International Research Center for Infectious Diseases

Department of Infectious Disease Control, Division of Systems Virology

感染制御系・システムウイルス学分野

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The aim of our laboratory is to expand the knowledge and methodology on virology, which were unable to shed light on by conventional experimental approach. To investigate the co-evolutionary relationship between viruses and hosts, we perform bioinformatic and molecular phylogenetic analyses as well as experimental virology. The interdisciplinary investigations based on experimental virology and other scientific fields/methods will pioneer a new science for deeply understanding infectious diseases.

1. Comparative description of the expression profile of interferon-stimulated genes in multiple cell lineages targeted by HIV-1 infection

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Immediately after viral infections, innate immune sensors recognize viruses and lead to the production of type I interferon (IFN-I). IFN-I upregulates various genes, referred to as IFN-stimulated genes (ISGs), and some ISGs inhibit viral replication. HIV-1, the causative agent of AIDS, mainly infects $CD4^+$ T cells and macrophages and triggers the IFN-I-mediated signaling cascade. Certain ISGs are subsequently upregulated by IFN-I stimulus and potently suppress HIV-1 replication. HIV-1 cell biology has shed light on the molecular understanding of the IFN-I production triggered by HIV-1 infection and the antiviral roles of ISGs. However, the differences in the gene expression patterns following IFN-I stimulus among HIV-1 target cell types are poorly understood. In this study, we hypothesize that the expression profiles of ISGs are different among HIV-1 target cells and address this question by utilizing public transcriptome datasets and bioinformatic techniques. We focus on three cell types intrinsically targeted by HIV-1, including $CD4^+$ T cells, monocytes, and macrophages, and comprehensively compare the expression patterns of ISGs among these cell types. Furthermore, we use the datasets of the differentially expressed genes by HIV-1 infection and the evolutionarily conserved ISGs in mammals and perform comparative transcriptome analyses. We defined 104 'common ISGs' that were upregulated by IFN-I stimulus in $CD4^+$ T cells, monocytes, and macrophages. The ISG expression patterns were different among these three cell types, and intriguingly, both the numbers and the magnitudes of upregulated ISGs by IFN-I stimulus were greatest in macrophages. We also found that the upregulated genes by HIV-1 infection included most 'common ISGs'. Moreover, we determined that the 'common ISGs', particularly those with antiviral activity, were evolutionarily conserved in mammals. To our knowledge, this study is the first investigation to comprehensively describe (i) the different expression patterns of ISGs among HIV-1 target cells, (ii) the overlap in the genes modulated by IFN-I stimulus and HIV-1 infection and (iii) the evolutionary conservation in mammals of the antiviral ISGs that are expressed in HIV-1 target cells. Our results will be useful for deeply understanding the relationship of the effect of IFN-I and the modulated gene expression by HIV-1 infec-

tion.

2. Retroviruses drive the rapid evolution of mammalian *APOBEC3* genes

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APOBEC3 (*A3*) genes are members of the *AID*/*APOBEC* gene family that are found exclusively in mammals. *A3* genes encode antiviral proteins that restrict the replication of retroviruses by inducing G-to-A mutations in their genomes, and have undergone extensive amplification and diversification during mammalian evolution. Endogenous retroviruses (ERVs) are sequences derived from ancient retroviruses that are widespread mammalian genomes. In this study we characterize the *A3* repertoire and use the ERV 'fossil record' to explore the long-term history of co-evolutionary interaction between A3s and retroviruses. We examine the genomes of 160 mammalian species and identify 1,420 *AID*/*APOBEC*-related genes, including representatives of previously uncharacterized lineages. We show that *A3* genes have been amplified in mammals and that amplification is positively correlated with the extent of germline colonization by ERVs. Moreover, we demonstrate that the signatures of A3-mediated mutation can be detected in ERVs found throughout mammalian genomes, and show that in mammalian species with expanded *A3* repertoires, ERVs are significantly enriched for G-to-A mutations. Finally, we show that *A3* amplification occurred concurrently with prominent ERV invasions in primates. Our findings establish that conflict with retroviruses is a major driving force for the rapid evolution of mammalian *A3* genes.

Publications

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