Journal of Bacteriology and Parasitology

Feng et al., J Bacteriol Parasitol 2012, 3:6
DOI: 10.4172/2155-9597.1000e108

Editorial Open Access

Regulation of Virulence in *Streptococcus suis*

Youjun Feng[1,2]*, Huimin Zhang[2], Min Cao[1] and Changjun Wang[1]*

[1]*Department of Epidemiology, Research Institute for Medicine of Nanjing Command, Nanjing, 210002, PR China*

[2]*University of Illinois at Urbana-Champaign (UIUC), Urbana 61801, USA*

Abstract

Streptococcus suis (*S. suis*) comprising thirty-five different serotypes, constitute a group of complex bacterial species that not only is swine pathogen, but also cause opportunistic infections in humans. A collection of virulence determinants have been largely elucidated that contribute to better understanding of pathogenesis underlying severe infections by *S. suis*. Here, we concentrated on control of *S. suis* virulence by a rainbow coalition of regulators, and discussed future perspectives in this field. It might provide a glimpse of the complex network of virulence regulation in *S. suis*.

Editorial

Streptococcus suis (*S. suis*) is a major swine pathogen that annually results in great economic loss worldwide [1,2]. Thirty-five serotypes (1-34, 1/2) have been classified, according to the differentiated capsule antigens of these heterogeneous *S. suis* species [3,4]. Of them, *S. suis* serotype 2 (SS2) is a previously-neglected but recently-emerging zoonotic agent that can lead to opportunistic infections in humans with close contact with swine and/or pork products [5-7]. Totally, more than 850 cases of human SS2 infections have been recorded, which are involved in over 30 countries and/regions, esp. Southeastern Asia like Vietnam, Thailand, China, etc [1,3]. Given that strong invasiveness and high virulence is manifested by this bug, world-wide extensive studies have been conducted (esp. after a big outbreak of human SS2 endemic in China, in 2005 [7]), which led to discovery of a collection of new bacterial virulence determinants underlying SS2 pathogenicity [1,8]. In terms of recent development in this field, we presented a brief view on the regulation network of SS2 virulence from bellowed three aspects: transcription factor, two-component signal transduction system (TCSTS), plus orphan response regulator.

First, no less than five transcription factors, some of which can sense environmental signals, have been implicated into the complex regulatory network of *S. suis* pathogenicity (Table 1). AdcR is a regulator controlling zinc transport in *S. suis*, was observed to be correlated with bacterial virulence in mouse model [9]. In contrast, we failed to note that Zur, the other zinc uptake regulator from 05ZYH33 strain of *S. suis* 2 is essential for strong pathogenicity in the infection model of piglets [10]. Given that host niche/micro-environment is critical for expression of bacterial virulence factors during the process of infections, Willenborg et al. [11] had addressed the effect of the sugar metabolism regulator catabolite control protein A (CcpA) on *S. suis* pathogenesis. As anticipated, expression level of several virulence factors (such as ArcB, Sao, Enolase, etc.) were altered in the Δ*ccpA* mutant. Moreover, the deletion of *ccpA* led to significant reduction of both capsule thickness and resistance to killing by porcine neutrophils. Unfortunately, its pathological role in bacterial virulence has not yet been verified with experiments of animal infections (Table 1). ArgR, a member of ArgR/AhrC arginine repressor family, was recently proved to regulate expression of *arcABC* operon encoding an arginine deiminase system that is recognized as a putative virulence factor [12,13]. Therefore, it is of much interest to test a role of *argR* in *S. suis* virulence (Table 1). Similar to what has been observed with Rgg regulators of other Gram-positive pathogen, we defined an rgg-like ortholog of *S. suis* 05ZYH33. Multiple roles of this regulator in bacterial metabolism were observed. Particularly, it was confirmed as a virulence determinant in the experimental model of piglets [14]. Very recently, Zhang and coworkers supplemented a Fur-like family of transcription factor, PerR, to the increasing list of virulence factors of *S. suis* [15]. This regulator is controlled by both H_2O_2 and metal ions, and directly modulates expression of two target genes (one is *dpr* encoding Dps-like peroxide resistance protein and the other is metQIN encoding a methionine transporter) [15].

Among the 15 putative TCSTS of the Chinese virulent SS2 strain (e.g., 05ZYH33) [16,17], four have been found to be involved in control of *S. suis* virulence (Table 1). In 2008, we reported a unique *salK-salR* TCSTS system within the 89K pathogenicity island [18]. The deletion of this two component system resulted in significant down-regulation of 26 genes' expression level, and increased its susceptibility to polymorphonuclear leukocyte (PMN)-mediated killing. Consequently, the virulence of the Δ*salK-R* mutant was seriously attenuated [18]. Subsequently, *ciaR-ciaH* was determined as the second TCS system that is essential for pathogenicity of SS2 in the infection models of CD1 mice and piglets both [19]. A homolog of the *Clostridium perfringens* VirR-VirS regulatory system was also observed in 05ZYH33 strain of SS2, and the isogenic knockout mutant (Δ*virRS*) was found to exhibit marked attenuation of virulence observed with the infection model of mice [20]. More recently, Han et al. [21] employed bacterial genetics combined with comparative proteomics to unveil that the *ihk-irr* TCSTS is necessary for SS2 pathogenicity via modulating bacterial central metabolism.

Additionally, only two orphan response regulators have been verified to be involved in SS2 pathogenesis thus far (one is RevSC21 [22], and the other is CovR [23], Table 1). In 2009, Wu et al. [22] reported that RevSC21 regulator positively regulates expression levels of virulence factors (such as *mrp, sly, cps,* etc.), and is required for bacterial

***Corresponding authors:** Youjun Feng, Department of Epidemiology, Research Institute for Medicine of Nanjing Command, Nanjing 210002, PR China, Tel: 86-025-84507094; Fax: 86-025-84507094; E-mail: fyj999@gmail.com

Prof. Changjun Wang, Department of Epidemiology, Research Institute for Medicine of Nanjing Command, Nanjing 210002, PR China, Tel: 86-025-84507094; Fax: 86-025-84507094; E-mail: science2008@hotmail.com

Received August 06, 2012; **Accepted** August 06, 2012; **Published** August 10, 2012

Citation: Feng Y, Zhang H, Cao M, Wang C (2012) Regulation of Virulence in *Streptococcus suis*. J Bacteriol Parasitol 3:e108. doi:10.4172/2155-9597.1000e108

Genes	Functional annotation	SS2 Strains	Animal models	Origins
Transcription factor (5)				
perR	PerR, a Fur-like protein	Strain SC-19 (China)	Balb/c mice	(25)
adcR	AdcR, a pleiotropic regulator	Strain P1/7 (Netherlands)	Balb/c mice	(1)
ccpA	Catabolite control protein A	Strain 10 (Netherlands)	No	(23)
argR	An ADS-associated repressor of the ArgR/AhrC arginine family	Strain 10 (Netherlands)	No	(9)
rgg	Rgg transcription factor	05ZYH33 (China)	Piglets	(26)
Two component signal transduction system (4)				
Ihk-irR	A homolog of the *Streptococcus pyogenes* Ihk/Irr TCS	Strain 05ZYH33 (China)	CD-1 mice	(13)
virR-virS	A homolog of the VirR-VirS regulatory system of *Clostridium perfringens*	Strain 05ZYH33 (China)	Balb/c mice	(20)
salK-salR	Two-component system in the 89K PAI	Strain 05ZYH33 (China)	Piglets	(14)
ciaR-ciaH	A two-component system	SC19 (China)	CD-1 mice & piglets	(5)
Orphan response regulator (2)				
covR	Orphan response regulator (CovR)	Strain 05ZYH33 (China)	Piglets	(16)
revSC21	Orphan response regulator RevSC21	Strain SC21 (China)	CD-1 mice	(24)

Table 1: Transcription factors and regulatory systems required for *S. suis* virulence.

virulence. In contrast, we had ever observed another orphan response regulator *CovR* with an opposite effect on *S. suis* pathogenicity [23]. The *covR*-defective (Δ*covR*) mutant displayed thicker capsules and increased hemolytic activity. Furthermore, adherence of this mutant to epithelial cells was greatly increased, as well as its resistance to phagocytosis and killing by neutrophils and monocytes. Eventually, the removal of *covR* gene was found to be correlated with increased lethality of piglets [23].

It still remains elusive whether some connection/linking are present among the complex regulatory networks constituted by above transcription factors and TSCTSs in modulating bacterial virulence. It is reasonable that presence of other transcription factors and/or regulatory systems that are associated with control of bacterial virulence in SS2. Unfortunately, nothing is known on post-transcriptional control of virulence by small non-coding RNA (sRNA) in *S. suis*, although it has been addressed in its closely-related organism, *S. pneumonia* [24]. Thus we believed that genome-wide systematic identification and functional assignment of small non-coding RNAs might contribute to better understanding control of SS2 virulence. In similar, it is also of great interest to elucidate the potential relevance and/or linking of machineries for post-translational modifications [25] (such as acetylation [26]) to *S. suis* pathogenesis.

Acknowledgements

The work from Dr. Wang's research group was in part supported by grants from the General Program of National Natural Science Foundation of China (31170124, 81071317, 30972638, 81172794 & 81171527), and the General Program of National Natural Science Foundation of Jiangsu Province (BK2011097,BK2010025 & BK2010114). Dr. Feng (whose present address is University of Illinois at Urbana-Champaign) is awarded as a young visiting scholar in Research Institute for Medicine of Nanjing Command.

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