DNA virus infections shape transposable element activity in vitro and in vivo

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Abstract

Transposable elements (TEs) have been shown to be activated in the context of viral infections, but the mechanisms and functional consequences of this induction are not understood.
Here, we show strong activation of TEs in the context of DNA virus infection and investigate the molecular mechanisms of how TEs are induced. We demonstrate that herpesvirus infection leads to a robust expression of the MLT and THE1-class of LTR containing retrotransposons as well as a subset of long-interspersed nuclear elements-1 (LINEs), Alu-elements and some HERVs. Mechanistically we demonstrate that this TEs upregulation is induced by two pathways that act synergistically: de-repression of KAP1/TRIM28 mediated by phosphorylation and expression of the pioneer factor double-homeobox 4 (DUX4). DUX4 is known to be crucial for TEs induction during zygotic genome activation in early embryonic development. In adults, DUX4 is usually silenced and we previously showed that DUX4 expression is induced by infection with various DNA viruses. We demonstrate binding of DUX4 to TEs upon herpesviral infection and analysis of genes adjacent to TEs shows pathways that are known to be crucial for tumor development. Overexpression of DUX4 significantly induced TEs expression, while its knockout (KO) diminished TEs expression upon HSV-1 infection, underscoring the essential role of DUX4 in TEs activation. Interestingly, analysis of single cell sequencing data from patients with DNA virus infection showed that expression of TEs is also of relevance in vivo, especially in tumors that are caused by oncogenic DNA viruses. Taken together, our data show how TEs are induced by DNA viruses, in particular oncogenic viruses of the herpesviridae, papillomaviridae and polyomaviridae families. TEs expression is known to be a hallmark of oncogenesis, and therefore it is tempting to speculate that viral induction of TEs contributes to viral oncogenesis.

Keywords: Transposable Elements, DNA virus, Herpesvirus, HSV, 1, HCMV, KAP1, TRIM28, DUX4, LINE, 1, LTR

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