Bacterial Pathogens Secretory System Components

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Bacterial secretory systems are essential for virulence in human pathogens. The systems have become a target of alternative antibacterial strategies based on small molecules and antibodies. Strategies to use components of the systems to design prophylactics have been less publicized despite vaccines being the preferred solution to dealing with bacterial infections.

Keywords: vaccine ; secretory system ; bacteria ; Yersinia pestis ; Salmonella enterica ; pathogenic Escherichia coli ; Pseudomonas aeruginosa ; Shigella flexneri

1. Introduction

Strategies to deal with bacterial infections can be divided into two major groups: therapeutics and prophylactics. The former relies on antibiotics, mostly, while the latter- predominantly on vaccines. Antibiotics-based strategies are becoming a major problem as the pathogens acquire resistance faster than the typical approval process for new drugs [1]. The situation is caused by economic disadvantages for the pharmaceutical companies to invest in new drugs when the typical therapy lasts only a week [2][3][4]. To remedy low revenues in this area, the strategy uses existing targets with minimal modifications of the basic drug scaffold [5]. Predictably, resistance generation among bacteria is also shortened and frequently involves small modifications of the same bacterial targets.

The existing antibiotic pipelines are based on 2 major targets: peptidoglycan biosynthesis and DNA replication, as proven over time [6][7]. While the first target generates relatively small side effects, the second one is frequently problematic and not recommended in many cases [8][9]. The selection of new targets and drugs is encouraged and funded by the public-private partnerships [10], but the speed at which it progresses is slow due to the inadequate funding, the economic viability of antibiotic research for pharmaceutical companies, legal requirements connected to the approval of new drugs, and the rapid rise of resistance fueled by massive and indiscriminate, frequently, antibiotics use in humans and farming [11][12]. The situation is critical and the corrective actions undertaken are not sufficient to prevent major drug resistance epidemics in the future [13]. Therefore, approaches favoring alternatives [14][15], including indirect strategies relying on blocking bacterial virulence systems [16], are becoming more prominent and receiving increased funding from the same public-private partnerships [17][18].

Preventive strategies for bacterial infections are favored in the long term as it is easier and cheaper to prevent the disease than to treat it in many cases. Vaccine design and selection are typically based on attenuated strains, inactivated pathogens (disfavored due to the complications), and acellular approaches frequently relying on selected bacterial proteins fused to bacterial lipopolysaccharides as adjuvants [19]. However, the selection process is a trial-and-error approach, with the majority of candidates failing in the clinical trials [20]. For many prophylactics, the vaccine design strategies did not account for the complexity of the infection process of the pathogen and did not always select animal models capable of fully reproducing the interaction process with the human host [21][22]. The strategy for bacterial pathogens should be optimized in the future. The recent response to the COVID-19 viral pandemic demonstrated a clear focus on functional vaccine delivery by combining funding, scientific knowledge, animal models, manufacturing, and logistics to deliver a set of viable candidates for human use, possibly making it an example of future work on bacterial prophylactics.

Bacterial pathogens all have specialized protein transport systems, and they are cataloged at the Kyoto Encyclopedias of Genes and Genomes (KEGG) database (https://www.genome.jp/kegg/). The infection process requires not only finding a receptor on the human host but also the ability to secrete protein components in a coordinated process to overcome the immune defenses of the host and establish a suitable niche to replicate after infection. Theoretically, blocking the bacterial transport by virulence systems would block the infection and render the bacterial pathogens defenseless [23][24][25]. Since the bacterial transport systems are required for bacterial pathogens to start and continue an infection process and can be easily identified bioinformatically from the DNA sequences [26], there is an alternative vaccine design strategy that could

be used to prevent bacterial infections. In the current work, such strategies involving bacterial secretory systems as targets are presented for selected pathogens and discussed based on experimental data.

The review concentrates on components of virulence systems as building blocks of vaccines (Table 1). Therefore, information on other vaccine candidates not based on components of virulence systems is substantially shortened.

Table 1. List of bacterial pathogens reviewed.

Pathogen	Approved Vaccine	Secretory Systems	Notes
Acinetobacter baumannii	**No**	**I, II, VI**	
Bacillus anthracis	**Yes (restricted use)**	**II (general), Tat**	**Select Agent**
Bordetella bronchiseptica	**Yes (animals)**	**I, II, Tat, III, VI**	
Bordetella pertussis	**Yes**	**I, II, Tat, III**	
Brucella abortus	**Yes (animals)**	**I, II, Tat, IV**	
Brucella melitensis	**Yes (animals)**	**I, II, Tat, IV**	
Chlamydia trachomatis	**No**	**II (general and pathogenic), III**	
Pathogenic E. coli	**Yes (selected variants)**	**I, II (general and pathogenic), III, VI**	**Select Agent (EHEC)**
Francisella tularensis	**Yes (restricted use)**	**I, II (general), VI**	**Select Agent**
Helicobacter pylori	**No**	**II (general), Tat, IV, V**	
Legionella pneumophila	**No**	**I, II (general and pathogenic), IV**	
Mycobacterium tuberculosis	**Yes**	**II, Tat, VII**	**BSL-3**
Proteus mirabilis	**No**	**I, II, III, V, VI**	
Pseudomonas aeruginosa	**No**	**I, II (general and pathogenic), III, Tat, VI**	
Salmonella enterica	**Yes (selected serovars)**	**I, II, III, Tat, VI**	
Shigella spp.	**No**	**I, II (general), III, Tat, VI**	
Yersinia pestis	**Yes (restricted use)**	**I, II (general and pathogenic), III, VI**	**Select Agent**

2. Discussion

The ability to design a vaccine for any bacterial pathogen *a priori* is still elusive. The methodology to predict putative targets exists but the quality of predictions has to be verified experimentally. In some cases, however, the required targets are known and verified, but the vaccine constructs still show a poor performance in terms of protection.

In general, live vaccines could present the full antigenic spectrum of the pathogen and stimulate both parts of the immune system: humoral and cellular. The approach typically offers a long-lasting immunity and is not prone to mutations inactivating the effectiveness of vaccines based on 1–2 antigens or their epitopes. The drawback of such an approach is side effects connected with the use of whole-cell products or live viruses.

Vaccines based on live viruses offer the option of stimulating both parts of the immune system, but the limited antigenic repertoire caused by structural limitations of modified viral proteins is their weak point as the vaccines can be easily rendered ineffective by mutations in the pathogen. The other drawbacks of live viruses are their side effects connected to the recognition of viral nucleic acids by the innate immune system and the replication cycle. However, the last feature is also an advantage due to the constant and prolonged stimulation of the immune system by the replicating virus.

Vaccines based on recombinant antigens stimulate the immune system strongly and selectively for a short time, but the immune response is frequently biased towards the humoral part. Therefore, different adjuvants are used to have the cellular part engaged and create a long-lasting immunity to correct the problem. The drawback of vaccines based on recombinant antigens is their limited antigenic repertoire that is easily bypassed by mutations in the pathogen. To overcome this limitation, multiple antigens are used, which, for practical reasons, are limited to no more than 3 different components in a given vaccine.

The use of Outer Membrane Vesicles is a new technology that offers a broad antigenic repertoire, but the quality of preparations may be problematic due to the heterogeneous mix of components. The strategy offers the possibility to bypass mutations in the pathogens inactivating vaccines based on a single component, but the technology has not reached a commercial stage.

Approaches based on the carbohydrate coats, LPS and its components, have been in use for a long time. They are typically based on the O-antigen or the whole LPS conjugated to a carrier, a diphtheria toxin or similar, to increase their antigenicity. As a result, the vaccines are highly specific and frequently very effective against a given serotype. However, the drawback of such an approach is the O-antigen and the LPS outer core variability, necessitating a constant addition of new components specific to a given serotype. In addition, the carbohydrate components require isolation from natural sources, frequently biohazardous materials, on a large scale as the technology to make in vivo recombinant O-antigens coupled to the carrier has not reached a commercial stage.

Vaccines based on nucleic acids can be divided into 2 groups: DNA-based and RNA-based. The first group uses plasmids replicating in the host as they are more stable than linear DNA, easier and cheaper to produce than recombinant proteins, and can be used by the host's machinery directly. The drawback of such an approach is the limited amount of antigen produced, relatively fast elimination of the plasmid by the host, and a limited antigenic repertoire. The RNA-based vaccines use encapsulated RNA delivered locally. The approach allows for engaging the host's machinery in the production of proteins without the necessity of going through an mRNA intermediate as for the DNA-based vaccines. The vaccines are easy to design and manufacture but are unstable due to the rapid degradation of the RNA component. Therefore, the vaccines require a deep-freeze (−70 °C) storage and offer a limited shelf life, making them difficult to deploy on a large scale without a preexisting logistical network. The vaccines offer a limited antigenic repertoire due to the limitations on the length of the used RNA and can be easily bypassed by mutations in the pathogens. However, they can be very effective, as demonstrated by the COVID-19 vaccines.

In the presented review of vaccines for selected bacterial pathogens, most of the published data is focused on constructs offering protection to bacterial challenges not exceeding 100–200 LD50, a level typically assumed to be background when designing commercial vaccines. An increase in the protection level as demonstrated for discussed vaccines was observed for constructs combining other components of the system not belonging to the secretory systems with the knowledge of its vulnerable points (F1-V vaccine for *Y. pestis*) or simply by using engineered/attenuated organisms (Select Agents vaccines against *F. tularensis* and *Y. pestis,* whole cell-based DTwP against *B. pertussis*, live attenuated Ty21 *S.* Typhimurium vaccine, BCG vaccine against *M. tuberculosis*). The strategy to use the full antigen spectrum of the pathogen is far superior to that based on a combination of a few antigens, as clearly demonstrated for the emerging cases of whooping cough in the population vaccinated with the acellular DTaP. Since the transition to acellular prophylactics based on potential side effects connected to the engineered live vaccines has been enforced by the regulatory bodies [27], the effectiveness of future vaccines has been degraded and is likely to stay so when using the same products in mass vaccination efforts over a long period. A correction of the biased immunity responsible for part of the observed results has been demonstrated [28], but the DTaP vaccine is still administered without the potential correction.

The virulence systems are an attractive target for vaccines, but the use of their components only has not been very successful except for the *S. flexneri* vaccine candidate based on translocator proteins IpaB-IpaD attached to bacteria-like particles [29] and the F1-LcrV construct for *Y. pestis* vaccine candidate [30]. The opposite strategy, engineering pathogens to remove virulence systems, was only modestly successful [25][31]. Thus, it is possible that combining virulence system components with other bacterial antigens could be a strategy to develop new and effective vaccines. The constructs, however, will offer limited antigenic repertoire when only recombinant proteins are used and could be easily bypassed by mutated pathogens. A much better option would be to use carriers containing empty bacterial shells to increase antigenic repertoire, but the cellular components may give rise to undesirable side effects.

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