HIV Research Beyond the “omics” Era

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In the last decade a number of impressive gene array, proteomic, metabolomic, and RNAi screens have been performed to identify the cellular interactome of human immunodeficiency virus type 1 (HIV-1). The extraordinary data sets generated from these experiments identified hundreds of candidate host cell factors that may be required for virus replication. The data obtained from these experiments are impressive alone; but even greater amount of research remains to validate candidate factors. With the push toward clinical-translation research in the United States, the onus is now on the field to prove these experiments produced valuable candidates that will lead to new paradigms in HIV research and ultimately the development of novel therapeutics. The first challenge is to establish how these candidates interact with HIV, and then determine whether their disruption can inhibit virus replication. The validation of a single candidate factor has the potential to transform HIV research.

A strong push must now be made to work through these candidates and identify the promising factors. Thus, the real challenge of these studies has just begun. There are hundreds of candidate factors, but not all will lead to new therapies. A major issue with “omics” studies is the presence of background or false factors. Past HIV “omics” studies have typically verified only a small number of factors, and the potential prevalence of false candidates in existing data sets was not discussed or estimated. Considering the paucity of overlapping proteins identified among the four global siRNA screens, and an expanded analysis of nine studies that identified no outstanding factors across the majority of studies [1], it may be that only a small number of proteins are bona fide HIV-1 factors. Since only a small number of candidate proteins have been independently validated from the four large RNAi screens thus far, the hundreds of candidates requiring additional verification likely contain a high percentage of false factors. Moreover, a number of these factors may have already been investigated by laboratories around the world. At best, failed candidates might be discussed briefly in manuscripts characterizing a validated factor. But without a system conducive to disseminating negative data, information on failed candidates is not easy to find, potentially leading to waste the investigative time and resources. In an era of tight funding, independent investigators need to be confident in the selection of a candidate factor. Thus, it would be prudent at minimum to maintain a database of false candidates.

The “post-omic” era of HIV research will be exciting as new candidate factors are characterized, new virus-host interactions defined, and new therapies are developed. These studies will be onerous as each factor will need to be individually investigated. This will require an exceptional amount of work hours compared to the screens that generated the data sets originally. If the inaccessibility of negative data can be addressed with an integrated approach a waste of resources could be minimized which will speed the discovery of critical factors. The same push that was made to undertake the initial screens for factors must now be made to identify the most promising candidate factors that can be exploited for new therapeutics. These studies will advance not only our understanding of HIV molecular virology, but also cell biology and related fields. If only one new class of inhibitor is discovered, the efforts will be justified.

References


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