GAVIN PUBLISHERS

Journal of Vaccines, Immunology and Immunopathology

Asamarai AM , J Vaccines Immunol 2016: J105.

DOI: 10.29011/2575-789X.000005

Editorial

The Future of Utilizing *in vivo* Interbacterial Interactions to Develop Novel Anti-Bacteria Therapeutics and Vaccines

Yang Fu*

*Department of Microbiology and Immunobiology, Harvard Medical School

***Corresponding author:** Yang Fu, Department of Microbiology and Immunobiology, Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA, 02115, USA. Tel: +1617 834-3608; E-Mail: yang_fu@hms.harvard.edu

Citation: Yang Fu (2017) The Future of utilizing *in vivo* Interbacterial Interactions to Develop Novel Anti-Bacteria Therapeutics and Vaccines. J Vaccines Immunol 2017: J105. DOI: 10.29011/2575-789X.000005

Received Date: 30 January, 2017; **Accepted Date:** 30 January, 2017; **Published Date:** 6 February, 2017

Abstract

Enteric infectious disease caused by bacteria pathogens is one of the major global public health issues for centuries. Through the long term effort of the generations of genius scientists, to date, we have already developed many effective vaccines and successful antibiotics to cope with the threat. On the other hand, pathogenic strains involved to counter the traditional drugs and achieve immune escape, side-effects caused by broad-spectrum antibiotics, emerging diseases and so on, remaining request the development of novel anti-bacteria therapeutics. Nowadays, with the high throughput NGS screening combined with the new powerful animal models, applications of bacteria type VI secretion systems and the recently boomed research of human gut microbiome, investigators have more and more pay attention to the potential to utilize both the intra and inter species bacterial interactions *in vivo*. Here, we attempt to make a mini review the recently findings in the field and give a perspective for the new approach to develop antimicrobial agents.

Challenges of Current Antibacterial Strategies

Diarrheal diseases such as cholera are one of the major threats to global public health for thousands of years and remaining responsible for millions of deaths per year [1], while food borne infectious disease caused by bacteria pathogens in the well-established public health systems such as United States still annually number in the millions [2]. Enteric pathogenic gram-negative bacteria species which can colonize the human gut are the causative agents for many of these cases. Many antibiotics can be used to cure such diseases and have been effective in treating infections. However, over the past 25 years, we are face to the challenge that the discovery of novel antibacterial drug classes is at extraordinarily low levels, even though high throughput small molecule screen, robust bioinformatics techniques and big data analysis are in use at pharmaceutical companies as well as academic laboratories over this period [3].Vaccination is another powerful tool to prevent the infection and spread, but shortages are also existing, such as reactogenicity, fail to prevent children under certain ages and hard to cope with the emerging evolutionary strains [4].

Currently booming human microbiome studies have attached importance to the dynamic gut micro ecosystem. Relatively stable, dense microbial community contained by the gut [5] plays a critical role in cooperation and competition with exogenous microbe and promoting health and diseases [6]. As such, controlling these microbial communities is important to maintaining health and mitigating disease. However, under the indistinctive attack by traditional antibiotics and with the escalating threat of drug resistance, controlling microbiome systems through drug intervention is becoming more challenging. The dysbiosis caused by collateral damage from antibiotics treatment can result in the emergence of even more problematic bacteria [7, 8]. Novel bacteriocins and phage therapy can circumvent some of these challenges, but they also suffer from drawbacks including resistance mechanisms, extremely narrow host range and poor stability [9].

Emerging High Specificity Anti-Bacteria Systems

Remarkably, bacteria have a plethora of immunity strategies that protect them not only against the host but also against attacks by unwanted genetic elements or aggressive bacteria cells. These

range from relatively nonspecific restriction-modification systems, to adaptable and target directed CRISPR systems [10], to highly specific toxin-antitoxin immunity systems [11]. In the latter case, immunity to toxic diffusible proteins such as bacteriocins, or toxic molecules associated with cell-cell contact dependent inhibitory systems (e.g., the CDI system of E. coli) is dependent on the ability of bacterial cell to produce proteins that bind to and inactivate single toxic or inhibitory effectors with a high degree of specificity. Recently, immunity proteins associated with type VI secretion systems (T6SS)have been recognized as critical players in protecting sister cells from the toxic effects of this anti-cellular system [11,12]. The bacterial T6SS corresponds to a dynamic, intracellular contractile organelle [13], that can translocate toxic effectors into both prokaryotic as well as eukaryotic cells [14,15]. Immunity proteins to such toxic effectors protect sister cells from random or induced attacks, the latter being driven by elaborate regulatory systems in some predatory species that detect aggressive T6SS activity in nearby prey cells [16].

A lesson from *Vibrio cholerae*, the causative agent of the severe diarrheal disease cholera recently has raised up the potential to use T6S as a novel anti-microbiome therapeutic *in vivo* [17]. Investigators have used transposon mutagenesis sequencing analysis (Tn-Seq) and competition assays to study *V.cholerae* El Tor C6706 strain intestinal colonization in the modified infant rabbit model [17,18]. Besides the well-known colonization factors overlapped with the ones previously reported in the suckling mice model and human patients, we found that *V.cholerae* also utilized different mechanisms to gain growth advantages in the host. A strong piece of evidence that *V. cholera* cell-cell competition occur *in vivo* is provided by phenotypes related to the T6S. Included in the severe colonization defect group were mutants carrying insertions in tsiV3 and tsiV1, which encode immunity proteins for self-protection to neutralize the cognate bacteriocidal effector proteins VgrG3 and TseL of T6SS, respectively. Further experiments showed that the reduced *in vivo* fitness of tsiV3 and tsiV1 mutants depends on their co-colonization with strains that have an intact T6SS locus and cognate T6SS effector genes. These results suggest that the T6S-Sof V. cholerae strain C6706 is functionally expressed *in vivo* and that antagonistic sister cell-sister cell interactions occur during the infection process. Later on, inter species bacterial competition was also found in planta bacterium pathogens [19] and human commensal bacteroidetes [20, 21]. Besides, intra species bacteria T6S interactions were also found *in vivo* during salmonella typhi infection [22], and through the development of probiotic commensal strains either sensitive or resistant to the *V. cholerae* T6SS (Zhao, Fu and Robins, Mekalanos group, unpublished results). All these clues revealed several novel anti-microbiome strategies such like the small molecules that inhibit T6S immunity proteins could be used for highly species-specific anti-infective drugs against Gram-pathogens and pre- or post-inoculated T6S+ probiotic strains that can specific targeting sensitive bacterium.

Speculation Of Utilize the *invivo* Cell-Cell Contact Microenvironment

Because the T6S is thought to deliver toxic effectors to neighboring cells only through direct cell-cell contact, directly or indirectly measure the extent of cell-cell contact in the animal model may offer more potential for the development of contact dependent probiotics and novel anti-virulence therapeutics. Such cell-cell contact tracking assays may also subject to investigate the dynamics of intestinal colonization process and potential *in vivo* horizontal genes transfer.

References

1. Kosek M, Bern C, Guerrant RL (2003) The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. Bull World Health Organ 81: 197-204.
2. Scallan E, Hoekstra RM, Angulo FJ, Tauxe RV, Widdowson MA, et al. (2011) Foodborne illness acquired in the United States--major pathogens. Emerging infectious diseases 17: 7-15.
3. Silver LL (2011) Challenges of antibacterial discovery. Clin Microbiol Rev 24: 71-109.
4. Parker LA, John Rumunu, Christine Jamet, Yona Kenyi, Dip et al (2017) Adapting to the global shortage of cholera vaccines: targeted single dose cholera vaccine in response to an outbreak in South Sudan. Lancet Infect Dis 3099: 30472-30478.
5. Faith JJ, Guruge JL, Charbonneau M, Subramanian S, Seedorf H, et al. (2013) The long-term stability of the human gut microbiota. Science 341: 1237439.
6. Zhang YJ, Li S, Gan RY, Zhou T, Xu DP, et al. (2015) Impacts of gut bacteria on human health and diseases. Int J Mol Sci 16: 7493-7519.
7. Brandl K, Plitas G, Mihu CN, Ubeda C, Jia T, et al. (2008) Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits. Nature 455: 804-807.
8. Ubeda C, Taur Y, Jenq RR, Equinda MJ, Son T, et al. (2010) Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. J Clin Invest 120: 4332-4341.
9. Sulakvelidze A, Alavidze Z, & Morris JG, Jr. (2001) Bacteriophage therapy. Antimicrob Agents Chemother 45: 649-659.
10. Seed KD, Lazinski DW, Calderwood SB, Camilli A (2013) A bacteriophage encodes its own CRISPR/Cas adaptive response to evade host innate immunity. Nature 494: 489-491.
11. Dong TG, Ho BT, Yoder-Himes DR, & Mekalanos JJ (2013) Identification of T6SS-dependent effector and immunity proteins by Tn-seq in Vibrio cholerae. Proceedings of the National Academy of Sciences of the United States of America 110: 2623-2628.

12. Brooks TM, Unterweger D, Bachmann V, Kostiuk B, Pukatzki S (2013) Lytic activity of the Vibrio cholerae type VI secretion toxin VgrG-3 is inhibited by the antitoxin TsaB. J Biol Chem 288: 7618-7625.

13. Basler M, Pilhofer M, Henderson GP, Jensen GJ, & Mekalanos JJ (2012) Type VI secretion requires a dynamic contractile phage tail-like structure. Nature 483: 182-186.

14. Ma AT, McAuley S, Pukatzki S, & Mekalanos JJ (2009) Translocation of a Vibrio cholerae type VI secretion effector requires bacterial endocytosis by host cells. Cell host & microbe 5: 234-243.

15. Pukatzki S, Ma AT, Sturtevant D, Krastins B, Sarracino D, et al. (2006) Identification of a conserved bacterial protein secretion system in Vibrio cholerae using the Dictyostelium host model system. Proceedings of the National Academy of Sciences of the United States of America 103: 1528-1533.

16. Basler M, Ho BT, & Mekalanos JJ (2013) Tit-for-tat: type VI secretion system counterattack during bacterial cell-cell interactions. Cell 152: 884-894.

17. Fu Y, Waldor MK, & Mekalanos JJ (2013) Tn-Seq analysis of Vibrio cholerae intestinal colonization reveals a role for T6SS-mediated antibacterial activity in the host. Cell host & microbe 14: 652-663.

18. Ritchie JM, Rui H, Bronson RT, Waldor MK (2010) Back to the future: studying cholera pathogenesis using infant rabbits. mBio 1: e00047-10.

19. Ma LS, Hachani A, Lin JS, Filloux A, & Lai EM (2014) Agrobacterium tumefaciens deploys a superfamily of type VI secretion DNase effectors as weapons for interbacterial competition in planta. Cell host & microbe 16: 94-104.

20. Chatzidaki-Livanis M, Geva-Zatorsky N, Comstock LE (2016) Bacteroides fragilis type VI secretion systems use novel effector and immunity proteins to antagonize human gut Bacteroidales species. Proceedings of the National Academy of Sciences of the United States of America 113: 3627-3632.

21. Wexler AG, Yiqiao Bao, John C. Whitney, Louis-Marie Bobay, Joao B. Xavier, et al (2016) Human symbionts inject and neutralize antibacterial toxins to persist in the gut. Proceedings of the National Academy of Sciences of the United States of America 113: 3639-3644.

22. Sana TG, Flaugnatti N, Lugo KA, Lam LH, Jacobson A, et al. (2016) Salmonella Typhimurium utilizes a T6SS-mediated antibacterial weapon to establish in the host gut. Proceedings of the National Academy of Sciences of the United States of America 113: E5044-5051.