Journal of Bacteriology and Parasitology

Kogenaru, J Bacteriol Parasitol 2014, 5:4
DOI: 10.4172/2155-9597.1000e123

Editorial Open Access

HrpX Transcription Factor - A Potential Common Target for Several Bacterial Diseases from a Synthetic Biology Perspective

Sunitha Kogenaru*

Division of Nephrology, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

***Corresponding author:** Sunitha Kogenaru, Division of Nephrology, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI 48109-0676, USA, Tel. 734-764-2924; E-mail: kogenaru@med.umich.edu

Rec date: Aug 20, 2014; **Acc date:** Aug 22, 2014; **Pub date:** Aug 26, 2014

Editorial

Understanding the design principles of bacterial pathogenesis is central to combat several infectious diseases in humans, animals and plants [1]. This includes identification of common bacterial pathogenicity mechanisms employed by a wide variety of bacteria, which infect diverse hosts [2]. Recent studies have identified one such common virulence mechanism: Type III Secretion System (T3SS), employed by several animal and plant pathogenic bacteria [3-6]. Classically, the components of T3SS physically assemble to form a complex needle-like structure that enables the bacteria to inject virulence factors directly into their host cell's cytoplasm. These factors in turn specifically interfere with their host cellular processes to elicit pathogenicity [7,8]. However, despite the common injection mechanism, each bacterial species injects unique set of species-specific virulence factors that define the host specificity [3,4].

The proteobacterial groups that primarily employ T3SS to infect variety of plants are *Xanthomonas*, *Ralstonia* and *Burkholderia* to mention a few [7-9]. Among them, the species of *Xanthomonas* genus are well studied and are known to infect wide spectrum of host plants, including several economically important plants like wheat, rice, beans, tomato, cotton, paper and citrus [10]. Currently around 27 plant-associated *Xanthomonas* species are known [11]. T3SS in these species are encoded by a cluster of hypersensitive response and pathogenicity (*hrp*) genes [9,12]. In most of these species, *hrp* cluster expression is regulated by a key transcription factor HrpX via the two-component response regulator HrpG [13]. HrpX is an AraC-type transcriptional activator that specifically recognizes the plant-inducible promoter (PIP-box) motifs present in the cis-regulatory regions of the regulated target genes [14,15]. The consensus sequence of PIP-box consists of a direct repeats of "TTCGC" with a spacer of 8-26 base pairs between the repeats [16].

Over the past three decades, the cataloguing of the HrpX target genes is underway by genetic, biochemical and high-throughput methods [10,17-23]. Recent genome-wide transcriptomic studies have reconfirmed many of these target genes, and additionally identified new ones, which lead to the discovery of a more comprehensive picture of the HrpX regulome [13,24]. Despite the detailed knowledge about HrpX regulome, the factor controlling the HrpX transcriptional activity is currently lacking.

The knowledge of protein sequence and domain composition is vital to the discovery of a factor controlling the HrpX function. Bioinformatics analysis of the HrpX sequence from *Xanthomonas citri subsp. citri* (Xcc) revealed the existence of tetratrico-peptide-repeats (TPRs) domain, and a jelly roll like domain, in addition to the already known AraC-type DNA-binding domain [25]. TPRs are known to mediate protein-protein interactions; hence, it can be hypothesized that the presence of this domain may facilitate HrpX to recruit the transcription machinery to the core promoter, thereby initiate the transcription of the target gene. On the other hand, the jelly roll like domain is known to bind to a host environment molecule in other pathogenic bacteria [26]. This tentatively suggests that jelly roll like domain in HrpX might also have a role to bind to a factor present in the host plant environment that ultimately controls the target gene regulation.

In order to demonstrate that exogenous factor controls the HrpX functioning, synthetic biology approaches would be advantageous to employ [27,28]. By this approach, a synthetic reporter system can be constructed by placing the regulation of a fluorescent reporter gene under the control of HrpX, using a known regulatory sequence motif of PIP-box. Further, the expression of *hrpX* can be controlled by an inducible transcription factor like AraC or LacI [29]. This synthetic transcriptional cascade will enable to determine, whether both HrpX and an environmental factor are required in order to regulate the target gene expression that can be assessed by directly measuring the fluorescence from a reporter. Establishment of this synthetic functional assay system will further allow to disentangle the *hrpX* from its native organism context, by implementing it in a standard model organisms like *Escherichia coli* [29]. This synthetic system will directly allow us to test whether a factor from the host environment controls the HrpX transcriptional activity or not. Conversely, this system will also be useful to screen for synthetic small-molecule inhibitor for the HrpX in a high throughput fashion.

This proof-of-concept experiment will provide a direct link to the host environment controlled regulation of virulence gene expression, hence helps in mechanistic understanding of HrpX functioning. Other interesting questions useful to be explored include the identification of the active molecule from the host environment responsible, and how similar is the identified molecule structurally across different *Xanthomonas* species. Based on the structural similarity of the molecule, one might be able to possibly design a master small-molecule inhibitor to control the diseases caused by *Xanthomonas* species. Future studies exploring on these questions will directly enable the development of a master strategy to fight many bacterial infections.

References

1. Groisman EA (2001) Principles of Bacterial Pathogenesis. San Diago: Academic Press a Harcourt Science and Technology Company, USA.
2. Todar K Mechanisms of Bacterial Pathogenicity,Todar's Online Textbook of Bacteriology.
3. Büttner D, Bonas U (2006) Who comes first? How plant pathogenic bacteria orchestrate type III secretion. Curr Opin Microbiol 9: 193-200.

4. Galán JE, Collmer A (1999) Type III secretion machines: bacterial devices for protein delivery into host cells. Science 284: 1322-1328.
5. Gauthier A1, Finlay BB (2001) Bacterial pathogenesis: the answer to virulence is in the pore. Curr Biol 11: R264-267.
6. Saier MH Jr (2004) Evolution of bacterial type III protein secretion systems. Trends Microbiol 12: 113-115.
7. Hueck CJ (1998) Type III protein secretion systems in bacterial pathogens of animals and plants. Microbiol Mol Biol Rev 62: 379-433.
8. Mota LJ, Cornelis GR (2005) The bacterial injection kit: type III secretion systems. Ann Med 37: 234-249.
9. Bonas U (1994) hrp genes of phytopathogenic bacteria. Curr Top Microbiol Immunol 192: 79-98.
10. da Silva AC, Ferro JA, Reinach FC, Farah CS, Furlan LR, et al. (2002) Comparison of the genomes of two Xanthomonas pathogens with differing host specificities. Nature 417: 459-463.
11. Hayward A (1993) The host of Xanthomonas. Swings JG CE (eds), Chapman & Hall London, United Kingdom.
12. E C (1984) Bacterial canker disease of citrus. J Rio Grande Vall Hortic Soc 37:127–145.
13. Guo Y, Figueiredo F, Jones J, Wang N (2011) HrpG and HrpX play global roles in coordinating different virulence traits of Xanthomonas axonopodis pv. citri. Mol Plant Microbe Interact 24: 649-661.
14. Astua-Monge G, Freitas-Astua J, Bacocina G, Roncoletta J, Carvalho SA, et al. (2005) Expression profiling of virulence and pathogenicity genes of Xanthomonas axonopodis pv. citri. J Bacteriol 187: 1201-1205.
15. Wengelnik K, Bonas U (1996) HrpXv, an AraC-type regulator, activates expression of five of the six loci in the hrp cluster of Xanthomonas campestris pv. vesicatoria. J Bacteriol 178: 3462-3469.
16. Koebnik R, Krüger A, Thieme F, Urban A, Bonas U (2006) Specific binding of the Xanthomonas campestris pv. vesicatoria AraC-type transcriptional activator HrpX to plant-inducible promoter boxes. J Bacteriol 188: 7652-7660.
17. Alfano JR, Collmer A (1997) The type III (Hrp) secretion pathway of plant pathogenic bacteria: trafficking harpins, Avr proteins, and death. J Bacteriol 179: 5655-5662.
18. Alfano JR, Collmer A (2004) Type III secretion system effector proteins: double agents in bacterial disease and plant defense. Annu Rev Phytopathol 42: 385-414.
19. Collmer A, Bauer DW (1994) Erwinia chrysanthemi and Pseudomonas syringae: plant pathogens trafficking in extracellular virulence proteins. Curr Top Microbiol Immunol 192: 43-78.
20. Cornelis GR (2006) The type III secretion injectisome. Nat Rev Microbiol 4: 811-825.
21. Noel L, Thieme F, Nennstiel D, Bonas U (2002) Two novel type III-secreted proteins of Xanthomonas campestris pv. vesicatoria are encoded within the hrp pathogenicity island, J Bacteriol. 184:1340-1348
22. Van Gijsegem F, Genin S, Boucher C (1993) Conservation of secretion pathways for pathogenicity determinants of plant and animal bacteria. Trends in microbiology 1:175-180.
23. White FF, Potnis N, Jones JB, Koebnik R (2009) The type III effectors of Xanthomonas. Mol Plant Pathol 10: 749-766.
24. Kogenaru S, Qing Y, Guo Y, Wang N (2012) RNA-seq and microarray complement each other in transcriptome profiling. BMC Genomics 13: 629.
25. Karpenahalli MR, Lupas AN, Söding J (2007) TPRpred: a tool for prediction of TPR-, PPR- and SEL1-like repeats from protein sequences. BMC Bioinformatics 8: 2.
26. Lowden MJ, Skorupski K, Pellegrini M, Chiorazzo MG, Taylor RK, et al. (2010) Structure of Vibrio cholerae ToxT reveals a mechanism for fatty acid regulation of virulence genes. Proc Natl Acad Sci U S A 107: 2860-2865.
27. Khalil AS, Collins JJ (2010) Synthetic biology: applications come of age. Nat Rev Genet 11: 367-379.
28. Mukherji S, van Oudenaarden A (2009) Synthetic biology: understanding biological design from synthetic circuits. Nat Rev Genet 10: 859-871.
29. Kogenaru M, Tans SJ (2014) An improved Escherichia coli strain to host gene regulatory networks involving both the AraC and LacI inducible transcription factors. J Biol Eng 8: 2.