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Review

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Achievements, challenges and prospects for the development of broadly protective multivalent vaccines and therapeutic antibodies against hand, foot and mouth disease

Ke Lyu · Rong Chen

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Abstract Hand, foot and mouth disease (HFMD) is a significant health concern in the Asia–Pacific regions for infants and young children in recent years. However, no vaccines or therapeutics are available at present. The causative agents for HFMD include human enterovirus 71 (EV71), coxsackievirus A16 (CVA16) and some other viruses. Recently, tremendous progress has been made in the development of monovalent and bivalent vaccines against HFMD. A few neutralizing monoclonal antibodies against EV71 or CVA16 have been identified and characterized. Here, we reviewed some achievements for the development of broadly protective vaccines and neutralizing antibodies against HFMD, and discussed challenges and prospects toward broadly protective multivalent vaccines and therapeutic antibodies against HFMD.

Keywords Hand, foot and mouth disease (HFMD) · Human enterovirus 71 (EV71) · Coxsackievirus A16 (CVA16) · Vaccine · Neutralizing antibodies

1 Introduction

Hand, foot and mouth disease (HFMD) is a worldwide infectious disease in infants and young children. In recent years, numerous outbreaks of HFMD occurred in the Asia–Pacific regions, causing significant morbidity and mortality [1]. The reported fatal cases of HFMD in the mainland of China has reached to over 3000 since 2008 (www.chinacdc.cn). It is noteworthy that the number of reported fetal cases caused by HFMD is 501 in 2014. Compared with 2013, the morbidity and mortality increased by 51.86 % and 98.92 %, respectively. However, no vaccines or therapeutics are available at present.

HFMD is commonly a mild disease, but it can be associated with severe neurological symptoms, such as acute fatal encephalitis, polio-like acute flaccid paralysis and neurogenic pulmonary edema [2]. The major causative agents for HFMD are human enterovirus 71 (EV71) and coxsackievirus A16 (CVA16), both belonging to species *Enterovirus* A genus *Enterovirus* family *Picornaviridae* [3]. Other enteroviruses, such as CVA6 [4], A10 [4], A12 [5] and B5 [5], echovirus30 [6], are also associated with outbreaks of HFMD. Therefore, for more effective control and prevention of HFMD, a multivalent vaccine eliciting broadly neutralizing antibodies is highly desirable.

Currently, a few vaccine candidates against EV71 have entered clinical trials [7–10], and other vaccine candidates are at the preclinical study stage. Here, we summarized major achievements in the development of vaccines and therapeutic antibodies against HFMD.

2 Vaccines

2.1 Vaccine development against EV71

EV71 is the leading causative agent for HFMD. Until now, a number of approaches have been taken to develop vaccines against EV71, including inactivated whole-virus vaccines [7–10], attenuated live virus vaccines [11], virus-like particles (VLPs) [12–17] and other types of EV71 vaccine candidates [18–27] (Table 1).

K. Lyu · R. Chen (✉)
Key Laboratory of Molecular Virology and Immunology, Institut Pasteur of Shanghai, Chinese Academy of Sciences, Shanghai 200031, China
e-mail: rongchen@ips.ac.cn

Table 1 Vaccine development against EV71

Vaccine type	Virus strain (subgenotype)	Expression system	Protective effects [references]
Inactivated virus	FY7VP5/AH/CHN/2008 (C4)	Vero cells	90.0 % efficacy against EV71-associated HFMD and 80.4 % against EV71-associated disease [8]
	H07 (C4)	Vero cells	94.8 % efficacy against EV71-associated HFMD or herpangina and 88.0 % against EV71-associated disease [9]
	FuYang2008 (C4)	Human diploid cell (KMB17 strain)	97.4 % efficacy against EV71-associated HFMD [10]
	E59 (B4)	Vero cells	Cross-neutralizing antibodies elicited against B1, B5 and C4a, but not C2 [7]
	INV21 (B3)	Vero cells	Not reported
Attenuated virus	BrCr-ts (A)	Vero cells	Attenuated neurovirulence in the central nervous system of monkeys [11]
VLPs	*neu* (C2)	Insect cells	Neutralizing antibodies elicited in mice and protection from lethal viral challenge [14]
	AH08/08 (HQ611148) (C4)	*S. cerevisiae*	Neonate mice protected by VLP immune sera from lethal EV71 challenge [15]
	EV71/G082 (C4)	*Pichia pastoris*	Neutralizing antibodies against homologous and heterologous EV71 strains in mice [16]
	Neu (pinf7-54A) (C2) (GenBank DQ060149)	293A cells	Ad-EVVLP-immunized antisera neutralized the EV71 B4 and C2 subgenotypes. Ad-EVVLP-vaccinated mice were 100 % protected from EV71 infection [17]
P1		*Pichia pastoris*	Good cross-protection with different EV71 strains [18]
VP1		Various systems	Neutralizing antibodies at a much lower titer than those induced by inactivated vaccines or VLPs [19–22]
Synthetic peptide	41 (5865/SIN/00009) (B4) (GenBank No. AF316321)	SP55 (aa 163–177 in VP1)	EV71-specific IgG response in mice as high as that obtained with the whole virion as immunogen [23]
		SP70 (aa 208–222 in VP1)	Neutralizing antibodies elicited with good passive protection against homologous and heterologous EV71 strains in suckling BALB/c mice [23]
	TW/2086/98	VP2-28 (aa 136–150)	Neutralizing antibodies elicited against different EV71 strains as well as CVA16 [24]
Heterologous systems		SP70 displayed on Ad3	Protection in neonatal mice [25]
		SP55 or SP70 fused with HBc	Carrier- and epitope-specific antibody responses in mice after immunization with chimeric VLPs [26]
		mTLNE-three linear neutralizing epitopes linked	Full protection against lethal challenge in neonatal mice after passive transfer with anti-mTLNE sera [27]

2.1.1 Inactivated EV71 vaccine

The first clinical trial of formalin-inactivated EV71 vaccine containing an aluminum hydroxide adjuvant was conducted in Bulgaria in 1975, in response to the epidemic [28]. However, the results were not reported. Recently, at least five EV71-inactivated whole-virus vaccines have entered clinical trials (Table 1). Beijing Vigoo, Sinovac and the Chinese Academy of Medical Science (CAMS) in the mainland of China have independently developed C4-subgenotype-based inactivated EV71 vaccine candidates, all of which have finished phase III clinical trials with high efficacy. Health Research Institute (NHRI) in Taiwan have completed phase I clinical trial of a B4-subgenotype-based inactivated EV71 vaccine candidate using formalin for inactivation, and the study showed more than fourfold increase in the neutralizing antibody titers against the B4 vaccine strain even after a single immunization and the presence of cross-neutralizing antibodies against subgenotypes B1, B5 and C4a, but not C2 [7]. Inviragen in Singapore initiated phase I clinical trial of a B2 subgenotype inactivated EV71 vaccine from Vero cells. However, the results are still pending.