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Research Article

Molecular Mechanisms of *Bordetella pertussis*-induced Immunosuppression: Effects on Cellular Homeostasis and Innate Immune Response in Children

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Abstract

Background: Bordetella pertussis remains a significant global health challenge, particularly in pediatric populations where the infection often leads to severe clinical outcomes. The pathogenicity of this bacterium is largely driven by its ability to secrete various virulence factors that systematically dismantle the host's primary defenses. *Purpose:* This study aims to synthesize the pathway-level molecular mechanisms by which Pertussis Toxin (PT), Adenylate Cyclase Toxin (ACT), and Tracheal Cytotoxin (TCT) collectively subvert host immunity. By mapping these interactions, the research seeks to identify critical therapeutic targets for neutralizing toxin activity. *Methods:* Through a comprehensive mechanistic analysis and a review of current biochemical literature, we elucidate how these specific toxins disrupt essential innate immune processes. The analysis focuses on signaling cascades in leukocytes and the structural integrity of the respiratory epithelium. *Conclusion:* Our findings demonstrate that PT impairs leukocyte recruitment by ADP-ribosylating G-protein-coupled receptors (GPCRs), effectively blinding immune cells to chemotactic gradients. Simultaneously, ACT elevates intracellular cyclic AMP (cAMP) levels, thereby paralyzing phagocytic functions such as pathogen engulfment and antigen presentation, thereby blunting both innate clearance and subsequent adaptive activation. Furthermore, TCT induces direct structural damage to the respiratory epithelium via the NOD1 pathway, compromising mucosal barrier integrity and facilitating persistent bacterial colonization. Together, these toxins orchestrate a multifaceted assault that exploits the developing immune systems of children. This research concludes that understanding these molecular disruptions is vital for restoring immune competence and informs the development of next-generation mucosal vaccines, ultimately reducing the clinical burden of *Bordetella pertussis.*

Keywords

Bordetella pertussis, Pertussis Toxin, Adenylate Cyclase Toxin, Innate Immunity, Pediatric Pathogenesis, Immune Evasion, ADP-ribosylation, Vaccine Development

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1. Introduction

In children, the innate immune system serves as the primary defense mechanism against infections because of the ongoing maturation of the adaptive immune system [1]. *Bordetella pertussis* exploits this critical developmental period by secreting a range of potent exotoxins that specifically target innate immune cells, such as macrophages, neutrophils, and dendritic cells, which are essential for the early detection and clearance of pathogens [2, 3]. The pathogenesis of pertussis is fundamentally based on the disruption of cellular homeostasis within these immune cells. By manipulating key intracellular signaling pathways, most notably those mediated by G protein-coupled receptors and cyclic AMP (cAMP), *B. pertussis* induces a state of "immunological silence," thereby paralyzing the immune response. This functional paralysis prevents the immune system from mounting an effective defense, allowing the bacteria to evade early clearance and establish infection.

This review provides an in-depth exploration of the molecular mechanisms by which B. pertussis virulence factors, including pertussis toxin (PT), adenylate cyclase toxin (ACT), and tracheal cytotoxin (TCT), act in concert to suppress innate immune activation. PT disrupts host G protein signaling, resulting in impaired immune cell trafficking and altered cytokine profiles, which diminish the recruitment and activation of immune effector cells [4, 5]. Concurrently, ACT elevates intracellular cAMP concentrations within phagocytes, leading to compromised phagocytic activity and reduced production of pro-inflammatory mediators [6]. TCT contributes by damaging respiratory epithelial cells, further weakening the local immune barrier, and facilitating bacterial persistence [7]. Together, these toxins orchestrate a multifaceted immunosuppressive environment that undermines the host's early immune defenses. This coordinated attack on innate immunity is particularly detrimental in pediatric patients, whose adaptive immunity is not yet fully developed, thereby increasing their susceptibility to prolonged and severe pertussis infection [8].

2. Methods

A systematic review was conducted to thoroughly examine the molecular signaling pathways disrupted by Bordetella pertussis toxins. To ensure comprehensive coverage of relevant literature, major biomedical databases including PubMed, PMC, and Google Scholar were systematically searched for peer-reviewed articles published up to early 2026 [9]. The search strategy was designed to capture a wide array of mechanistic studies that specifically investigate the effects of *B. pertussis* toxins on cellular signaling processes. Inclusion criteria were rigorously defined to focus on studies utilizing human pediatric cell models or well-established animal models that closely mimic the pathophysiological conditions of pertussis infection [10]. This selection criterion was intended to enhance the biological relevance and translational applicability of the findings.

Key areas of interest for inclusion encompassed detailed analyses of how *B. pertussis* toxins interfere with G protein-coupled receptor (GPCR) signaling pathways, disrupt cyclic adenosine monophosphate (cAMP) homeostasis, and compromise the integrity of epithelial barriers [11, 12]. These molecular disruptions are critical to understanding the mechanisms by which the toxins undermine host immune defenses. To integrate the diverse findings from individual studies, a pathway-focused analytical framework was employed. This approach facilitated the synthesis of toxin-specific effects into a unified model illustrating the failure of the innate immune barrier. By mapping the convergent and divergent molecular events triggered by different toxins, the analysis provided a comprehensive mechanistic insight into the cellular processes that contribute to pertussis pathogenesis.

The systematic methodology and targeted inclusion criteria ensured that the review captured the most relevant and mechanistically informative studies, enabling a detailed exploration of signaling cascades and cellular dysfunctions induced by *B. pertussis* toxins. This integrative review framework not only elucidates the complex interactions between bacterial toxins and host cellular pathways but also highlights potential molecular targets for therapeutic intervention aimed at restoring immune barrier function in pertussis infections.

3. Results: Mechanisms of Immune Subversion

The immune subversion mechanisms employed by *Bordetella pertussis* are multifaceted, targeting key components of host immune signaling and cellular function to ensure bacterial survival and persistence. Pertussis toxin (PT) disrupts intracellular signaling by ADP-ribosylating the inhibitory G-proteins, which prevents the normal inhibition of adenylate cyclase [13]. This interference halts the production of pro-inflammatory cytokines and severely impairs leukocyte chemotaxis, effectively "blinding" neutrophils and macrophages to chemotactic signals and preventing their migration to infection sites [14, 15]. This early immune evasion strategy undermines the host's initial inflammatory response, allowing the bacteria to establish infection with reduced immune resistance. Complementing this, adenylate cyclase toxin (ACT) directly paralyzes phagocytic cells by elevating intracellular cAMP to supraphysiological levels, which suppresses phagocytosis, oxidative burst, and antigen presentation [16]. The toxin also triggers apoptosis in macrophages and dendritic cells, weakening the host's capacity to mount an effective adaptive immune response [17]. Meanwhile, tracheal cytotoxin (TCT) targets the structural integrity of the respiratory epithelium by inducing ciliostasis and epithelial cell shedding through activation of the NOD1 receptor pathway [18, 19] and subsequent nitric oxide and interleukin-1 production. This destruction of the mucociliary escalator not only facilitates bacterial persistence by impairing mechanical clearance but also creates a localized immunosuppressive environment that further inhibits immune cell recruitment. Together, these toxins orchestrate a comprehensive immune subversion strategy that disrupts both innate and adaptive defenses, promoting chronic infection [20].

4. Discussion: Pediatric Vulnerability

The pediatric immune system is inherently "naive," characterized by an underdeveloped adaptive immunity that relies predominantly on innate immune signaling pathways to initiate T-cell priming and subsequent immune responses. This developmental immaturity results in a limited capacity to mount effective and rapid adaptive immune responses, leaving children particularly susceptible to infections. In the context of Bordetella pertussis infection, this vulnerability is exacerbated by the pathogen's ability to manipulate and impair host immune defenses [21].

B. pertussis produces several toxins, notably pertussis toxin (PT) and tracheal cytotoxin (TCT), which play crucial roles in immune evasion and pathogenesis. Pertussis toxin induces functional paralysis of dendritic cells, which are essential antigen-presenting cells responsible for bridging innate and adaptive immunity. By incapacitating dendritic cells, *B. pertussis* disrupts the activation and differentiation of naive T cells, thereby impairing the development of a robust and specific adaptive immune response, including the generation of immunological memory [22]. This blockade not only delays the clearance of the bacteria but also contributes to prolonged infection and increased disease severity in pediatric patients.

Simultaneously, the immature respiratory tract in children shows heightened sensitivity to the cytotoxic effects of TCT, a peptidoglycan fragment released by *B. pertussis* that damages ciliated epithelial cells in the trachea and bronchi. The necrosis of these epithelial cells compromises mucociliary clearance, a primary defense mechanism of the respiratory system, leading to the accumulation of mucus and bacteria. This damage manifests clinically as the characteristic "paroxysmal cough," which is a hallmark of pertussis infection and contributes significantly to morbidity in pediatric populations [8]. The combination of impaired immune signaling and structural damage to the respiratory epithelium creates an environment conducive to bacterial persistence and severe symptomatology.

These molecular and physiological vulnerabilities collectively enable *B. pertussis* to evade immune clearance effectively and establish a persistent infection, even in the absence of a mature memory response [23]. This persistence is particularly problematic in children, whose immune systems are still developing and who rely heavily on effective vaccination strategies for protection.

Vaccine-induced immunity against *B. pertussis* also reflects these immunological complexities. Whole-cell pertussis vaccines (wP) stimulate a broad immune response, including Th1 and Th17 pathways, which are critical for mucosal immunity and bacterial clearance. In contrast, acellular pertussis vaccines (aP), while effective at preventing systemic symptoms, predominantly induce a Th2-skewed immune response and often fail to elicit a strong Th17-mediated mucosal immunity [24]. The Th17 response is particularly important for recruiting neutrophils and enhancing local immune defenses at the respiratory mucosa, counteracting the immunosuppressive effects of *B. pertussis* toxins. The relative deficiency of this response with aP vaccines may explain the observed resurgence of pertussis cases and the persistence of bacterial colonization despite vaccination.

Furthermore, the differential vaccine-induced immune profiles highlight the need to consider the unique immunological environment of the pediatric respiratory tract when designing and implementing vaccination strategies. Enhancing mucosal immunity and overcoming toxin-mediated immunosuppression are critical goals for improving vaccine efficacy and reducing the burden of pertussis in children.

5. Conclusion

The molecular mechanisms underlying Bordetella pertussis-induced immunosuppression represent a sophisticated example of microbial subversion, wherein the pathogen employs a multifaceted arsenal to actively dismantle host immune defenses rather than merely evading detection. Central to this process are the concerted actions of pertussis toxin (PT), adenylate cyclase toxin (ACT), and tracheal cytotoxin (TCT), each targeting distinct yet interconnected components of the host immune system. PT exerts its effect by ADP-ribosylating key G-protein-coupled signaling proteins, thereby incapacitating intracellular communication pathways essential for immune cell activation and coordination. Concurrently, ACT elevates intracellular cyclic AMP (cAMP) levels to supraphysiological concentrations, which disrupts critical cellular functions, including phagocytosis, cytokine secretion, and leukocyte chemotaxis. TCT further exacerbates immune dysfunction by inflicting damage on epithelial cells, compromising mucosal barrier integrity, and facilitating bacterial persistence.

In pediatric populations, whose immune systems are still developing and thus inherently more vulnerable, these molecular disruptions have particularly devastating consequences. The impaired recruitment of leukocytes to sites of infection, coupled with the apoptosis of antigen-presenting cells, creates a profound immunological "blind spot," effectively blinding the host to the presence of the pathogen and allowing *B. pertussis* to establish persistent colonization within the respiratory tract. This immune evasion manifests clinically as the hallmark symptoms of pertussis, including prolonged paroxysmal coughing and severe respiratory distress, which can be life-threatening in infants and young children. The pathogenesis highlights the critical need for therapeutic interventions that target these immunosuppressive mechanisms at an early stage.

Looking forward, future therapeutic strategies must prioritize the neutralization of these virulence factors to restore immune homeostasis and enhance host defense. Potential approaches include the design and development of small-molecule inhibitors specifically targeting the enzymatic activity of ACT, thereby preventing the aberrant cAMP accumulation that cripples immune cell function. Additionally, the generation of highly potent and specific antitoxin antibodies could provide a means to neutralize PT and ACT, mitigating their immunomodulatory effects. Complementing these interventions, advances in mucosal vaccine technology aimed at eliciting robust local immunity within the respiratory tract hold promise for preventing colonization and subsequent disease. Together, these strategies represent a comprehensive approach to counteracting the sophisticated immunosuppressive tactics of *B. pertussis* and improving clinical outcomes, particularly in vulnerable pediatric populations.

Abbreviations

ACT	Adenylate Cyclase Toxin
ADP	Adenosine Diphosphate
aP	Acellular Pertussis Vaccine
B. pertussis	*Bordetella pertussis*
cAMP	Cyclic Adenosine Monophosphate
CR3	Complement Receptor 3
DC	Dendritic Cell
GPCR	G Protein-Coupled Receptor
IL-1	Interleukin-1
NOD1	Nucleotide-binding Oligomerization Domain-containing Protein 1
NO	Nitric Oxide
PMC	PubMed Central
PT	Pertussis Toxin
TCT	Tracheal Cytotoxin
Th1	T Helper Type 1 Cells
Th2	T Helper Type 2 Cells
Th17	T Helper Type 17 Cells
wP	Whole-cell Pertussis Vaccine

Author Contributions

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Conflicts of Interest

The authors declare no conflicts of interest.

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