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Short Communication

Shigella Vaccine Development: The Model Matters

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Abstract

Bacillary dysentery or shigellosis is mediated by the pathogenic enterobacteria *Shigella*. Shigella are transmitted through the fecal-oral route, no animal reservoir has been described, and remain a major cause of moderate-severe diarrhea worldwide since no *Shigella* vaccine is yet commercialized. The design of a pan-*Shigella* vaccine has been made difficult by the large variety of *Shigella* species and serotypes and the continuous identification of new serotypes due to the genomic plasticity of *Shigella*. The assessment of *Shigella* vaccine candidates remains complicated by the lack of a suitable animal model of shigellosis. Until know, several model of shigellosis have been characterized in the rhesus macaque, the rabbit, the mouse or the guinea pig, although none of them is satisfactory to assess the whole *Shigella* virulence process from an oral inoculation to the colonic mucosa colonization and disruption. The potential and limits of the different animal model of shigellosis used so far to study *Shigella* virulence mechanisms and to evaluate vaccine candidates' efficacy are described here. Since no optimal animal model of shigellosis has been characterized, further efforts should be made to develop a suitable one, as a pre-requisite for the development of a successful *Shigella* vaccine.

INTRODUCTION

Bacillary dysentery or shigellosis remains nowadays a major burden disease especially in developing countries; annual shigellosis mortality was estimated in 2010 at 123,000 deaths worldwide among 88.4 million cases, mainly children under the age of five [1]. Bacillary dysentery is associated with fever, abdominal cramps and rectal inflammation. Dysenteric stools characteristically contain erythrocytes, polymorphonuclear neutrophils (PMNs) and mucus. Although the etiologic agents, *Shigella* spp., have been identified more than a century ago, shigellosis represents a major threat to public global health since no licensed vaccine is available.

*Shigella*s are a Gram-negative pathogenic enterobacteria infecting and colonizing specifically the human colon during shigellosis. *Shigella* encompasses four species (*S. flexneri*, *S. sonnei*, *S. dysenteriae* and *S. boydii*). Within each species, different serotypes were classified based on the structure of the O-antigen repeats that comprise the polysaccharide moiety of the lipopolysaccharide (reviewed in [1,2]). There is a large variety of serotypes among *Shigella* isolates: *S. dysenteriae* encompasses 15 serotypes, *S. flexneri*, 14 serotypes, *S. boydii*, 20 serotypes and *S. sonnei* a single serotype. Brutal epidemics of bacillary dysentery can be caused by *S. dysenteriae*1, which produces the Shiga toxins, whereas the endemic forms of the disease are caused essentially by *S. flexneri* and *S. sonnei* [2]. The distribution of sero groups varies in different geographical regions; *S. flexneri* serotypes are most prevalent in India and in Asia [3,4]. In industrialized countries, *S. sonnei* is the prevalent serotype, which also recently emerged in China, Brazil, Vietnam or Bangladesh following the rapid industrialization of these countries [5-9]. The main causes of these changing geographical distributions remain elusive in some extents. Recent Global Enteric Multicenter Study (GEMS) confirmed the global threat of *Shigella* as a major cause of moderate-severe diarrhea among children under the age of five in sub-Saharan Africa and South Asia [10,11].

Shigella Vaccine Candidate Development

The design of a pan-*Shigella* vaccine protecting against all *Shigella* infections has been made difficult by the diversity of *Shigella* species and serotypes. In addition *Shigella* genome is continuously modified by the acquisition or deletion of genes mediated by mobile genetic elements (plasmids, transposons, insertion sequences and integrons). These modifications are the main cause of the generation of novel antibiotic resistant strains, but also the formation of novel *Shigella* serotype variants [12-15]. Main efforts have been focused on *Shigella* species and serotypes considered to be important causal agents of human shigellosis: *S. sonnei*, *S. flexneri* 2a, 3a and 6. Most *Shigella* vaccine candidates contain the specific Lipopolysaccharide-associated O-specific polysaccharide (O-SP) antigen, which is specific to one *Shigella* serotype and is highly antigenic: this is the case for cellular candidates (live-attenuated strains), glycoconjugate candidates (O-SP-protein conjugates) [16], novel antigen candidates, such as Generalized Modules for Membrane Antigens (GMMA) [17] or outer-membrane vesicles (OMVs) alone or encapsulated in

nanoparticles [18]. It has to be noticed that protein-based vaccine candidates in the presence of an adjuvant (i.e. dmLT or MPML) were also successfully evaluated using conserved cell-surface exposed antigen common to all *Shigella* species such as IpaB/IpaD [19] or PSSP-1 (pan-Shigella surface protein 1) [20]. Several *Shigella* vaccine candidates' safety and efficacy were validated in pre-clinical trials and are currently evaluated in humans. Most candidates are in Phase I and II, including live-attenuated strains (*S. flexneri* 2a CVD 1204, *S. flexneri* 2a CVD 1208S, *S. flexneri* 2a SC602, *S. sonnei* WRSs1 and *S. dysenteriae* 1WRSd1), conjugated antigenic molecules (*S. flexneri* 2a LPS-rEPA, *S. sonnei* PLS-rEPA, Invaplex, and O-antigen mimic-tetanus toxoid) (as recently reviewed in [21]).

The main difficulty for the assessment of *Shigella* vaccine candidates' efficacy remains the lack of an ideal animal model of shigellosis. Shigellosis is characterized by the specific invasion and destruction of the human colonic mucosa by *Shigella* and rarely occurs in animals other than humans. *Shigella* are transmitted through the fecal-oral route, no animal reservoir has been described. However, several reports described sporadic shigellosis cases in experimental monkeys [22], pigs [23] or chicken [24]. Several animal models of *Shigella* infection have been described and used to replicate human shigellosis and assess *Shigella* virulence or Shigella vaccine candidates' efficacy, although few of them allowed a step-by-step evaluation of *Shigella* virulence mechanisms from an oral infection to the colonic invasion and destruction. As a consequence, the evaluation of *Shigella* vaccine candidates' protective action remains complicated. The potential and limits of the different animal models of shigellosis are hereafter described.

Animal Models of Shigellosis

Sansonetti and colleagues went on to pioneer the characterization of the essential role of the *Shigella flexneri* virulence plasmid (pWR110) in ligated rabbit ileal loops and in the guinea pig kerato conjunctivitis model (Sereny test) [25]. The attenuation of a *Shigella dysenteriae* 1 Tox- mutant was validated in ligated rabbit ileal loops and upon intragastric challenge of rhesus macaques (*Macaca Mulatta*) [26].

Until now the non-human primatesrhesus macaque (*Macaca Mulatta*) model of *Shigella* infection is the one, which mimics best the shigellosis. It allows to follow *Shigella* adaptation to the gastric acidic environment, its survival to the small intestine-associated immune response and the invasion, colonization and destruction of the colonic mucosa, associated with bloody stools, intestinal ischemia and the inflation of polymorphonuclear neutrophils [26,27]. However, this model of shigellosis is expensive and its use is now limited by reglementary and ethical constraints.

Among other large animal model of shigellosis, a young (4-week-old) domestic pig (*Susscrofadomestica*) model was evaluated, although no colonic colonization by *Shigella* strains (*S. dysenteriae* and *S. flexneri*) was observed upon oral administration of pathogens [23]. At the opposite, *Shigella dysenteriae* 1 oral administration in a piglet model lead to the gastrointestinal track epithelium invasion with a more profound destruction of the colonic mucosa and lamina propria, associated with high levels of IL-8 and IL-12 [28].

Rabbits have been widely used for *Shigella* infection studies, in particular the ligated rabbit ileal loop model of *Shigella* infection. This surgical model consists in ligating loops (between 8 and 10 per animal) along the rabbit ileum, allowing replicates of *Shigella* infections, potentially with different strains in one animal [29,30]. However, in this model the targeted organ is the ileum, not the colon as observed in humans. More specifically, it has been observed that M cells, located in the ileum Gut-associated lymphoid tissue (GALT) are preferentially invaded [29,31]. GALTs are composed of a specialized follicle associated epithelium (FAE), which overlies a subepithelial dome containing numerous macrophages, dendritic cells, T and B lymphocytes, and special antigen sampling microfold cells (M cells). The structure and the organization of M cells containing GALTs in the gut are diverse: Peyer's patches (PPs) are found in the small intestine and isolated lymphoid follicles (ILFs) are present in the colon [32-34]. The invasion of M cells by *Shigella* in colonic ILFs remains elusive (as discussed in [35]). More recently a non-surgical rabbit model of enteric *Shigella* infection was characterized by oral administration of the pathogen. Consistently, the ileum, not the colon, was the major site of tissue infection and necrosis observed in this model [36]. However, this use of this model of shigellosis is now also limited by ethical constraints (moderate animal suffering) since alternative small animal models became available.

Mice are the experimental tool of choice for most host-pathogen interaction studies. However, adult mice do not develop shigellosis upon oral, intragastric or intrarectal challenge with *Shigella*, for reasons which remain elusive. Among other hypothesis, polymorphonuclear neutrophils, which play a central role during *Shigella* infection in humans, represents only 10-25% in mouse blood as compared to50-70% circulating white blood cells in humans (reviewed in [37]). Second, the gene coding for IL-8, a key chemokine mediating the polymorphonuclear recruitment during *Shigella* invasion [38] is absent in mice. Despite these limitations, several mouse models have been proposed and used exploiting different inoculation routes rather than oral and/or different targeting organs rather than the colon. Most of these alternative models do not mimic the step-by-step infectious process (from an oral infection to the colonic invasion and destruction). One exception is the newborn mouse model in which the colonic invasion and destruction are observed upon an oral challenge with *Shigella* strains [39]. However, the newborn mouse innate immune system is still immature: low IL-6 and G-CSF production lead to an inefficient granulopoiesis [40])

The most widely used mouse model of shigellosis is the lethal pulmonary infection (pulmonary pneumoniae model), consisting in an intranasal challenge of adult mice and the subsequent infection of lungs. Although, the targeted organ is not the colon and considering that the lung environment is drastically different from the colonic lumen, this model allowed the validation of glycoconjugate [41] or protein-based vaccine candidates [19]. An intraperitoneal infection mouse model of *Shigella* infection was proposed, leading to the colonic mucosa invasion, although the dissemination route was not clearly stated [42]. A last interesting mouse model described was the SCID mouse-human intestinal Xenograft model, which consists in the engraftment of human colonic tissue. This model mimics the interaction of *Shigella* with human intestine *in vivo*. Inflammation and tissue damages were observed and human intestinal production of IL-1β and IL-8 was

associated with a major influx of polymorphonuclear neutrophils into the graft [43].

Guinea pigs were originally used as the kerato conjunctivitis model, called the Sereny test, consisting in the inoculation of *Shigella* strains into guinea pigs eye. Conjunctivitis and keratitis occurred when virulent strains were inoculated [25]. More recently, a model of intrarectal challenge of young guinea pigs with *Shigella* was described and validated by different groups [35]. Adult guinea pigs were not efficiently infected by *Shigella*. In young infected animals, an acute phase associated with the colonic mucosa invasion and destruction by *Shigella* and a major influx of polymorphonuclear neutrophils was observed (4-12h). *Shigella* infection was associated with a weight loss and tenesmus. Subsequently, infected animals naturally recover (2-3 days). Although the inoculation route is not oral as compared to shigellosis, the targeted organ is the colon, like in humans. This model has proven to be adapted for the characterization of early innate immune responses during *Shigella* infection, in particular focusing on the polymorphonuclear neutrophil recruitment at the infection site [44]. However, the potential validation of vaccine candidates' safety or efficacy or the analysis of the adaptive immune response in this model remains limited, when animals naturally recover after few days.

Other animal models were previously described and deserve further confirmatory experiments, such as the intraperitoneal infection of young chicken [24], the oral challenge of rats with *Shigella dysenteriae* [45], or the intraveneous microinjection of *Shigella flexneri* in zebrafish larvae [46].

PERSPECTIVES

Until now, *in vitro* experimentation (genetics, biochemistry, cell biology) and the use of various animal models described here allowed a comprehensive characterization of *Shigella* virulence mechanisms and the identification of most cell-surface exposed or secreted antigenic factors (Lipopolysaccharide, Peptidoglycan, Type Three Secretion Apparatus, auto transporters) (reviewed in [2,47]). The colonic luminal environment and the inflammatory response are likely to modulate *Shigella* virulence mechanisms and the production of antigenic factors. Continuous efforts should be made to validate novel animal models of shigellosis allowing the assessment of *Shigella* virulence mechanisms from an oral infection to the colonic mucosa colonization and disruption. Several potential models such dedicated CRIPR-Cas9 genome edited mice [48-51] humanized mice or miniature pigs (mini pigs) should be evaluated for their susceptibility to *Shigella* infection. Taking into account the time (more than 10 years) and the cost of a vaccine development (estimated between US$ 200 million and US$500 millions per vaccine), characterizing a suitable animal model of shigellosis should be the priority for the evaluation of *Shigella* vaccine candidates.

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