

# HIV-1 host interactions: integration of large-scale datasets

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## Abstract

HIV-1 replication and viral pathogenesis are dependent on numerous host factors. A series of recent papers apply genome-wide and large-scale approaches to map host-virus interactions and to identify host proteins capable of restricting (that is, controlling) the virus. Strategies include genome-wide association studies, small interfering RNA screens, genome-wide transcriptome profiling, proteome studies, and the assessment of the role of host-encoded microRNAs in infection. The various layers of large-scale data are brought together through meta-analytical procedures.

## Introduction and context

HIV-1 research has traditionally led to or rapidly adopted new approaches, tools, and concepts from the life sciences. It is thus no surprise to witness the pace of implementation of large-scale genome approaches in the understanding of HIV-1 biology and pathogenesis. Recent years have seen the publication of genome-wide association studies, small interfering RNA (siRNA) screens, and transcriptome and proteome analyses. These approaches have a number of distinctive features: they focus more on the host than on the virus, they are large-scale and are inspired by the hope of discovery that is not *a priori*, and they bring into the field new researchers from different and more quantitative fields. Moreover, the appetite for novelty means that a number of increasingly available tools and techniques – such as new sequencing equipment – will rapidly contribute new layers of data.

I have purposefully used the expression ‘new layers of data’ rather than ‘knowledge’ to emphasize the parallel development of tools to visualize and integrate data and, hopefully, create a more complete view of the makings of HIV-1. Some experts have identified needs in the field and are orchestrating the joint research efforts that should bring about solutions to the enormous puzzle of host-virus interactions. The present report builds on the recent publication by Bushman and colleagues [1], evaluated in *Faculty of 1000 Medicine* [2].

## Major recent advances

The last two and a half years have seen a large number of studies that use technical platforms to genotype the host genome at high density; now between 500,000 and 1 million single-nucleotide polymorphisms are analyzed per individual. Three publications have applied this technology to the field of HIV-1. Fellay and colleagues [3] investigated the genetic associations with the level of viral load and with rates of disease progression. They identified the major histocompatibility complex (MHC) region in chromosome 6 as the main contributor to HIV-1 control. Two later studies confirmed these findings [4,5]. Currently, the field faces two challenges: (a) how to identify the exact contributors to viral control within the MHC, a region that contains the classical *HLA* genes as well as other genes involved in inflammation and immunity, and (b) how to bring the published and additional follow-up studies into a joint study to complete the assessment of the role of common human variation in HIV-1 disease.

Four siRNA screens have been reported in the last year and a half [6-9]. These studies used transfected libraries of siRNA, or stably transduced short hairpin RNAs (shRNAs), to knock down expression of more than 20,000 genes, followed by infection/transduction of the cells by HIV. Combined, the three siRNA studies identified more than 800 genes as being possibly

relevant for HIV replication; only 34 genes were shared by two or more screens. The more recent study using shRNAs to stably silence Jurkat T cells had only six genes shared with the other studies [9]. In addition, the study design favored the identification of genes that supported HIV replication; there are no data on genes that, when knocked down, lead to increased viral replication (that is, restriction factors).

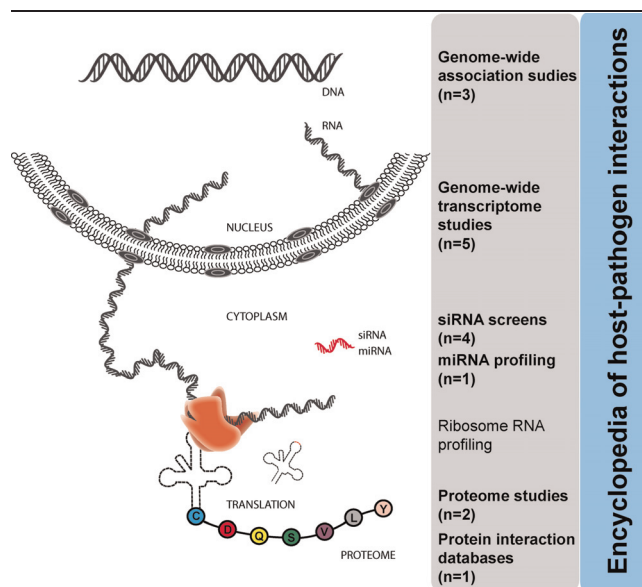
There have been a number of transcriptome studies in HIV-1 target cells (CD4<sup>+</sup> T cells, monocytes/macrophages), in non-targets such as natural killer cells and B cells, and in dendritic cells and total peripheral blood mononuclear cells (reviewed in [10]) [11-13]. Transcriptome analyses of cell lines transfected with individual viral proteins or mutant viruses have also been reported. These studies provide insight into gene expression changes associated with virus replication and persistence. Studies are limited by the number of genes interrogated or by the number of individuals investigated. However, more recent work is bringing to the *in vivo* setting a more dynamic measure of the transcriptome response to infection in models of pathogenic and non-pathogenic primate infection [14,15] as well as in human infection [16].

RNA interference (RNAi) represents a vital component of the innate anti-viral immune response in plants and invertebrate animals. It also serves as a gene regulation mechanism that is triggered by the expression of microRNA (miRNA) molecules. Understanding the role of cellular miRNAs in the defense against viral infection in mammalian organisms and the influence of viral replication on the abundance and distribution of miRNAs within the host cell is a highly relevant research question. Recent work highlights the role of miRNAs in restriction of HIV-1 infection [17-19]. Triboulet and colleagues [17] reported a role of Drosha and Dicer in human cell defense against HIV-1. miRNAs act both through direct targeting of the 3' untranslated region of HIV-1 [18,19] and indirectly through modulation of the cellular environment [17]. Huang and colleagues [18] identified miR-28, miR-125b, miR-150, miR-223, and miR-382 as contributing to HIV-1 latency in quiescent CD4 T cells. Wang and colleagues [19] identified miR-28, miR-150, miR-223, and miR-382 as possibly protecting monocytes/macrophages from HIV-1 infection. Three recent papers assessed the involvement of miRNA in controlling HIV-1 replication: Chable-Bessia *et al.* [20] showed that RNAi effectors repress HIV-1 replication through HIV-1 mRNA targeting to processing bodies and translational inhibition, and Ahluwalia *et al.* [21] and Nathans *et al.* [22] evaluated the direct targeting of HIV-1 mRNA by cellular miR-29a. A recent report presented the

miRNA profile in peripheral mononuclear cells from 36 HIV-1-seropositive individuals and compared the profile with that of 12 seronegative subjects [23].

Proteome studies have also been reported in recent times in the field of HIV-1. Analysis of infected T cells by two-dimensional in-gel electrophoresis detected 15% of 2,000 protein spots as differentially expressed at peak infection [24]. Analysis of 3,200 proteins using liquid chromatography-mass spectrometry coupled with stable isotope labeling identified 21% of proteins as differentially expressed upon infection [25]. Biological pathways included ubiquitination, nucleocytoplasmic transport, cell cycle progression, and the citrate cycle. The latter study also identified changes in the abundance of proteins with known interactions with HIV-1 viral proteins [25]. The incorporation of host proteins to viral particles has been investigated in the past [26]. The National Center for Biotechnology Information maintains a HIV-host protein interaction database [27,28]. The National Institutes of Health has also committed to a large effort on HIV structural biology by the funding of three centers that are establishing a comprehensive structural picture of interactions between HIV viral proteins and intracellular host molecules and applying new computational and functional methods for analyzing virus/host complexes (the Center for the Structural

**Figure 1. Genome-wide and large-scale cellular studies published since 2007 in the field of HIV**



The number of studies is in parenthesis. Diverse sets of results and data are compiled in an encyclopedia of overlaps between studies [32]. This approach serves to identify networks used by HIV-1 to support its replication. miRNA, microRNA; siRNA, short interfering RNA.

Biology of Cellular Host Elements in Egress, Trafficking, and Assembly of HIV [29], the University of California San Francisco and Berkeley HIV Accessory and Regulatory Complexes Center [30], and the Pittsburgh Center for HIV Protein Interactions [31]).

Studies such as those discussed above lead naturally to the possibility of cross-evaluation and validation (Figure 1). This effort, spearheaded by Bushman and colleagues [1], used meta-analytical procedures to assess nine genome-wide studies. While pairwise comparisons of the studies resulted in modest overlaps, data analyses in the context of cellular networks and subsystems led to the identification of at least 11 densely connected clusters. These clusters, enriched for proteins identified in multiple separate screens, specify cellular subsystems associated with HIV replication: the proteasome, subunits of RNA polymerase II and associated factors, the mediator complex, the Tat activation machinery, RNA-binding and -splicing proteins, and the BiP/GRP78/HSPA5 and CCT chaperones. The study went one additional step to organize data in an 'encyclopedia' of host factors assisting HIV replication [32]. The growing need for analyzing layers of data in the genomic context has also led to the development of 'viewers'. These are web-based tools designed for visualization of large-scale genetic and genomic data, allowing the aggregation or intersection of diverse data tracks [33,34].

### Future directions

Novel technology and the accumulation of genome data across species will contribute additional layers to the analyses. Examining intra- and inter-species genome data under the principles of comparative and evolutionary genomics gives investigators the potential to map genes under positive selective pressure due to pathogens. Chromatin immunoprecipitation combined with deep sequencing or with microarrays will provide more quantitative data of mRNA expression, on small non-coding RNAs, and from experiments on epigenetic reprogramming due to infection [35]. Particularly attractive techniques are those using ribosome profiling to generate precise quantitative data on the precise mRNA that is being translated – a closer surrogate of protein expression than that afforded by conventional transcriptome profiles [36]. Eventually, integration of data will complement or guide experiments designed to capture large-scale data in cycles of experimental perturbation – the core definition of systems biology.

### Abbreviations

BiP, binding immunoglobulin protein (also called GRP78); CCT, chaperonin containing T complex protein 1 (TCP-1); GRP78, glucose-regulated protein 78;

HSPA5, heat shock protein 5; MHC, major histocompatibility complex; miRNA, microRNA; RNAi, RNA interference; shRNA, short hairpin RNA; siRNA, small interfering RNA.

### Competing interests

The author declares that he has no competing interests.

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