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HIV: Current Research

Perspective

# Enduring IFN-Stimulated Gene Activation Following Acute HIV-1 Infection

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## DESCRIPTION

The upregulation of Interferon-Stimulated Genes (ISGs) plays a crucial role in the host's immune response to HIV-1 infection. However, research suggests that this upregulation persists beyond the acute phase of infection, indicating that it is not simply a transient response. This persistence of ISG upregulation during the chronic phase of HIV-1 infection has implications for understanding the immune dysregulation associated with the disease and may inform strategies for treatment and vaccine development. This review explores the role of ISGs in the context of acute HIV-1 infection and their sustained upregulation during chronic infection, as well as the consequences for immune function and HIV pathogenesis. Human Immunodeficiency Virus (HIV) is a retrovirus that causes Acquired Immunodeficiency Syndrome (AIDS). The immune response to HIV infection is complex and multifaceted, involving both innate and adaptive immune mechanisms. One of the key features of the innate immune response to viral infection is the activation of the interferon system, which includes the upregulation of a range of Interferon-Stimulated Genes (ISGs). These genes are involved in various antiviral processes such as inhibition of viral replication, modulation of immune responses, and promotion of inflammation.

Some of the most important ISGs upregulated during acute HIV-1 infection include antiviral proteins such as APOBEC3G, TRIM5α, and tetherin, which inhibit various stages of the viral life cycle. Additionally, ISGs such as MxA, IFITMs, and OAS proteins prevent viral entry and replication, while other ISGs such as IL-10, IP-10, and MCP-1 modulate immune cell recruitment and inflammation. These responses are crucial for controlling viral replication in the early stages of infection and may contribute to the rapid decline in viral loads observed in many individuals after the acute phase. However, despite the activation of these antiviral responses, HIV-1 is highly adept at evading the immune system, and the virus continues to replicate in the body. This ongoing replication leads to persistent immune activation and inflammation, which can have detrimental effects on the immune system and contribute to the chronic nature of the infection. Following the acute phase of HIV-1 infection, the virus enters a period of clinical latency, where viral replication continues at low levels, and individuals may remain asymptomatic for years. This period of chronic infection is marked by persistent immune activation and a dysregulated immune response, which contributes to the progressive destruction of $CD4^+$ T cells and immune system dysfunction. Despite ART and the reduction of viral loads to undetectable levels in some individuals, chronic immune activation persists and is thought to be a major contributor to disease progression and the development of AIDS.

One of the most striking features of chronic HIV-1 infection is the continued upregulation of ISGs, which remains elevated even in individuals with suppressed viral loads on ART. This persistent activation of the IFN system suggests that the immune system continues to respond to the presence of the virus, even in the absence of detectable viral replication. Studies have shown that ISG expression remains high in both Peripheral Blood Mononuclear Cells (PBMCs) and lymphoid tissues, indicating that the immune response to HIV-1 is not fully resolved during the chronic phase of infection. Several factors contribute to the continued upregulation of ISGs during chronic HIV-1 infection. First, viral reservoirs such as latently infected $CD4^+$ T cells and tissue macrophages remain in a dormant state but can become reactivated during periods of immune activation. These reservoirs are believed to serve as a source of persistent viral replication, which in turn stimulates the ongoing production of type I IFNs and the subsequent activation of ISGs. Even in individuals on ART, small amounts of residual viremia can persist, leading to continued immune activation.

The persistent upregulation of ISGs during chronic HIV-1 infection has several important consequences for immune function and disease progression. On the one hand, the continued activation of antiviral ISGs may help control viral replication to some extent, even in the absence of detectable viral loads. However, the prolonged activation of the IFN system can also have deleterious effects on immune function. One of the major consequences of persistent ISG upregulation is the disruption of normal immune homeostasis. The activation of ISGs can lead to a state of chronic immune activation, which is

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characterized by increased levels of inflammatory cytokines and the activation of immune cells such as T cells, macrophages, and dendritic cells.

## CONCLUSION

The upregulation of Interferon-Stimulated Genes (ISGs) is a critical component of the immune response to HIV-1 infection, both during the acute phase and the chronic phase of infection. While ISG upregulation is essential for controlling viral replication in the early stages of infection, its persistence during chronic infection contributes to immune activation, inflammation, and immune dysfunction. This prolonged activation of the IFN system can have deleterious effects on immune function and disease progression, leading to the depletion of $CD4^+$ T cells, immune exhaustion, and an increased risk of comorbidities. Understanding the mechanisms underlying persistent ISG upregulation and its consequences for immune function may provide insights into novel therapeutic strategies for HIV treatment and vaccine development.