Toxin expression during *Staphylococcus aureus* infection imprints host immunity to inhibit vaccine efficacy

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1. 簡述論文的概要與重大發現：

金黃色葡萄球菌(*S. aureus*)感染是重大的公共衛生問題，急需疫苗來解決。儘管在動物實驗中表現出相當大的前景，但到目前為止，所有測試的疫苗都未能保護人類免受 *S. aureus* 感染。與實驗室小鼠不同，人類在一生中都會接觸到 *S. aureus*。假設先前接觸過 *S. aureus* 可能會影響免疫系統的反應，從而抑制疫苗的保護作用。所以他們建立一個小鼠模型，先感染 *S. aureus* 造成皮膚和軟組織感染（SSTI）後接種疫苗，然後再次感染 *S. aureus* 造成 SSTI。跟沒感染過 *S. aureus* 的老鼠相比，感染過 *S. aureus* 的老鼠，在打了失活的 α-hemolysin Hla 突變體 (Hla_{H35L})疫苗後，無法完全防止 *S. aureus* 的二次感染。這種保護抑制是特定於 Hla_{H35L} 疫苗，在 *S. aureus* 初次感染期間會表達 hla，並抑制疫苗產生 T 細胞和 DC 細胞的反應，進而降低 Hla_{H35L} 疫苗的效果。但是，若在疫苗中添加 T cell-stimulating adjuvant (CAF01)，就可以讓疫苗重新恢復作用，保護小鼠免受 *S. aureus* 感染。總之，作者發現了潛在機制，解釋為什麼 *S. aureus* 疫苗無法從小鼠模型轉化為臨床實踐，並提出解決方案以預防 *S. aureus* 的感染，這些結果將有助於未來疫苗的研發。

2. 對論文內容的提問：

在本文中使用的小鼠品系為 C57BL/6，但未說明為何選擇這個品系。若使用其他品系如 BALB/c 小鼠，在 SSTI 後再接種疫苗，是否會導致不同的反應仍需要進一步研究。

3. 論文的缺點及評價：

儘管此研究所使用的小鼠模型不能完全反映人類在 *S. aureus* 感染後的發病機制和相關免疫反應。但作者的研究為疫苗的開發提供了寶貴的啟示。此外作者尚未闡明在原發性 SSTI 期間 hla 的表達如何抑制疫苗特異性的 IL-17 和 IFN-γ 反應的機制，以及感染後在引流淋巴結中產生的局部效應是如何影響全身的疫苗反應。此外該研究僅限於 C57BL/6 小鼠遺傳背景。儘管如此，作者開發的小鼠模型以及疫苗佐劑 CAF01 的發現更接近打疫苗時的真實狀況，這將有助於疫苗研發的推進。

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Toxin expression during *Staphylococcus aureus* infection imprints host immunity to inhibit vaccine efficacy

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Staphylococcus aureus infections are a major public health issue, and a vaccine is urgently needed. Despite a considerable promise in preclinical models, all vaccines tested thus far have failed to protect humans against *S. aureus*. Unlike laboratory mice, humans are exposed to *S. aureus* throughout life. In the current study, we hypothesized that prior exposure to *S. aureus* "imprints" the immune response to inhibit vaccine-mediated protection. We established a mouse model in which *S. aureus* skin and soft tissue infection (SSTI) is followed by vaccination and secondary SSTI. Unlike naïve mice, *S. aureus*-sensitized mice were incompletely protected against secondary SSTI by vaccination with the inactivated α-hemolysin (Hla) mutant Hla_{H35L}. Inhibition of protection was specific for the Hla_{H35L} vaccine and required *hla* expression during primary SSTI. Surprisingly, inhibition occurred at the level of vaccine-elicited effector T cells; *hla* expression during primary infection limited the expansion of T cells and dendritic cells and impaired vaccine-specific T cell responses. Importantly, the T cell-stimulating adjuvant CAF01 rescued inhibition and restored vaccine-mediated protection. Together, these findings identify a potential mechanism for the failure of translation of promising *S. aureus* vaccines from mouse models to clinical practice and suggest a path forward to prevent these devastating infections.

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INTRODUCTION

Skin and soft tissue infections (SSTI) are a major public health problem with a national economic burden of $15 billion/year[1]. *Staphylococcus aureus* is the most common cause of SSTI, and recurrent infections are common[2,3]. Antibiotic treatment is the mainstay of therapy, but antibiotic-resistant *S. aureus* isolates have emerged[4]. Therefore, preventative strategies are urgently needed. Unfortunately, despite considerable effort, no vaccine is currently licensed to prevent *S. aureus* infections[5].

It is not clear whether "natural" immune responses against *S. aureus* protect against infection. The high rates of recurrent infection in individuals with SSTI—up to 50% within a year—suggest that protection is incomplete at best[3,6,7]. Given the failures of all vaccine efforts to date[8], it is imperative to determine the nature of protective immunity against *S. aureus*. Paradoxically, most individuals have detectable levels of *S. aureus*-specific antibodies[9] and memory T cells[10,11], consistent with the notion that exposure to *S. aureus* is ubiquitous and persists throughout the lifespan. These findings support the hypothesis that natural exposure to *S. aureus* "imprints" the immune system resulting in resistance to vaccination. Indeed, Tsai et al. recently reported that *S. aureus* infection may imprint non-protective antibody responses that interfere with protective antibodies elicited by vaccination[12]. Natural exposure to pathogens is thought to be a challenge in vaccination against a variety of pathogens. For example, exposure early in life to influenza shapes the immune system in such a way that subsequent responses to vaccination with a heterologous strain are inhibited at the expense of recall of responses against the original strain[13]. Francis called these patterned responses "Original Antigenic Sin"[14]. Whether human exposure to *S. aureus* contributes to the failure of vaccine efforts is not yet clear.

It is also not clear what immunologic mechanisms should be targeted with candidate vaccines. Although there is evidence in murine models that both cellular and humoral immune responses are important for protection against *S. aureus*, human studies suggest that T cells are most important in determining susceptibility to infection[15]. We and others have identified immune responses against the staphylococcal α-hemolysin (Hla) as protective against *S. aureus* SSTI[16,17]. Although Hla-specific antibody responses are clearly important for protection in mouse models, there is also a role for T cell responses[18–22]. We reported that concomitant *S. aureus* SSTI interferes with vaccine-mediated protective antibody and T cell responses in a mouse model by the preferable presentation of immunodominant, but not protective, epitopes in a manner dependent on the host major histocompatibility complex, providing one potential mechanism by which *S. aureus* may thwart vaccine-mediated protection[18].

In the current study, we sought to understand how prior exposure to *S. aureus* could inhibit vaccine-mediated protection. Using a novel mouse model of *S. aureus* SSTI in which infection "imprints" host immune responses, we found that prior infection inhibits the ability of vaccination to elicit protection against secondary infection. Importantly, this inhibition was dependent on *hla* expression during primary infection and specific to Hla-targeted vaccination. Our findings demonstrate that toxin expression during infection inhibits vaccine-specific T cell-mediated protection against secondary infection and can be overcome by targeting T cell responses using alternative vaccine adjuvants.

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