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Doctoral Defense Announcement

Abstract

STAT3 as a critical host determinant of murine gammaherpesvirus 68 latency

By

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The human herpesviruses Epstein-Barr virus (EBV, human herpesvirus 4) and Kaposi sarcoma herpesvirus (KSHV, human herpesvirus 8) establish long term latency without clinical manifestations in most healthy individuals. However, these gammaherpesviruses (GHVs) are the etiologic agents of numerous lymphomas and carcinomas that are a significant clinical burden to immune-compromised individuals, including people living with HIV. GHV latency is a dormant viral state with restricted viral gene expression and the absence of progeny virion production. Due to this quiescent state, current GHV antivirals that target lytic infection are ineffective against latency-driven cancers. Cancers associated with the oncogenic gammaherpesviruses Epstein-Barr virus and Kaposi sarcoma herpesvirus are notable for their constitutive activation of the transcription factor STAT3. This suggests that STAT3 or associated pathways could be targeted by therapeutics to control gammaherpesvirus-associated cancers. To better understand the role of STAT3 during gammaherpesvirus latency and immune control, we use the closely related murine gammaherpesvirus 68 infection of mice as a surrogate host-pathogen system. Genetic deletion of STAT3 in B cells of $CD19^{cre/+}Stat3^{f/f}$ mice reduced peak latency approximately 7-fold. However, infected $CD19^{cre/+}Stat3^{f/f}$ mice exhibited disordered germinal centers and heightened virus-specific CD8 T cell responses compared to WT littermates. To circumvent the systemic immune alterations observed in the B cell-STAT3 knockout mice and more directly evaluate intrinsic roles for STAT3, we generated mixed bone marrow chimeras consisting of WT and STAT3-knockout B cells. Using a competitive model of infection, we discovered a dramatic reduction of latency in STAT3-knockout B cells compared to their WT B cell counterparts in the same lymphoid organ. RNA sequencing of sorted germinal center (GC) B cells determined that viral gene expression was tightly restricted, with very low levels of expression across the viral genome. Viral infection of WT GC cells upregulated cell cycle pathways, while reducing interferon α and γ responses. STAT3 loss in GC cells lead to increased expression of genes *Il9r* and *Fcer2a*, while upregulating pathways such as the interferon responses. Together, our data provide mechanistic insight into the role of STAT3 as a latency determinant in B cells for oncogenic gammaherpesviruses.

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