COMMENTARY

Smoking's Achilles heel demystified: Triggering persistent adaptive immunity by variability responses to immunogens

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The COVID-19 pandemic has illuminated the extensive array of individual and population responses to immune challenges, as evidenced by the diverse clinical outcomes following SARS-COV-2 infection. Although age, sex, and genetic variations significantly influence how individuals respond to infection, these factors are not consistently considered in treatment or vaccine design. This emphasizes the importance for scientists to identify the variables associated with immune response diversity.

Violaine Saint-Andre and colleagues recently published a study in the journal Nature.[1] The researchers exposed blood samples from 1,000 healthy individuals to molecules, microorganisms, and viruses known to trigger the immune system, aiming to identify the primary determinants of individual immune differences. Intriguingly, after analyzing numerous factors related to social demographics, diet, and lifestyle, the researchers discovered that smoking, cytomegalovirus (CMV) infection, and body mass index (BMI) have

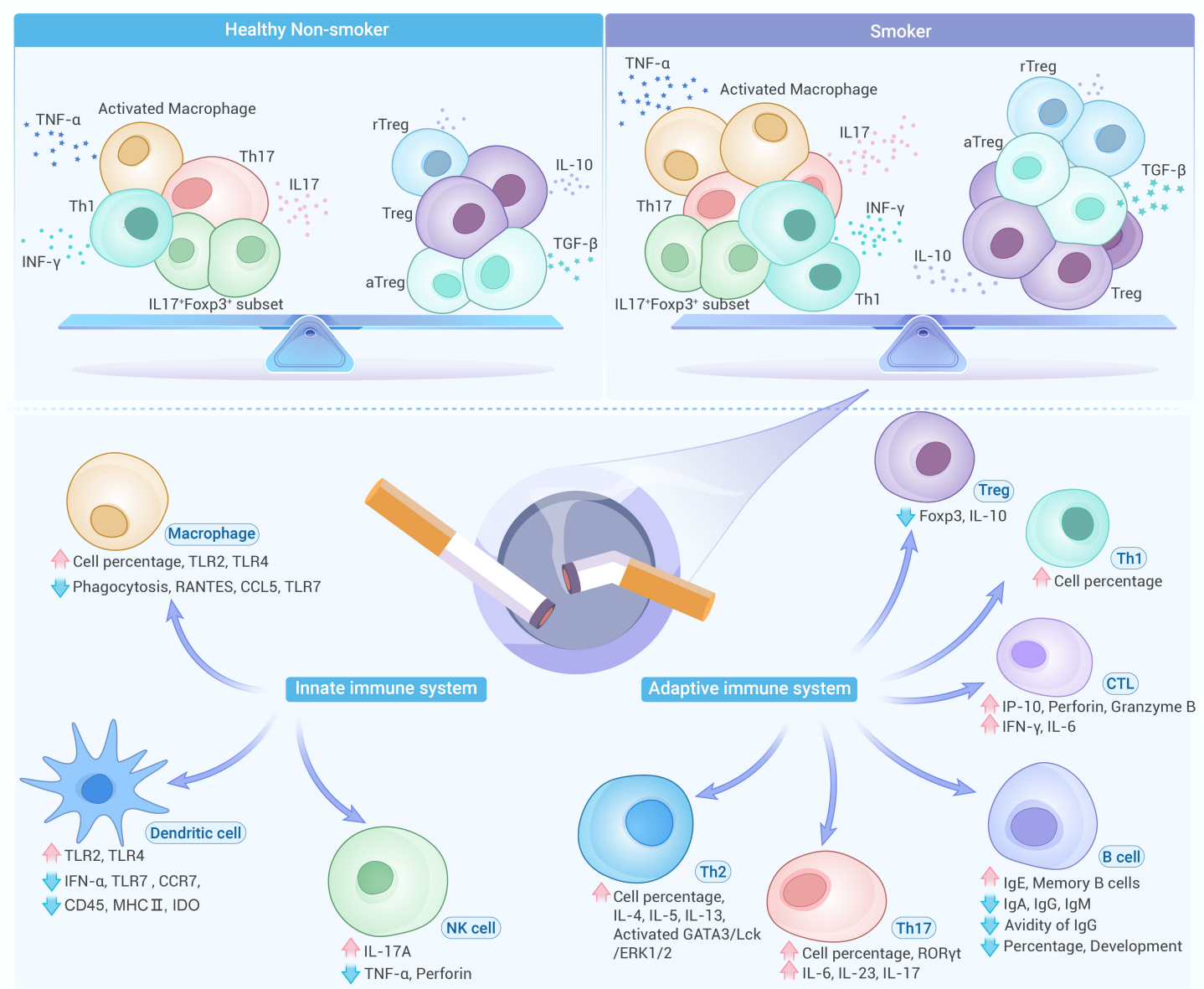

Figure 1. Different effects of smoking on innate immunity and adaptive immunity.

the most significant impact on immune function. Of particular note is the impact of smoking, as it can influence adaptive immunity by altering epigenetics, with effects persisting for many years after quitting smoking.

How does smoking affect the immune system? The core component of the immune system is lymphocytes, which enable the immune system to recognize and remember potential threats. Following exposure to antigens, the body mounts an immune response and forms immune memory, leading to lasting immunity. Previous studies have indicated that smoking hampers the activity of certain cells involved in immune memory.[2] This study investigates the link between smoking and the immune system from the perspective of cytokine secretion. Research has shown that smoking is associated with the secretion levels of several key cytokines, including interleukin-2 (IL-2) and interleukin-13 (IL-13). Upon comparing the immune responses of smokers and former smokers, the researchers observed that the influence of smoking on innate immune response diminishes rapidly after quitting and is linked to plasma CEACAM6 levels, while its impact on adaptive immunity persists for a prolonged period, up to 10 to 15 years. Notably, the CEACAM6 protein is involved in inflammatory processes and immune regulation, and is considered by scientists as a clinical biomarker for various cancer diseases. Consequently, smokers tend to exhibit higher levels of CEACAM6 protein compared to non-smokers, indicating that smoking may contribute to cancer development. These findings suggest a clear distinction: the short-term effects of smoking on innate immune response and the long-term effects on adaptive immune response. The immune system appears to retain long-term memory akin to the enduring effects of smoking. Although the adaptive immune function can partially recover after smoking cessation, some irreversible changes will continue to have lasting effects and heighten the risk of illness and cancer.

Additionally, the researchers also uncovered the mechanism underlying the sustained impact of smoking on adaptive immune response. The authors assessed baseline DNA methylation at CpG sites and identified CpG sites directly associated with smoking. At these sites, smokers exhibited pronounced DNA hypomethylation compared to non-smokers, while quitters displayed intermediate methylation levels. In essence, smoking can engender enduring effects on adaptive immunity by modifying DNA methylation, particularly at gene loci such as the aromatic hydrocarbon receptor repressor protein (AHRR) and retinoic acid receptor (RARA). DNA methylation serves as an epigenetic marker capable of regulating gene expression, thereby influencing the physiological function of cells. Hence, smoking-induced alterations in DNA methylation may lead to abnormal adaptive immune function, potentially elevating the risk of infection, cancer, and autoimmune diseases.

The effects of smoking on the immune system are multifaceted, encompassing alterations in the number of immune cells, impairment of immune cell function, modulation of immune response, and impacts on long-term immune memory.[1,2] Moreover, smoking disrupts the normal functioning of immune cells, diminishing their effectiveness in recognizing and combating pathogens. Understanding the mechanisms through which smoking affects the immune system provides valuable insights for public health policy. It highlights smoking as a significant public health concern, underscoring the need for policy interventions aimed at reducing smoking prevalence and associated health risks. By examining molecular signatures in smokers and non-smokers, policymakers can gain deeper insights into the hazards of smoking and develop targeted prevention and treatment strategies. Additionally, it emphasizes the importance of smoking cessation in enhancing individual health outcomes and alleviating strain on healthcare resources. This study reveals the key factors influencing individual immune ability, particularly emphasizing the far-reaching influence of smoking, a modifiable lifestyle factor, on the immune system. Analyzing the impact of smoking on the immune system also underscores the significant influence of lifestyle on human health. Numerous examples illustrate how lifestyle modifications can profoundly affect individuals' well-being. For instance, the imbalance of maternal intestinal microbiome and inflammatory environmental changes caused by infection, dietary alterations, or stress during pregnancy may induce epigenetic memory in the fetus and systemic signals that affect brain development and neuronal behavior of offspring.[3]

Smoking can impact the function of immune cells, affecting the activity and quantity of T and B cells, potentially compromising the immune system's memory capacity.[2] Furthermore, smoking can alter the behavior of immune cells through epigenetic mechanisms, such as modifying the expression of genes associated with immune cell metabolism via DNA methylation changes, thereby affecting immune memory. Therefore, the article highlights the significant implications of immune memory and epigenetic memory for human health. Immune memory is a crucial evolutionary trait that enhances the host's survival rate upon reinfection, enabling the immune system to combat infections more effectively, thereby fortifying the body's defenses and preventing disease occurrence. Trained immunity relies on two key elements: epigenetics and metabolic reprogramming of cells. Some studies suggest that it can induce a well-trained immunophenotype to enhance the body's defense capabilities.[4] However, epigenetic memory may impact individuals' adaptability to environmental factors, thereby regulating disease susceptibility and overall health status. Studies have shown that following skin wounds, entrained epithelial stem cells accumulate and retain distinct epigenetic memories of their various experiences, enhancing their function and flexibility.[5] This demonstrates the plasticity of cell fate at the level of epigenetic memory. Overall, research on immune memory and epigenetic memory provides a deeper understanding of the body's response to diseases, offering more effective strategies and approaches for disease prevention, personalized medicine, and health management.

Certainly, this article prompts a great deal of contemplation. The mechanisms through which DNA methylation regulates and influences adaptive immunity, as presented in this paper, remain unknown. In the future, further exploration can focus on reversing the long-term effects of smoking on adaptive immunity. Additionally, it is crucial to investigate how smoking interacts with other lifestyle factors such as diet and exercise to collectively impact the immune system. Furthermore, it is important to consider whether alterations in adaptive immunity caused by smoking may affect individuals' long-term health, including the risk of chronic diseases and lifespan. Will these changes impact the efficacy of vaccines or the response to other treatments? All these issues warrant ongoing exploration. Moreover, exploring whether other tobacco products, such as e-cigarettes, exert similar impacts on the immune system as traditional cigarettes would be valuable for comprehensive public health strategies. These avenues of research hold promise for elucidating the complex interplay between smoking, immune function, and overall health outcomes (Figure 1).

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AUTHOR CONTRIBUTIONS

Y.H. and M.W. provided the conception, funding support, revision and supervision. T.P. conducted the literature research and wrote the initial manuscript and made the figure. All authors have read and approved to publish the article.

DECLARATION OF INTERESTS

The authors declare no competing interests.