



Community-Acquired Methicillin-Resistant Staphylococcus Aureus an Important Enemy against us; Why Investigation of Their Main Toxins Reveals Contradictory Data

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Community-Acquired Methicillin-resistant *Staphylococcus aureus* (CA-MRSA) strains are serious human pathogens because of their micro floral abilities; resistance to clinically important antibiotics and ability to evade the host immune defences. Panton–Valentine leucocidin (PVL) and Phenol-soluble modulins (PSMs) are the main important virulence factors of CA-MRSA. The aim of this work was to provide an explanation on why there are contradictory findings in studies of PVL and PSMs. Several factors such as differences in growth media or in injection mode, species-specific interaction, contamination in culture supernatants, the concentration of toxin, and exposure time that have an effect on conducting of these studies were discussed in this paper.

Keywords: CA-MRSA; PVL; MRSA; *staphylococcus aureus*.

1. INTRODUCTION

Staphylococcus aureus is an important bacterium of the Staphylococci due to its disease's burden

[1]. *S. aureus* is a ubiquitous pathogen, found in several environments such as contaminated food, soil, human anterior nares and the skin [2]. This bacterium is contagious

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and can be spread by touching, sneezing and coughing [3]. There are around 2 billion people in the worldwide who are carry this pathogen. Moreover, of the people carrying the pathogen, methicillin-resistant *Staphylococcus aureus* (MRSA) infects around 53 million of those people [3]. MRSA is generally resistant to multiple antibiotics and also its infections are difficult to treat [3]. *S. aureus* is considered as a major causative of bacteraemia [4]. This infection can lead to severe invasive infections such as infective endocarditis and sepsis [3]. During this infection, *S. aureus* interacts with platelets through producing many surface proteins and toxins that affect physiological functions of the host [5]. *S. aureus* produces molecules such as Pantón–Valentine leucocidin (PVL), Phenol-soluble modulins (PSMs) [6,7]. PVL and PSMs are considered as important virulence factors of Community-Acquired Methicillin-resistant *Staphylococcus aureus* (CA-MRSA) [5,8]. CA-MRSA are dangerous human pathogens due to their ability to resist the host immune defenses and also to their ability to resist to clinically important antibiotics [7]. CA-MRSA infection has become a global problem and causes a significant rise in the rate of human mortality and morbidity (David *et al.*, 2010). PVL and PSMs toxins have a crucial role in diverse facets of CA-MRSA pathogenesis. However, the abilities of these toxins were a subject of controversy by several studies [6,9,10,11] [12,13,14]. In this paper, we try to reveal why these studies produce contradictory findings.

2. DISCUSSION

As mentioned earlier, PVL and PSMs play a vital role in different aspects of CA-MRSA pathogenesis, confirming that these toxins have an effect on the progression of CA-MRSA disease.

The severity of diseases such as infections of skin and soft tissue caused by CA-MRSA, highly correlates with the production of PVL and PSMs, because of their strong cytolytic effects [6,8]. However, their cytolytic activities and role on formation of abscesses are subject of controversy due to contradictory findings. There are several proposed reasons for those unexpected findings. One of these proposed reasons are different growth media that are used in various studies. When assayed using *S. aureus* culture media that favour selective high production of PVL and PSMs. Many reports reveal that there is a correlation between formation of abscesses and increased production

of PVL and PSMs [6,9,10,11]. For example, Use of CCY medium, a selective medium for high production of PVL, can increase PVL concentration. Therefore, enhancing its ability to cause cytolysis in vitro or in vivo [15]. Others utilize different growth media e.g. Tryptic Soy Broth, which are not selective for high production of PVL. They failed to detect this cytolytic activity of PVL, showing no difference in abscess formation among CA-MRSA strains that have PVL of and CA-MRSA strains that lack PVL [12,13,14]. This may explain why there are different results in the previous studies. Furthermore, one more possible explanation of these different findings is due to the use of different of injection modes in the studies of Kobayashi *et al.* [13] and Lipinska *et al.* [10]. Third proposed reason for these contradictory findings is due to species-specific interaction. For example, there are debate about ability of PVL to lysis neutrophils. Works from Genestier *et al.* (2005) and Löffler *et al.* (2010) shows PVL is able to lyse human and rabbit neutrophils at low concentrations (Genestier *et al.*, 2005; Löffler *et al.*, 2010). While, other researchers failed to detect this effect on murine neutrophils [16]. For instance, PSMs show ability to destroy human neutrophils, therefore damaging the immune system [8], while these toxins have a non cytolytic activity on human dendritic cells [17]. A possible explanation of these different findings of PSMs is recognition by Formyl peptide receptor 2 on neutrophils [8], while PSMs works independently of FPR2 in dendritic cells [17]. Forth proposed reason is due to contamination in culture supernatants. For example, a researcher group investigated the recognition of PSMs by host cells. They found that PSMs are recognition Toll-like receptor 2 [18]. However, this unexpected finding is due to PSMs contaminated with lipoproteins from staphylococcal culture supernatants. PSMs and lipoproteins together cause strong activation of Toll-like receptor 2 [19]. Fifth reason is due to the concentration of toxin and exposure time that conducted in experiments. These factors may have a significant impact on toxin activity. For instance, 100 µg/mL of PSMs causes lysis of osteoblasts after 23 hours incubation. Whereas low concentrations of PSMs up to 62.5 µg/mL with short period of incubation (around 45 min) cause lysis of horse erythrocytes [20,6].

3. CONCLUSION

Differences in growth media and injection mode have limited ability to affect on the contribution of

PVL and PSMs to CA-MRSA pathogenesis. Species-specific interaction may be reasonable explanation for these unexpected findings of PVL and PSMs.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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