓冲液,可形成稳定的VLP。

2.3 其他表达系统试验亚单位疫苗

酵母表达系统具有营养要求低、发酵密度高和遗传稳定等特点。一些学者利用毕赤酵母、酿酒酵母或

马克斯克鲁维酵母系统表达制备了 PCV2 Cap 重组蛋白,并证明其可以组装成 VLP,可诱导机体产生免疫保护作用^[30-32]。植物表达系统已经被用于表达多种功能蛋白或研制新型疫苗。研究人员采用烟草表达系统表达 PCV2a Cap 蛋白,动物试验证明其能够诱导产生特异性免疫应答和免疫保护作用^[33-34],韩国 Bioapp 公司研制了 PCV2 亚单位疫苗(HERBA-VAC Circo Green Vaccine)。此外,Deng 等^[35]采用纳米抗体(Nanobody)技术,将 PCV2 Cap 蛋白和中性单克隆抗体 mAb-1E7 免疫骆驼,筛选出 1 株纳米抗体 Nb61,其能够阻断 mAb-1E7 与 Cap 蛋白结合,免疫小鼠和仔猪可以抵抗 PCV2 攻击,为 PCV2 抗独特性抗体疫苗研究奠定了基础。

亚单位疫苗免疫效力与疫苗重组抗原 VLP 密切相关。Mo 等^[36]和 Xi 等^[25]采用大肠杆菌表达制备了纯化的 Cap 重组蛋白,解析了 Cap 蛋白晶体结构及 VLP 组装形成的分子机制,明确了 Cap 蛋白核定位信号(NLS)及¹⁵PRSHLGQILRRRP²⁷(α -helix)和³³RHRYRWRRKN⁴²(NLS-B)互作对 Cap 重组蛋白 VLP 形成及其颗粒稳定性发挥重要作用。Cap 蛋白 N 端缺失 27 个氨基酸的截断体可形成 VLP,但缺失 30 个氨基酸则不能形成 VLPs。Zhan 等^[37]发现 C 末端 PXXP 基序对 VLP 自组装及入侵细胞尤为重要。Wang 等^[38]解析了 Cap VLP 表面 loops 结构,发现 MP loop 可展示外源小肽,并且不影响 VLP 组装。Luo 等^[39]将 Cap 蛋白删除 N 端 1~41 aa,与 IgG1 Fc 融合,在 HEK293F 细胞中获得表达,纯化的重组蛋白 Cap Δ 1-41aa-mFc(PCFM)可形成 22.6 nm VLP,可诱导小鼠产生 PCV2 Cap 蛋白抗体及 IFN- γ 和 IL-10 的表达。

3 合成肽疫苗

PCV2 Cap 蛋白存在多个中和抗原表位及中和抗原诱骗表位^[40-44]。Jeong 等^[44]比较了欧洲、北美和亚洲 PCV2 流行毒株 Cap 蛋白序列,设计合成了 5 条疫苗抗原氨基酸序列短肽,采用氢氧化铝、氧化钴和脂质体等佐剂配制 3 种疫苗,证明其 2 次免疫能够提供对 PCV2b 攻击的部分免疫保护,脂质体佐剂疫苗效果优于其他 2 种疫苗,可显著降低淋巴结组织中病毒抗原载量,但其免疫效果低于 CicroFLEX PCV 疫苗,一次免疫效果不够理想。吴胜昔等^[45]采用 DNASTar 和 BcePred 软件预测 PCV2 Cap 的 B 细胞表位,设计筛选了 3 个多肽表位,以赖氨酸为核心基质构建表位单体相同的 4 分支肽(MAP 肽),并串联 1 个通用型 Th 表位(命名为 PCV CP98-156-228 多肽),制备合成肽疫苗,免疫小鼠及家兔,可诱导产生 PCV2 特异性抗体,为 PCV2 合成肽疫苗研究奠定了重要基础。姜平等^[46]根据 PCV2 Cap 蛋白抗原表位氨基酸序列,设计合成了 4 条多肽,长度 46~51 个氨基酸,纯度 90%以上。采用 ISA50V 佐剂配制疫苗,动物试验证明,2 条多肽混合疫苗 2 次免疫可诱导机体产生较高的 ELISA 抗体和中和抗体,显著降低 PCV2 攻击引起的病毒血症和淋巴结病毒载量,减轻临床症状和病理损伤,提高仔猪相对日增重,其免疫效果与商品化的亚单位疫苗相似。栗利芳等^[47-48]根据 PCV2 Cap 蛋白 B 细胞抗原表位,通过不同抗原表位组合,利用 ϵ K 氨基酸作为连接子(Linker)将 T 细胞表位和 B 细胞表位进行串联,设计合成了 6 条多肽,证明其可有效诱导猪体产生免疫应答和免疫保护作用。鉴于此,南京农业大学和中牧实业股份有限公司合作,成功研制了世界首个猪圆环病毒 2 型合成肽疫苗。该疫苗安全有效,免疫保护效力与 PCV2 灭活疫苗相似,可有效预防和控制 PMWS,降低临床发病率和死亡率。但由于受到 ISA50V 矿物油佐剂限制,该疫苗尚未大量推广使用。

4 基因工程活载体疫苗

PCV2 重组活载体疫苗研究较多,采用的载体病毒或细菌有腺病毒、疱疹病毒、痘病毒、乳酸乳球菌、支气管炎博德特氏菌、鼠伤寒沙门氏菌和枯草芽胞杆菌等,但目前尚无商品化的 PCV2 重组活载体疫苗。

4.1 病毒载体活疫苗

Wang 等^[15]构建了 PCV2b 重组腺病毒,免疫后可以阻止 PCV2 感染发病,产生良好的免疫保护作用。猪 CD40 配体(CD40L)、粒细胞-巨噬细胞集落刺激因子(GM-CSF)及假结核耶尔森菌透明质酸酶 C 末端基因(*InvC*)能够增强重组腺病毒表达的 Cap 蛋白免疫效果^[49-51]。猪伪狂犬病毒被广泛用于研究 PCV2 重组活病毒载体疫苗^[16,52-53]。Lu 等^[54]构建了表达 PCV2 Cap 蛋白的 *gE/TK* 基因缺失的重组伪狂犬病毒(Pseudorabies virus, PRV),其可以诱导产生针对 PCV2 和 PRV 体液免疫和细胞免疫抗体,并且可以抵抗 PRV 变异株、PCV2b 和 PCV2d 攻击。Li 等^[55]构建了表达 PCV2 Cap 和 PCV3 Cap 蛋白、缺失 TK/*gI/gE* 的重组 PRV,可诱导产生抗 PRV、PCV2 和 PCV3 特异性抗体和高水平 IFN- γ 、IL-2 和 IL-4,并且可以抵抗

PRV 变异株 SX-10 和 PCV2 的攻击。Pavulraj 等^[56]和 Silva 等^[57]采用 PRV 毒株构建了 *TK*、*gG* 和 *gE* 基因缺失毒株 PRV_{tmv},并在 *TK* 基因缺失位置插入 PCV2 *Cap* 基因,*gG* 基因缺失位置插入猪瘟病毒 (CSFV) *E2^{ms}* 基因-*GM-CSF*,*gE* 基因缺失位置插入 CSFV *E2* 基因,构建了 PCV2 和 CSFV 重组 PRV 活载体疫苗 PRV_{tmv}⁺,其可诱导产生针对 PCV2 和 CSFV 免疫保护作用。Pei 等^[58]将猪繁殖与呼吸综合征病毒 (PRRSV) 弱毒株作为载体,构建了能够稳定表达 PCV2 *Cap* 蛋白的重组 PRRSV;Tian 等^[59]利用 PRRSV 弱毒株 DS722 作为活载体,构建了可表达 PCV2 *Cap* 蛋白和猪流感病毒 HA 蛋白的重组 PRRSV,并证明其可以产生很好的免疫保护作用。此外。de Oliveira Daian 等^[60]构建了表达 PCV2b *Cap* 蛋白的重组安卡拉痘病毒,2 次免疫可诱导小鼠产生 PCV2 特异性免疫反应。

4.2 细菌活载体疫苗

近年来,一些学者对 PCV2 重组细菌载体疫苗进行了研究。采用的细菌载体有支气管炎博德特氏菌^[61]、鼠伤寒沙门氏菌^[62-63]、枯草芽胞杆菌^[64]和乳酸乳球菌^[65-66]等。Lloren 等^[63]构建了 PCV2d *Cap* 真核表达质粒 pJHL204,转染至弱毒鼠伤寒沙门氏菌,获得重组鼠伤寒沙门氏菌 JOL2995 (p204:cap),证明其可诱导小鼠产生 PCV2 中和抗体、CD4⁺ 和 CD8⁺ T 细胞免疫应答,并降低攻毒小鼠病毒载量。Zhang 等^[64]构建了表达 PCV2 *Cap* 的重组枯草芽胞杆菌,口服免疫猪体可以激活骨髓来源的树突细胞分泌 CD40、CD80 和 MHC II,促进 T 细胞增殖;肠道和呼吸道黏膜 PCV2 特异的 IgA 和血清特异性抗体显著升高;回肠 CD3⁺ T 细胞和 CD4⁺ T 细胞显著升高。TLR2/9、IL-1 β 、IL-6、INF- γ 和 β -防御素分泌明显增加。Wang 等^[66]构建表达 PCV2 *Cap* 的重组乳酸乳球菌 pAMJ399-*Cap*/MG1363,小鼠口服后该菌可刺激其胃肠,停留至少 11 d,并诱导产生 PCV2 特异性体液免疫、细胞免疫和黏膜免疫,为研制口服疫苗奠定了基础。

5 基因疫苗

PCV2 基因疫苗的研制起始于 21 世纪初,但至今没有成功。Fenaux 等^[67]构建了 PCV1 *ORF1* 和 PCV2 *ORF2* 的嵌合病毒基因组 PCV1-2a,免疫仔猪可有效减少淋巴结组织 PCV2 载量,避免出现病毒血症,从而有效预防 PCV2 感染。PCV1-2 DNA 疫苗类似减毒活疫苗。此后,一些学者构建了 PCV2 *ORF2* DNA 疫苗,证明其可诱导小鼠产生 PCV2 抗体,降低 PCV2 攻毒病毒含量,减轻病理损伤^[17,68-72]。为了提高 DNA 疫苗免疫效果,将 IL-15 和结核分枝杆菌热休克蛋白 70 (*HSP70*) 与 PCV2 *ORF2* 基因串联或融合表达,取得一定效果^[73-74]。Hou 等^[75]将多个拷贝的 C3d 分子或其最小结合域 C3d-p28 偶联到 *ORF2* 基因上,构建了 pVAX1-*ORF2*-C3d-P28 DNA 疫苗,并证明其可以诱导 PCV2 特异性体液和细胞免疫反应,明显增强 DNA 疫苗的特异性应答反应,保护猪体免受 PCV2b 和 PCV2d 的攻击。

6 活疫苗

PCV2 活疫苗研究主要是 PCV1-2a 和 PCV1-2b 嵌合病毒活疫苗。该类疫苗毒力评价难度较大,目前尚无商品化的 PCV2 活疫苗。PCV1-2a 嵌合活疫苗在细胞培养中遗传稳定,在猪体内可连续传代,毒力明显较弱,没有引起临床疾病,而且可以诱导猪体免疫保护作用,能够抵抗 PCV2b 或 PCV2d 攻击^[2,76]。PCV1-2b 嵌合病毒毒力和免疫原性与 PCV1-2a 相似,可诱导猪体产生强烈的体液免疫,诱导猪对 PCV2a 和 PCV2b 产生交叉保护免疫反应^[2,77]。我国学者也构建了 PCV1-2b 嵌合弱毒疫苗,并证明其能够诱导产生较高免疫应答,可以提供对 PCV2b 和 PCV2d 交叉免疫保护作用^[78-80]。为了区分疫苗免疫抗体和 PCV2 野病毒感染抗体,Beach 等^[81]构建了携带 2 个分子标签 (GLU 和 KT3) 的 PCV1-2 嵌合病毒,其能够诱导猪体产生 PCV2 中和抗体及 KT3 和 GLU 抗体。Huang 等^[82]构建了携带分子标签 V5 的重组 PCV2,其诱导小鼠产生 PCV2 中和抗体及 V5 抗体。Rakibuzzaman 等^[83]通过 PCV2b *Cap* 57~609 bp 区域丝氨酸和亮氨酸基因密码子去稳定性突变,同时,在 *Cap* 基因末端插入 *SRS2* 标签,构建了自杀性复制的 sPCV2-Vac,免疫 SPF 仔猪,诱导产生高水平中和抗体,且无病毒血症,能够抵抗 PCV2d 攻击,为 PCV2 弱毒标记活疫苗研究提供了新思路。

7 联合疫苗

7.1 PCV2 不同基因亚型毒株联合疫苗

试验条件下,PCV2 疫苗对不同基因亚型毒株均具有交叉保护^[84-87],但近些年临床应用结果显示,

PCV2a 和 PCV2b 商品疫苗免疫保护效力有所下降。Ju 等^[88]选择 3 个猪场(PCV2、PRRSV、猪肺炎支原体和大肠杆菌感染猪群),PCV2a 疫苗免疫后 4~8 周龄或 8~12 周龄仍然出现 PCV2 感染临床症状。他们改用 PCV2d Cap 蛋白 VLP 疫苗接种,结果 3 个猪场 PCV2 病毒血症明显下降,2 个猪场 PCV2 中和抗体明显提高,免疫后 12 周,猪群体重明显高于非免疫对照组,证明 PCV2d Cap VLP 疫苗可以提供有效免疫保护。Yu 等^[89]制备了 PCV2a、PCV2b 和 PCV2d 三种灭活疫苗,仔猪试验结果显示,3 种灭活疫苗免疫组针对同基因亚型 PCV2 的 IPMA 抗体及病毒中和抗体水平高于其他异源基因亚型 PCV2 的抗体水平。PCV2d 攻毒后,PCV2a、PCV2b 和 PCV2d 灭活疫苗组淋巴结组织中 PCV2d 核酸分别减少 93.8%、99.8% 和 98.3%,表明 PCV2a 疫苗免疫保护效率低于 PCV2b 和 PCV2d 灭活疫苗。PCV2a 和 PCV2b 疫苗免疫失败的猪群,采用 PCV2d VLP 疫苗可有效增强疫苗免疫保护效力。Kroeger 等^[90]采用 21 日龄仔猪 PCV2d 和 PRRSV 共感染模型,比较了 PCV2a 和 PCV2d 商品疫苗的免疫保护效力。PCV2d 攻击后,PCV2d 商品疫苗组没有出现明显临床症状,淋巴结、扁桃体淋巴细胞耗竭、PCV2 含量显著减少;而 PCV2a 商品疫苗组约 20% 仔猪出现中重度淋巴细胞耗竭和较高含量的 PCV2,表明 PCV2 商品疫苗对同源毒株免疫保护效力优于异源毒株。为了提高 PCV2 疫苗免疫保护效力,国外企业研发了 PCV2d、PCV2a 和 PCV2b 多毒株联合疫苗,如:美国硕腾公司的 PCV1-2a-PCV2b-猪肺炎支原体(Mhyo)三价灭活疫苗(CircoMax Myco[®])、PCV2a-PCV2b-Mhyo 三联灭活疫苗(Fostera[®] Gold PCV MH)及 PCV1-2a-PCV1-2b-Mhyo 三价灭活疫苗(类似于 CircoMax Myco[®]),它们对 PCV2d 感染均有较好免疫保护作用^[91-93]。

7.2 PCV2 与猪重要病原联合疫苗

为了减少猪群免疫次数和减轻免疫应激反应,国内外很多学者和疫苗企业对 PCV2 与其他病原的联合疫苗进行了广泛研究,其中 PCV2-Mhyo^[94]、PCV2-猪细小病毒^[85]、PCV2-猪瘟病毒^[95-96]、PCV2-副猪嗜血杆菌、PCV2-Mhyo-副猪嗜血杆菌、PCV2-副猪嗜血杆菌-猪链球菌、PCV2-PRRSV-Mhyo、PCV2(含 PCV2a、PCV2d Cap 蛋白)-Mhyo-胞内劳森菌等多联灭活疫苗的研究取得了重要进展。Chen 等^[97]利用 CHO 细胞分别表达 CSFV E2 和 PCV2 Cap 蛋白,制备 CSFV-PCV2 二联亚单位疫苗,1 次免疫即可诱导产生病毒抗体,并能有效抵抗 CSFV 和 PCV2 强毒攻击。Allen 等^[98]报道,PCV2(含 PCV2a、PCV2d Cap 蛋白)-Mhyo-胞内劳森菌三联灭活疫苗免疫猪可有效抵抗 PCV2a、PCV2d、猪肺炎支原体及胞内劳森菌攻击。Yang 等^[99]比较了商品化的 PCV2-猪肺炎支原体二联疫苗及其单苗的猪体免疫效果,证明其对 2 种病原均有免疫保护作用。Cho 等^[100]在 PCV2d 感染并有肺炎临床表现的猪场,比较了 180 头仔猪对 PCV2a-Mhyo 和 PCV2b-Mhyo 二联灭活疫苗的免疫保护效果,证明 2 种疫苗免疫保护效力没有明显差异。Venegas-Vargas 等^[91]研究 PCV1-2a-PCV2b-Mhyo 三价灭活疫苗(Circumax Myco[®])仔猪免疫效果,并与重组杆状病毒表达的 PCV2a-Mhyo 二联疫苗(Circumvent[®] PCV-M G2)进行了比较。仔猪免疫 2 次,间隔 3 周,第 2 次免疫后 3 周采用 PCV2d 攻击,结果表明 PCV1-2a-PCV2b-Mhyo 疫苗对 PCV2d 感染具有较好保护效果。Pleguezuelos 等^[93]研究 PCV1-2a-PCV1-2b-Mhyo 三价灭活疫苗临床免疫效果,证明其对 PCV2a、PCV2b、PCV2d 感染均有较好免疫保护作用。Um 等^[92]比较了 PCV2a-PCV2b-Mhyo 三价灭活疫苗(Fostera[®] Gold PCV MH)和 PCV2a-Mhyo 二联灭活疫苗(Porcilis[®] PCV M Hyo)的临床免疫保护效果,证明三价灭活疫苗 1 次免疫和 2 次免疫效果相似,但其对 PCV2d 的免疫保护效果优于二联灭活疫苗一次免疫效果。Pálmai 等^[101]比较了 3 周龄仔猪对 5 种商品化 PCV2-Mhyo 联合疫苗的免疫效果,包括 PCV2d-Mhyo 二联灭活疫苗(Cirbloc[®] M Hyo,)、PCV2a-Mhyo 联合疫苗(FLEXcombo, Porcilis[®] PCV M Hyo, CircoMax[®] Myco 及 MHYOSPHERE[®] PCV ID),结果表明,PCV2d-Mhyo 二联灭活疫苗优于其他商品疫苗,说明疫苗抗原与 PCV2 流行毒株抗原匹配性非常重要。

目前,我国的 PCV2-Mhyo 二联灭活疫苗、PCV2-Mhyo-副猪嗜血杆菌三联疫苗、PCV2-副猪嗜血杆菌-链球菌三联灭活疫苗实现了产业化生产。邱冬等^[102]采用 HP-PRRS 活疫苗(TJM-F92,华威特)和国药动保有限公司的 PCV2 灭活疫苗进行单点肌肉注射的联合免疫试验,结果显示,2 种疫苗联合免疫未产生相互干扰。此外,进口注册的 2 种 PCV2-Mhyo 二联灭活疫苗对猪病防控也起到了积极作用。西班牙海博莱公司还研制了世界第 1 个皮内注射的表达 PCV2a Cap 蛋白的重组猪肺炎支原体 Nexhyon 株灭活疫苗,对 PCV2d 和猪肺炎支原体均具有较好的免疫保护效果^[103-104]。

8 PCV2 Cap VLP 纳米颗粒平台多价多联疫苗

PCV2 Cap 蛋白有 7 个 Loop。除 Loop FG 外,其他 Loop 环均位于 VLP 表面,相邻的 Loop 环之间紧密

接触,对 VLP 的装配和稳定具有重要作用,而且 Loop CD 区可插入外源基因^[105]。PCV2 Cap 蛋白的 N 末端隐藏在 VLP 内,而 C 末端延伸到 VLP 表面形成突起,且最后 4 个氨基酸形成构象表位。Beach 等^[81]在 Cap 蛋白 C 末端插入外源 Tag 多肽,构建了含不同长度外源 Tag 多肽的重组 PCV1-2 嵌合病毒,证明其在体内、外均有感染性,能诱导产生 Tag 多肽表位抗体和 PCV2 中和抗体,并且 Cap 蛋白 C 末端可容受至少 27 个氨基酸多肽。Li 等^[106]在 Cap 蛋白 C 末端融合生长抑素(SS)基因,表达形成 PCV2 嵌合 VLP,诱导小鼠产生 PCV2 Cap 和 SS 抗体。Zhang 等^[107]将 CSFV B/T 细胞表位替换 PCV2 Cap N 末端核定位信号区(NLS)构建了嵌合 Cap 蛋白,虽然可形成 VLP,但不能诱导产生 CSFV 中和抗体。Jung 等^[108]将 PRRSV 4 个 B 细胞线性抗原表位替代 PCV1-2b 弱毒株 Cap 蛋白 C 端的诱骗表位,动物试验证明其可诱导小鼠产生 PRRSV 中和抗体,表明 PCV2 Cap 蛋白 C 末端在病毒组装和与宿主细胞相互作用中起关键作用。

Biotin-avidin、HaloTag 和 SpyTag/SpyCatcher 等标签偶联系统能够实现抗原的独立表达和模块化装配,为颗粒疫苗构建提供了新思路。Liu 等^[109]将 PCV2 Cap 蛋白 C 端与 SpyCatcher 融合,组装为 26 nm 的 VLP(Cap-SC),将 CSFV E2 与 SpyTag 融合,获得重组蛋白 E2-SpyTag,再通过 SpyCatcher 和 SpyTag 体外共价结合,形成 E2-Cap VLP(Cap-E2 NP)。该 Cap-E2 NP 颗粒疫苗可被抗原提呈细胞(APC)有效提呈,促进 APC 成熟和细胞因子产生,可诱导小鼠产生 PCV2 中和抗体及 CSFV E2 特异性抗体。张改平院士团队的 Chen 等^[110]将 PCV2 VLP 与模块化连接元件 SpyTag/SpyCatcher 相结合,开发了 Cap-Cat VLP 纳米抗原展示平台,证实 Cap-Cat VLP 可自组装成直径为 20 nm 的颗粒,具有良好温度、冻融和储存稳定性,75 ℃ 孵育 1 h 后仍能保持溶解度,可抵抗 10 次冻融循环并在 4 ℃ 下储存 30 d 以上。Cap-Cat VLP 平台可展示不同大小和多聚体结构的 PRRSV GP53、PEDV COE、CSFV E2 和流感病毒 HA 等猪源病毒保护性抗原,可增强机体免疫应答,提升病毒特异抗体水平、细胞免疫水平及流感病毒攻毒保护能力,为 PCV2 Cap 蛋白病毒样颗粒多价多联疫苗研究奠定了重要基础。

PCV3 和 PCV4 作为新发现病毒,逐渐受到国内外学者关注。PCV2 疫苗对 PCV3 和 PCV4 均无交叉保护作用^[111-112]。Wu 等^[113]通过嵌合 PCV2 中和抗原表位,构建了 PCV3 Cap 蛋白 VLP(pCap3-Cap2E VLP)可以诱导小鼠和豚鼠产生细胞免疫和 PCV2 免疫保护作用。PCV3 分离培养存在一定困难,目前尚无商品化疫苗。美国 Sequivity 平台(默克动物健康公司)研制了一种猪场专用的 PCV3 复制子颗粒疫苗,可提供对 PCV3 的保护,但其经济效益还需进一步评估。

9 结论与展望

免疫接种是预防和控制猪圆环病毒的最有效方法。PCV2a、PCV2b 和 PCV2d 商品疫苗对不同基因型流行毒株具有较好免疫保护效力,其中 PCV2d Cap 蛋白疫苗免疫效力最佳,但不能有效清除 PCV2 感染。PCV2 疫苗不能交叉保护 PCV3 和 PCV4 感染。随着 PCV2 基因的变异,目前商品疫苗的免疫保护效果下降。因此,研发具有清除 PCV2 功能的新型高效疫苗和标记疫苗及其对应的鉴别诊断技术很有必要。此外,研发无针皮内免疫或呼吸道途径免疫的 PCV2 疫苗,可以提高生物安全和动物福利,实现疫苗抗原精准递送。目前尚无雾化 PCV2 疫苗的研究报道。

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白娟,南京农业大学教授,博导,国家生猪产业技术体系病毒病防控岗位专家,农业农村部动物细菌学重点实验室副主任,南京农业大学预防兽医学系副主任,中国畜牧兽医学动物传染病学分会/生物制品与动物药品学分会理事。长期从事猪繁殖与呼吸综合征、流行性腹泻、非洲猪瘟等新发与再现疾病的病原学、流行病学、致病机制及免疫防控技术研究,主持国家和部省级课题13项,以第一/通信作者发表论文45篇,制定国家及地方标准4项,获授权发明专利20项,新兽药注册证书9项(一类和二类各1项),实现产业化生产。获教育部科技进步奖一等奖(第3)、江苏省科学技术一等奖(第3)、大北农科技奖(第3)、中国产学研合作创新成果奖(第4)。



姜平,南京农业大学动物医学院教授,博导,教育部动物健康与食品安全国际合作联合实验室主任,全国农业科研杰出人才与创新团队,享受国务院政府特殊津贴。国务院学位委员会第八届兽医学科评议组成员,第五届全国兽医专业学位研究生教育指导委员会秘书长,国家农业转基因生物安全委员会委员,国家生猪产业技术体系岗位专家,中国畜牧兽医学动物传染病学分会和生物技术学分会副理事长。1998年在加拿大圭尔夫大学兽医学院进修,2000—2001年在美国芝加哥Rush医学中心博士后研究,2018—2023年任南京农业大学动物医学院院长。主持国家和部省级课题40余项,长期从事畜禽传染病研究,研制成功中国首个猪圆环病毒2型灭活疫苗、合成肽疫苗和基因工程亚单位疫苗、猪繁殖与呼吸综合征活疫苗及猪伪狂犬病基因缺失灭活疫苗,新兽药注册证书9个(一类、二类各1个),实现产业化生产,在国内外核心期刊发表研究论文300多篇(SCI论文150余篇),发明专利21项,国家标准2项。主编《兽医生物制品学》(第二、三版)、《兽医传染病学》(第七版)等教材和专著9部。培养博士研究生74名(留学生3名)和硕士研究生224名。获部省级科技进步奖9项(一等奖2项),国家发明专利优秀奖1项。