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Editorial: Innate and adaptive immune responses to viral infection

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Editorial on the Research Topic
Innate and adaptive immune responses to viral infection

Viral infections, such as Hepatitis C virus (HCV) and the emerging SARS-CoV-2, continue to pose significant public health challenges due to their ability to evade immune clearance and induce immune dysregulation and long-term health complications. The research explored in this Research Topic focuses on the complex interactions between viral infections and the host immune system, with particular emphasis on how these infections affect CD8+ T cell responses, immune exhaustion, and viral persistence. This Research Topic summarizes the key insights from these studies and suggests potential future directions in viral immunology.

Were the initial objectives of the Research Topic met?

The primary objective of this Research Topic was to better understand the interplay between innate and adaptive immune responses in chronic viral infections, particularly how these infections alter immune function. Studies reviewed in this Research Topic explored the immune dysfunction associated with chronic HCV infection and its broader implications for immune responses to other pathogens, including SARS-CoV-2.

A key study by Maretti-Mira et al. demonstrated that chronic HCV infection disrupts the immune response to its antigens and shapes the broader immune landscape, impacting responses to other viral infections. Specifically, they found that chronic HCV infection induces immune modulation, leading to dysfunction in CD8+ T cells, which are crucial for viral clearance. Over time, these cells enter a state of exhaustion, impairing the immune system's ability to control the virus and other infections. These findings provide crucial insights into the broader impact of chronic viral infections on immune function.

Similar patterns of immune dysregulation and T cell exhaustion were observed in both chronic HCV and acute SARS-CoV-2 infections, emphasizing the generalizability of immune dysfunction across different viral infections.

What themes and insights did the Research Topic reveal?

One of the central insights from this Research Topic is the phenomenon of immune exhaustion, which occurs in chronic viral infections. Both HCV and SARS-CoV-2 infections lead to T cell dysfunction, particularly in CD8+ T cells, which are essential for controlling viral replication. This dysfunction is marked by the upregulation of exhaustion markers like PD-1 and TIM-3, and a reduction in effector memory T cell responses, hindering effective immune clearance.

The study by Maretti-Mira et al. illustrated how chronic HCV infection impairs HCV-specific CD8+ T cells and also alters immune responses to other co-infections, such as cytomegalovirus (CMV) and influenza. Indeed, these researchers found that CD8+ T cells specific to non-HCV viruses, like CMV and influenza, exhibited heightened cytotoxicity and a pro-inflammatory phenotype. This highlights how chronic infections broadly affect the immune system, increasing susceptibility to secondary infections and complicating vaccine responses. These insights are particularly relevant for understanding SARS-CoV-2 infections, as patients with long COVID or concurrent viral infections exhibit similarly altered immune profiles.

Recent studies have also highlighted the critical role of host restriction factors in limiting viral replication. In the case of SARS-CoV-2, host restriction factors—components of the innate immune system—act to inhibit the viral life cycle. These factors offer potential antiviral targets, helping to control viral spread (Marivate et al.).

Chronic diseases and immune dysregulation

Chronic diseases, such as end-stage kidney disease (ESKD), further exacerbate immune responses during viral infections. A study by Bumbea et al. examined how ESKD alters immune responses in patients with mild COVID-19. Specifically, they found that monocyte subsets, particularly CD14-low CD16+ monocytes, were significantly altered in ESKD patients, demonstrating prolonged pro-inflammatory immune activation even months after infection. This underscores how chronic conditions can contribute to ongoing immune dysfunction and exacerbate inflammatory responses long after the viral infection has resolved.

Vaccine uptake and seroprevalence in Africa

In a study conducted in Nairobi, Kenya, Otindo et al. assessed SARS-CoV-2 seroprevalence and vaccine uptake in university students. The study found that 87.8% of participants had anti-SARS-CoV-2 IgG antibodies, suggesting widespread exposure to the virus, either through natural infection or vaccination. However, the study also revealed significant vaccine hesitancy (43.4%), with mistrust, health concerns, and lack of information cited as the main reasons. This highlights the importance of addressing vaccine hesitancy through community engagement and educational efforts to improve vaccination uptake and ensure effective public health interventions.

Emerging infections and fatal cases

The recent study of Crimean-Congo Hemorrhagic Fever Virus (CCHFV) in Senegal (Mhamadi et al.) provides additional insights into viral infection and immune response. The study observed a high IL-6 titer, low IL-10 titer, and delayed IgG response in a fatal CCHFV case. These biomarkers may serve as indicators of disease severity, allowing for early intervention and tailored treatment strategies for severe infections.

Immunotherapy and viral manipulation of host mechanisms

The manipulation of host DNA repair mechanisms by viruses also emerged as a significant theme in this Research Topic. Both HCV and SARS-CoV-2 exploit host cell machinery, including DNA repair pathways, to avoid immune detection and sustain viral replication. A review by Saladino and Salamango explored how viruses alter cellular repair pathways, promoting viral survival and contributing to immune dysfunction. These mechanisms underscore the complexity of viral persistence and offer potential targets for antiviral therapies.

Understanding SARS-CoV-2 seroprevalence in Uganda

Additionally, a study conducted in Uganda among people living with HIV (PLWH) revealed a 93% SARS-CoV-2 seroprevalence among unvaccinated individuals, despite a relatively low proportion of participants having a laboratory-confirmed infection. This high seroprevalence could be attributed to widespread exposure to the Omicron variant following the lifting of restrictions. The findings reinforce the idea that while humoral immunity (i.e., antibody-mediated immunity) can be robust in certain populations, the asymptomatic or mild nature of many infections could lead to underreporting of true infection rates. These results have important implications for understanding immune responses in PLWH, where previous exposure to SARS-CoV-2 may enhance immune readiness, even without formal diagnosis or vaccination (Ainembabazi et al.). The study underscores the potential for high antibody concentrations despite a low rate of confirmed infections, suggesting a robust immune response that could inform future vaccine strategies.

Future directions in viral immunology

While this Research Topic has significantly advanced our understanding of immune dysfunction in chronic viral infections, several key questions remain. Future research should further investigate the mechanisms of T cell exhaustion, particularly the role of epigenetic changes, cellular metabolism, and microenvironmental factors in driving T cell dysfunction. Understanding these processes could lead to novel therapeutic strategies aimed at rejuvenating exhausted T cells in chronic and emerging viral infections.

Another promising direction is the exploration of immune checkpoint manipulation in chronic infections. Both HCV and SARS-CoV-2 exploit immune checkpoints like PD-1 and TIM-3 to evade immune surveillance. Developing therapies that target these pathways could enhance viral clearance and promote immune recovery, particularly for patients suffering from long COVID or other post-viral syndromes.

Additionally, future studies should examine how chronic infections impact vaccine efficacy. Chronic infections like HCV can alter T cell responses to other pathogens, which may affect how the immune system responds to vaccines. Understanding these dynamics is crucial for developing tailored vaccine strategies.

Conclusion: a path toward integrated approaches in chronic infection management

The insights from this Research Topic emphasize the complexity of immune responses in chronic viral infections. Both HCV and SARS-CoV-2 illustrate the ways in which viruses modulate immune function, especially through T cell exhaustion and immune dysfunction. These findings are critical for developing novel therapeutic strategies that not only clear the virus but also restore immune function and prevent long-term complications.

Future research into host restriction factors, immune modulation, and viral manipulation of host DNA repair mechanisms holds promise for advancing antiviral therapies. As we continue to unravel the mechanisms behind immune dysregulation, we can develop integrated approaches to manage chronic infections more effectively, improving public health outcomes and addressing the long-term consequences of viral infections.

Author contributions

SV: Conceptualization, Writing – original draft. EM: Conceptualization, Writing – original draft.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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