NADH oxidase, a new player in the field of *Streptococcus suis* infection

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**ARTICLE HISTORY** Received 25 July 2016; Accepted 25 July 2016

**KEYWORDS** NADH oxidase; streptococci; *Streptococcus suis*; virulence factor; zoonosis

*Streptococcus suis* is a zoonotic pathogen that causes meningitis and bacteremia in patients consuming raw pork meat/blood or having close contact with infected pigs. Although the first human case was reported in 1968 in Denmark,<sup>1</sup> this pathogen is best known for its ability to infect swine. However, after the outbreak in 2005 in Sichuan province, China,<sup>1</sup> *S. suis* infections in humans have received increasing attention from researchers and clinicians in many other countries, including Thailand and Vietnam. In Vietnam, *S. suis* has been reported to be the most common pathogen infecting the central nervous system.<sup>2</sup> In northern Thailand, a prospective study revealed that the incidence rate of *S. suis* infection was 6.2 per 100,000 individuals in the general population.<sup>3</sup> In contrast, in Europe and North America, cases of *S. suis* infections are limited to individuals who work closely with pigs, such as butchers and pig breeders.<sup>4</sup> *S. suis* infection is not only the major cause of bacterial meningitis and sepsis but also frequently causes hearing loss as a sequela. The route of infection for this pathogen is thought to be entry through damaged or injured skin because pig farmers and butchers have higher infection rates. However, recent studies have suggested that *S. suis* infection may also occur through consumption of raw pork products.<sup>3,5</sup> Based on these observations, wound and oral infections are both likely to be caused by *S. suis* infection. Once *S. suis* enters the blood vessels, it circulates throughout the body and causes sepsis or meningitis. *S. suis* harbors various virulence factors, including the major virulence factor suilysin.<sup>6</sup> This cholesterol-dependent cytolysin can bind to the cell membrane and forms pores by oligomeric assembly, exhibiting cytotoxicity and hemolysis in host cells. Several publications have reported that the cytotoxicity of suilysin in immune cells facilitates immune evasion in infected hosts<sup>7-9</sup>; however, the clinical manifestations of *S. suis* infection cannot be completely explained by suilysin alone.

In this issue of *Virulence*, Zheng et al. report that the NADH oxidase of *S. suis* may represent another virulence factor responsible for escape of *S. suis* from detection and targeting by the host immune system.<sup>10</sup> Previously, Spx proteins were found to modulate the expression of virulence-associated genes, acting as global regulators of *S. suis*.<sup>11</sup> Under the control of one of the Spx proteins, SpxA1 was found to protect against oxidative stress tolerance and contributed to virulence. Microarray analysis also revealed that SpxA1 regulated the expression of proteins involved in the oxidative stress response; one candidate protein involved in this response was identified as NADH oxidase, and subsequent analyses successfully demonstrated that this protein exhibited tolerance against oxidative stress and contributed to the development of disease in a mouse model.

NADH oxidase catalyzes the reduction of oxygen to *H₂O₂* or *H₂O* through electron transfer from NADH to *H₂O₂* or *H₂O* through electron transfer from NADH. In *Streptococcus suis*, the clinical manifestations of *S. suis* infection cannot be completely explained by suilysin alone.

To estimate the involvement of NADH oxidase in bacterial pathogenesis, particularly in streptococci, researchers...
showed that NADH oxidase was localized in the cell wall of *S. pneumoniae* and functioned as an adherence factor. Moreover, mice immunized with recombinant NADH oxidase survived a lethal challenge with *S. pneumoniae*. This observation may be confirmed using similar methods in *S. suis* infection, and the protective effects of immunization by NADH oxidase may explain the influence of NADH oxidase on the development of *S. suis* infection. It will be interesting to determine whether the NADH oxidases expressed in *S. suis* and other streptococci function as adherence factors in host cells. Because successful infection of *S. suis* is dependent on NADH oxidase activity, elucidation of the relationships between NADH oxidase activity in *S. suis* and its adherence activity in culture cells will provide insights into the entire process of *S. suis* infection.

In summary, NADH oxidase of *S. suis* has been shown to contribute to the pathological manifestations of invasive *S. suis* infection. Combined with findings regarding the pathogenic factor suilysin, these results provide us with a more comprehensive understanding of infection by *S. suis* and other pathogenic streptococci.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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