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Environmental exposures are hidden modifiers of anti-viral immunity

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Abstract

Significant advances have been made recent years elucidating antiviral immune mechanisms that protect the host from viral infection. Similarly, our understanding of how viruses bind, enter, and replicate within host cells has continued to grow. Yet, viruses continue to take a toll on human health. The influence of chemicals in the environment is among key factors that influence outcomes of viral infection. There is a growing appreciation of the effects that exogenous environmental chemical exposures have on the immune system and antiviral immunity. Epidemiological studies have linked a variety of chemical exposures to poorer health, increased incidence of infection, and worsened vaccine responses. However, the mechanisms that govern these associations are not well understood, limiting our ability to predict or mitigate the effects of environmental exposures on public health. This brief review focuses on recent advances in the field, highlighting novel *in vitro* and *in vivo* findings informed by past foundational studies. Furthermore, current information suggests avenues of investigation that have yet to be explored, but which will significantly impact on our understanding about how environmental exposures impact viral defenses, vaccine efficacy, and the spread of contemporary and emerging viral pathogens.

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1. Introduction

There are over 1400 known human pathogens, of which 219 are classified as viral agents of disease [1,2]. In spite of continuous improvements in public health and medicine, infectious diseases continue to cause substantial morbidity, mortality, and socioeconomic loss. Viruses regularly instigate localized epidemics, and can give rise to pandemics. Viruses constitute a particular global health concern due to the limited range of therapeutic agents, the ability of many viruses to reassort and mutate, and their multiple transmission routes. Notably, influenza viruses and respiratory syncytial virus are among major causes of virally mediated respiratory illness [3], while hepatitis viruses are transmitted via oral–fecal exchange and blood [4]. In addition to these common viral diseases, there is increasing awareness of emerging viral diseases, such as those triggered by outbreaks of Zika and Ebola viruses. As such, the World Health Organization and many national public health programs maintain substantial focus on the continue threat of viral epidemic and pandemic diseases.

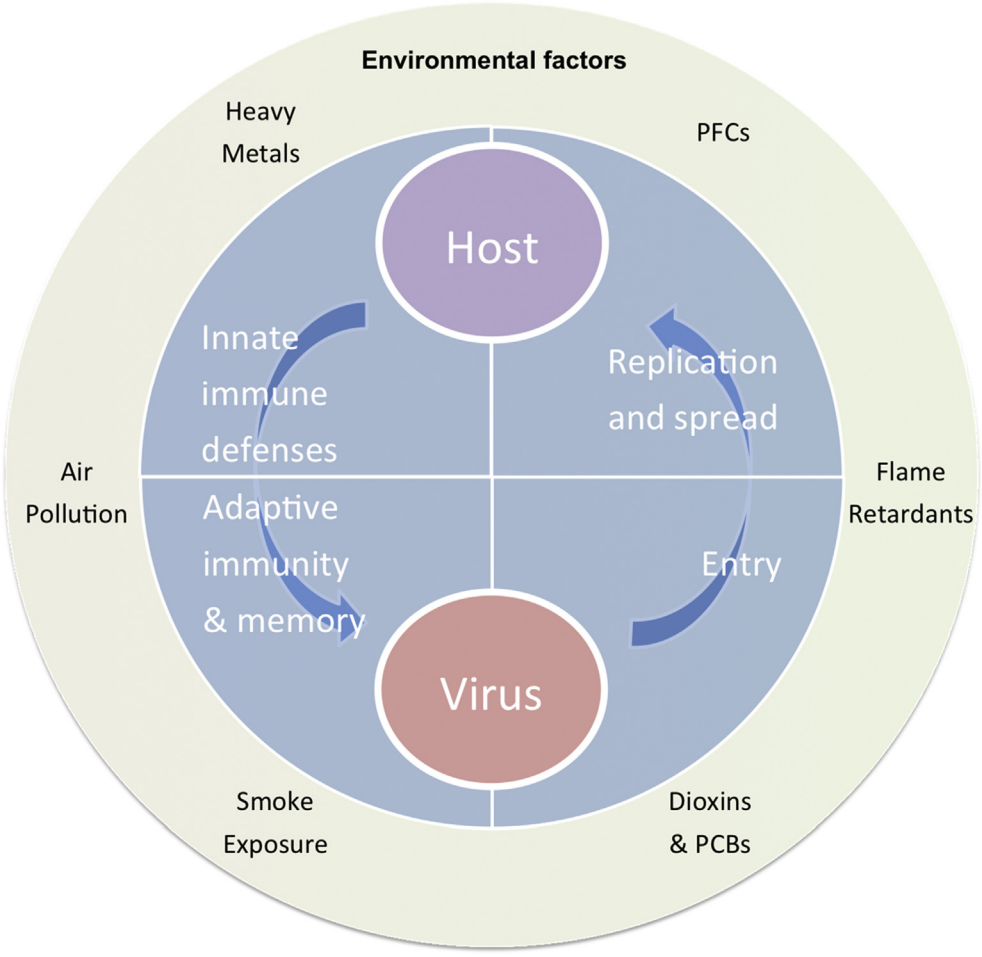
The past several decades have heralded major advances in our understanding of immune responses to viral infection. Yet, differences in vulnerability to viral infection remain. For instance, it is still a mystery why, during outbreaks of the same viral subtype, illness ranges from asymptomatic to severe within immunocompetent populations. Some variances are explained by age, sex, and genetics; however, these are not adequate to account for all disparities. The host's environment is one extrinsic factor rarely taken into account. In general, "environment" encompasses characteristics of where one lives and works, diet, chemicals, and natural products to which one comes into contact. We are constantly exposed to a broad assortment of substances from our environment, skew regulatory and inflammatory pathways, and predispose the host to exacerbated pathology subsequent to viral infection (Fig. 1).

This is not theoretical. Emerging evidence points to environmental exposure as important, often unnoticed, contributors to individual and population level differences in antiviral responses [5]. Yet, the mechanisms by which environmental factors affect antiviral defenses remain poorly defined. Delineating cause-and-effect relationships between specific environmental factors and viral diseases will reveal new opportunities to intervene and prevent disease. With these ideas in mind, this commentary has two goals: 1) highlight recent advances in knowledge of ways in which environmental exposures influence antiviral defenses; and 2) frame key opportunities for future study.

2. Antiviral defense mechanisms

The immune system consists of an integrated cellular network that protects the host from infection, and

Fig. 1



Host–Virus interactions consist of a balance between host immune defenses and viral immune evasion mechanisms. Emerging evidence shows that environmental factors play a major role in shaping host responses to viral infection, and may also shape how viruses bind, replicate, and spread during the course of infection.

eliminates viruses and virus-infected cells during infection [6]. Initially, protection is conferred in a general way, via innate immunity. Innate immune responses are usually rapid, unspecific, and not long lasting. For example, viral infection triggers host cells to produce interferons (IFNs), which restrict viral replication by influencing events in host cells, and activating leukocyte defense mechanisms [7,8]. Deregulation of the innate immune system allows viruses to replicate unfettered, endangering the host, and contributing to the continued spread of the virus. Viruses have evolved mechanisms to thwart the innate immune system. Examples include inhibition of type I interferon (IFN-I) [9], and decoy molecules that assist in evading intracellular detection by cells of the innate immune system [10].

In addition to viral control, signals from the innate immune system stimulate the adaptive immune system. Adaptive responses to viral infection rely on the activation, expansion, and differentiation of $CD4^+$ and $CD8^+$ T lymphocytes and B lymphocytes. Virus-specific cytotoxic T cells (CTL) are mainly responsible for complete viral clearance during primary infection, while a combination of CTL, helper T cells, and virus-specific antibodies contribute to host protection during recurrent infections. Consequently, improper or insufficient adaptive immune responses can affect outcomes from both initial and repeated infections.

Establishing immunological memory is the underpinning of vaccination, the most effective means of combating viral disease. The efficacy of most vaccines is mediated by sustained production of highly specific antibodies to conserved viral antigens. Current vaccination efforts have led to an unparalleled reduction in outbreaks of rubella, measles, polio, and mumps, and the global eradication of small pox [11]. Some viruses, such as influenza viruses, are highly mutable and require