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Viral Perturbations of Host Networks Reflect Disease Etiology

Natali Gulbahce¹,²,⁴,⁵, Han Yan²,³,⁴, Amélie Dricot²,³,⁴, Megha Padi⁴, Danielle Byrdsong²,³, Rachel Franchi²,³,⁵,⁶, Deok-Sun Lee¹,⁶, Orit Rozenblatt-Rosen⁷, Jessica C. Mar⁴, Michael A. Calderwood²,⁸, Amy Baldwin⁸,⁹, Bo Zhao⁸, Balaji Santhanam²,³, Pascal Braun²,³, Nicolas Simonis²,³,⁴, Kyung-Won Huh⁵,⁶, Karin Hellner⁸, Miranda Grace⁸, Alyce Chen⁸, Renee Rubio⁴, Jarrod A. Marto⁹, Nicholas A. Christakis¹⁰, Elliott Kieff⁸,⁸,⁹, Frederick P. Roth⁸,¹¹, Jennifer Roecklein-Canfield²,³,⁵, James A. DeCaprio⁷,¹, Michael E. Cusick²,³, John Quackenbush⁴,¹², David E. Hill²,³, Karl Münger⁸, Marc Vidal²,³,¹, Albert-László Barabási¹,²,¹²

¹ Center for Complex Networks Research (CCNR) and Department of Physics, Northeastern University, Boston, Massachusetts, United States of America, ² Center for Cancer Systems Biology (CCSB) and Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States of America, ³ Department of Genetics, Harvard Medical School, Boston, Massachusetts, United States of America, ⁴ Center for Cancer Computational Biology (CCCB), Department of Biostatistics and Computational Biology and Department of Cancer Biology, Dana-Farber Cancer Institute and Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, United States of America, ⁵ Department of Chemistry, Simmons College, Boston, Massachusetts, United States of America, ⁶ Department of Natural Medical Sciences and Department of Physics, Inha University, Incheon, Korea, ⁷ Department of Medical Oncology, Dana-Farber Cancer Institute, and Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, United States of America, ⁸ Infectious Diseases Division, The Channing Laboratory, Brigham and Women’s Hospital and Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States of America, ⁹ Blais Proteomics Center and Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States of America, ¹⁰ Department of Health Care Policy, Harvard Medical School and Department of Sociology, Harvard University, Cambridge, Massachusetts, United States of America, ¹¹ Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts, United States of America, ¹² Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, United States of America.

Abstract

Many human diseases, arising from mutations of disease susceptibility genes (genetic diseases), are also associated with viral infections (viraly implicated diseases), either in a directly causal manner or by indirect associations. Here we examine whether viral perturbations of host interactome may underlie such virally implicated disease relationships. Using as models two different human viruses, Epstein-Barr virus (EBV) and human papillomavirus (HPV), we find that host targets of viral proteins reside in network proximity to products of disease susceptibility genes. Expression changes in virally implicated disease tissues and comorbidity patterns cluster significantly in the network vicinity of viral targets. The topological proximity found between cellular targets of viral proteins and disease genes was exploited to uncover a novel pathway linking HPV to Fanconi anemia.


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* E-mail: marc vidsal@dfci.harvard.edu (MV); alb@neu.edu (ALB)

¹ Current address: Department of Cellular and Molecular Pharmacology, University of California, San Francisco, California, United States of America
² Current address: Midwestern University-Arizona College of Osteopathic Medicine, Glendale, Arizona, United States of America
³ Current address: Department of Microbiology, School of Medicine, St. George’s University, Grenada, West Indies
⁴ Current address: Laboratoire de Bioinformatique des Genomes et des Re´seaux, Universite´ Libre de Bruxelles, Bruxelles, Belgium
⁵ Current address: Department of Biochemistry and Molecular Biology, Louisiana State University Health Science Center, New Orleans, Louisiana, United States of America
⁶ Current address: Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, Toronto, Ontario, Canada and Samuel Lunenfeld Research Institute, Mt. Sinai Hospital, Toronto, Ontario, Canada
⁷ These authors contributed equally to this work.
⁸ Member of the Genomic Variation and Network Perturbation Center of Excellence in Genomic Science, Center for Cancer Systems Biology (CCSB), Dana-Farber Cancer Institute, Boston, Massachusetts, United States of America.
**Introduction**

Functional interactions between cellular targets of viral proteins and disease susceptibility genes [1,2,3,4,5] might play key roles in disease etiology. Advances in the mapping of the human interactome network, as well as in the systematic identification of gene-disease associations, provide functional data that can be used to explore fundamental connections between viral targets and disease genes. Here we formulate a *local impact* hypothesis, stating that diseases that can be either genetic or virally implicated can be better understood from a network perspective [6]. By this hypothesis the products of disease susceptibility genes should reside in the network vicinity of the corresponding viral targets [7,8].

To test this hypothesis we focused on Epstein-Barr virus (EBV) and human papillomavirus (HPV) type 16, two human viruses that differ in their host tropism, genome and proteome size, and disease etiology. We find that the disease susceptibility genes of known virally implicated diseases are in the immediate network vicinity of the host proteins that are targeted by these viruses. We could identify a viral disease module for EBV and HPV, representing a subnetwork of the interactome that contains key mechanistic pathways responsible for the observed virus-disease associations. A computational prioritization procedure, joined by large-scale comorbidity and expression pattern analyses, identified new potential mechanistic disease pathways. To validate several of these pathways, HPV16 E6 and E7 oncoproteins were independently expressed in primary human fibroblast (IMR90) and keratinocyte (HFK) cell populations to identify disease-associated genes whose expression levels were significantly altered in these E6/E7-expressing cell populations. We could identify a novel pathway that links HPV to a specific form of Fanconi anemia. The systematic network-based framework we applied works to decipher the interplay between viruses and disease phenotypes.
from high-throughput investigations. The average shortest path remained significantly shorter than random (average shortest path = 1.0; \( P = 4.9 \times 10^{-5} \) for EBV and average shortest path = 1.0; \( P = 3 \times 10^{-4} \) for HPV16, based on empirical calculation; Figure 1C,D). The shortness of the path lengths between viral targets and genes associated with virally implicated diseases is mostly due to the tendency of the viral targets being hubs, and to a lesser degree to the properties of disease genes (Text S1).

The relative shortness of the paths from viral targets to disease genes validates the hypothesis that genes in the “neighborhood” of viral targets are more likely associated with virally implicated diseases, compared to genes in distant regions of the host interactome. But still, given the small world nature of the interactome, large numbers of proteins are within a few hops of the viral targets, potentially implicating hundreds of diseases for which there is no known relationship to HPV or EBV. Accordingly, a procedure is needed to identify the set of host cellular components (genes, proteins, and metabolites) that are most likely impacted by the virus, representing the network neighborhood of viral targets. Do the three kinds of interactions used to build the interactome — protein-protein, metabolic and regulatory interactions — play a comparable role in linking viral

Table 1A

<table>
<thead>
<tr>
<th>EBV-implicated diseases</th>
<th>Mapped genes</th>
<th>ICD-9 code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. B cell lymphomas incl. Burkitt’s lymphoma</td>
<td>BCL3, BCL2, CCND1, MYC</td>
<td>200</td>
</tr>
<tr>
<td>2. Breast cancer</td>
<td>SLC22A1B, TP53, TSG101</td>
<td>174, 217, 239.3</td>
</tr>
<tr>
<td>3. Hemophagocytic lymphohistiocytosis</td>
<td>FH1L3</td>
<td>288.4</td>
</tr>
<tr>
<td>4. Hepatocellular carcinoma</td>
<td>APC, TP53</td>
<td>155, 211.5</td>
</tr>
<tr>
<td>5. Lung cancer</td>
<td>EGFR, SLC22A1B</td>
<td>162, 231</td>
</tr>
<tr>
<td>6. Nasopharyngeal carcinoma</td>
<td>TP53</td>
<td>147</td>
</tr>
<tr>
<td>7. Severe combined immunodeficiency</td>
<td>ADA</td>
<td>279.2</td>
</tr>
<tr>
<td>8. Stomach carcinoma</td>
<td>APC, IL1B, RIT</td>
<td>151</td>
</tr>
<tr>
<td>9. T cell lymphomas</td>
<td>MSH2</td>
<td>202</td>
</tr>
<tr>
<td>10. Classical Hodgkin lymphoma</td>
<td>-</td>
<td>201</td>
</tr>
<tr>
<td>11. Salivary carcinoma</td>
<td>-</td>
<td>142</td>
</tr>
<tr>
<td>12. Wiskott-Aldrich syndrome</td>
<td>-</td>
<td>279.12</td>
</tr>
<tr>
<td>13. X-linked lymphoproliferative disorder</td>
<td>-</td>
<td>238.79</td>
</tr>
<tr>
<td>14. Infectious mononucleosis</td>
<td>*</td>
<td>075</td>
</tr>
<tr>
<td>15. Lymphocytic interstitial pneumonia</td>
<td>*</td>
<td>516.8</td>
</tr>
<tr>
<td>16. Oral hairy leukoplakia</td>
<td>*</td>
<td>528.6</td>
</tr>
<tr>
<td>17. Thymus carcinoma</td>
<td>*</td>
<td>164</td>
</tr>
</tbody>
</table>

Table 1B

<table>
<thead>
<tr>
<th>HPV-implicated diseases</th>
<th>Mapped genes</th>
<th>ICD-9 code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bladder cancer</td>
<td>RB1</td>
<td>188</td>
</tr>
<tr>
<td>2. Breast cancer</td>
<td>BRCA1, CASP8, RAD54, TP53</td>
<td>174, 217, 239.3</td>
</tr>
<tr>
<td>3. Colon cancer</td>
<td>APC, BAX, EP300, MSH2, ODC1, RAD54, RAD54L, TP53</td>
<td>153</td>
</tr>
<tr>
<td>4. Head and neck squamous carcinoma</td>
<td>TNFRSF10B</td>
<td>173</td>
</tr>
<tr>
<td>5. Ovarian cancer</td>
<td>BRCA1, ERBB2, FN1, MSH2</td>
<td>183, 220</td>
</tr>
<tr>
<td>6. Prostate cancer</td>
<td>CD82</td>
<td>185, 233.4</td>
</tr>
<tr>
<td>7. Squamous cell carcinoma of the lung</td>
<td>CASP8, ERBB2, EGFR, IRF1</td>
<td>162, 231</td>
</tr>
<tr>
<td>8. Carcinoma of cervix uteri</td>
<td>-</td>
<td>180, 233.1</td>
</tr>
<tr>
<td>9. Laryngeal carcinoma</td>
<td>-</td>
<td>161</td>
</tr>
<tr>
<td>11. Conjunctival carcinoma</td>
<td>*</td>
<td>190.3</td>
</tr>
<tr>
<td>12. Intraepithelial neoplasia</td>
<td>*</td>
<td>233</td>
</tr>
<tr>
<td>13. Oral carcinoma</td>
<td>*</td>
<td>140, 141</td>
</tr>
<tr>
<td>14. Oral leukoplakia</td>
<td>*</td>
<td>528.6</td>
</tr>
</tbody>
</table>

A. EBV-implicated diseases, B. HPV16-implicated diseases. Mapped gene column lists the genes found in the neighborhood of viral targets. An asterisk (*) in the “mapped gene” column corresponds to diseases where no known genes are reportedly associated with the disease in OMIM database, and (-) corresponds to diseases where there are genes reportedly associated with the disease in OMIM database but are not identified with our approach. Diseases marked with (i) correspond to EBV-implicated diseases within the framework of B cell lymphoma. doi:10.1371/journal.pcbi.1002531.t001
targets to virally-implicated diseases, and how deep into the interactome should one go, keeping in mind that most proteins are approximately three links from the viral proteins.

To find the optimal neighborhood responsible for the phenotypic impact of a virus, we tested several “configurations” that govern the maximum hops allowed from the viral targets for each type of biological interaction. The simplest configuration includes only viral targets, while the more extended configurations capture increasing number of hops along the links of the interactome network, connecting an increasing number of proteins. The best configuration, as measured by the odds ratio of the enrichment of virally implicated diseases, defined the optimal neighborhood as the viral targets themselves and the genes regulated by them, and was the same for both viruses (Figure S4A,B in Text S1; Tables S3,S4 in Text S1). This agrees with our finding that genes associated with virally implicated diseases are themselves viral targets or are the interaction partners of viral targets (local impact hypothesis). For both viruses protein-protein and metabolic

Figure 1. Linking a viral proteome to virally implicated diseases through the host interactome. A, Viral proteins (virome) interact with host proteins (viral targets) in the host interactome, which in turn are linked to various human diseases (phenome) through mutations in particular disease susceptibility genes (variome). B, Determining topological proximity between viral targets and genes associated with virally implicated diseases by measuring the shortest path lengths between them. For each disease, the minimum number of hops of interactions needed to connect any of its associated genes to any viral targets is designated as the shortest path. C,D, The average shortest path for either EBV (C) or HPV16 (D) was significantly shorter than random expectation.

doi:10.1371/journal.pcbi.1002531.g001
interactions in the host interactome were of secondary importance in linking the viral targets to the diseases they cause. For other viruses, however, these interactions could prove to be important. Indeed, analyses restricted to high-throughput data suggested additional relevance of host protein-protein and metabolic interactions (Figure S4C,D in Text S1; Tables S3,S4 in Text S1). In the selected optimal configuration, 9 out of the 13 virally implicated diseases for EBV were associated with genes in the neighborhood of EBV targets (Table 1a), and 7 out of 9 virally implicated diseases for HPV were associated with genes in the neighborhood of HPV16 targets (Table 1b). Both of these numbers were significantly higher than random expectation (Figure 2A,B; $P=0.0012$ for EBV and $P=0.0005$ for HPV based on empirical calculation). We therefore chose this configuration to define the network neighborhood of the viral targets, representing the viral disease modules, leaving aside the host metabolic and protein interactions.

According to the local impact hypothesis, the genes regulated by viral targets should have significantly altered expression levels in virally implicated disease tissues within the viral disease modules. To test this, we collected microarray gene expression data for two representative EBV-implicated diseases, Burkitt’s lymphoma and B cell lymphoma [26], and for two HPV16-implicated diseases, cervical cancer [27] and head and neck squamous cell carcinoma [20] (Methods). We compared gene expression levels between disease tissues to control (unaffected) tissues. We defined genes with significantly altered expression levels (“differentially expressed genes”) as those whose changes in expression level between disease and normal tissues were among the top or bottom 5% of all genes (conclusions were unaltered across a wide range of cutoffs) (Table S5 in Text S1 and Text S1). In disease samples there were significantly more differentially expressed genes in the neighborhood of viral targets than in the neighborhood of randomly sampled host genes that are regulated by at least one transcription factor in the TRANSFAC database (Figure 2C,D; Figures S5, S6 and Table S5 in Text S1).

Viral disease network

Given the high interconnectedness of the host interactome, the number of all potential distinct paths linking viral targets to genes (or gene products) associated with virally implicated diseases exceeds $10^{200}$ for both viruses (Text S1). Yet, the local impact hypothesis argues that only paths within the neighborhood of viral targets should have significantly altered expression levels in linking the viral targets to the diseases they cause. For other viruses, however, these interactions could prove to be important. Indeed, analyses restricted to high-throughput data suggested additional relevance of host protein-protein and metabolic interactions (Figure S4C,D in Text S1; Tables S3,S4 in Text S1). In the selected optimal configuration, 9 out of the 13 virally implicated diseases for EBV were associated with genes in the neighborhood of EBV targets (Table 1a), and 7 out of 9 virally implicated diseases for HPV were associated with genes in the neighborhood of HPV16 targets (Table 1b). Both of these numbers were significantly higher than random expectation (Figure 2A,B; $P=0.0012$ for EBV and $P=0.0005$ for HPV based on empirical calculation). We therefore chose this configuration to define the network neighborhood of the viral targets, representing the viral disease modules, leaving aside the host metabolic and protein interactions.

The neighborhoods of viral targets in the host interactome, along with their disease associations, represent “viral disease networks” (Figure 3A,C). The viral proteins, their viral targets, the proteins in their local neighborhood and diseases associated with all the host genes are included in the disease network. In line with the local impact hypothesis, we expect that these neighborhoods contain most cellular components that play a role in the phenotypic impact of the virus on the host. The neighborhood of randomly chosen human proteins as viral targets yields a much sparser and smaller network (Figure 3B,D), indicating that the observed viral disease networks had not emerged by chance, but instead reflect the functional adaptation of viruses to the host interactome. Randomly chosen degree-controlled viral targets also yielded random disease networks with significantly smaller connected components (Figure S6 in Text S1).

Prioritizing virally implicated diseases

The uncovered viral disease networks contain several diseases that have not been previously associated with infection by the corresponding viruses (grey squares in Figure 3A,C). These diseases arise by mutations in cellular pathways that are targeted by these viruses. Some of these diseases might arise from infection with HPV or EBV. Given the large number of such disease candidates (128 for EBV and 141 for HPV), it is important to prioritize them based on their proximity to viral targets, inferring the likelihood that the virus-induced perturbations could contribute to the particular disease phenotype. We implemented a topology-based network flow algorithm [31] that simultaneously exploits the local modularity of the interactome and the non-random placement of the disease associated components in the network. Initially, only the viral targets have non-zero scores, and the score of other proteins in the entire interactome is zero. The algorithm iteratively distributes scores to host genes based on their potential association with viral perturbation, prioritizing the genes in the neighborhood of the viral targets. Using literature-derived virally implicated diseases (Table 1) as a positive reference set, we evaluated the precision-recall performance of the prioritization for both EBV and HPV16 (Figure S9 in Text S1) and found enrichment of virally implicated diseases among the high-ranking diseases (e.g. Burkitt’s lymphoma for EBV and bladder cancer for HPV16, Tables S6, S7 in Text S1), supporting the feasibility of the prioritization procedure.

To independently benchmark the prioritization of candidate diseases, we turned to relative risk measurement [24,32,33], which provides population-based clinical associations between candidate diseases and viral infection in patients (Text S1). Using U.S. Medicare patient medical history data [24,34] derived from 13 million patients, we found that higher-ranked diseases in the prioritization are more often associated with viral infection, for either EBV or HPV (Figure 3E). This comorbidity analysis indicates that diseases with associated genes in the network vicinity of viral targets are strong candidates for being virally implicated. The prioritized virally-implicated disease candidates (Tables S6, S7 in Text S1) indicate, for example, that malignant neoplasms of retina and bladder, ranked in the top three by the flow algorithm regarding their potential association with HPV, have relative risk 15.7 and 2.7 (Table S7 in Text S1), meaning that HPV patients have 15.7 and 2.7 times increased chance of developing these diseases. Several diseases that ranked high in our prioritization procedure are not commonly linked to the studied viruses, but their potential viral association was supported by recent suggestive reports, such as malignant neoplasm of thyroid gland association with EBV [35] and retinoblastoma association with HPV [36,37].
Figure 2. Virally implicated diseases associated with genes in the neighborhoods of viral targets. A,B. The number of virally implicated diseases in the neighborhoods was higher than randomly expected for EBV (A) and HPV16 (B). C,D. The number of differentially expressed genes in the neighborhood of viral targets of either EBV (C) or HPV16 (D) was significantly higher compared to that in the neighborhood of randomly sampled host genes. The total number of genes regulated by EBV and HPV targets is 109 and 122, respectively. Expression level was measured in tissues of two virally implicated diseases respectively, Burkitt’s lymphoma (EBV) and cervical cancer (HPV), and compared to normal tissues. E,F. Known virally
Experimental validation

To demonstrate the value of the network-based approach to generate new biological hypotheses, we explored whether the cellular perturbations induced by expression of individual viral proteins are similar to those seen in particular disease phenotypes. We generated primary human keratinocyte (HFK) populations with stable expression of the HPV16 E6 or E7 oncoproteins and analyzed the gene expression profiles of multiple independent samples for these cells in concert with expression data from IMR90 cells expressing HPV16 E6 or E7 proteins (Methods and Text S1). Of the 104 human genes regulated by the 15 human protein targets of E6 and E7 (i.e., those two degrees away from E6 and E7 in Figure 3C), 22 were found to be differentially expressed in E6 or E7 induced IMR90 and/or HFK cell populations (Figure 3F; Table S14 in Text S1). Of these 22 genes 15 of them were also differentially expressed in cervical carcinoma tissues evaluated previously to test the local impact hypothesis (Text S1). These 22 genes have been linked to 39 diseases in OMIM, among which only six belong to known HPV-related diseases (Table 1B).

We therefore asked if any of the remaining 33 diseases might be virally implicated (Figure 3F). Illustrative of our approach is ovarian cancer, which is linked to HPV via three lines of evidence: (i) the disease has significant comorbidity with HPV associated diseases; (ii) four of the ovarian cancer associated genes in the disease network are differentially expressed in E6 or E7 induced IMR90 or HFK cell populations; (iii) three of these, FNI, BRCA1, ERBB2, are differentially expressed in ovarian carcinoma tissues (GEO dataset: GDS3592; two-tailed t-test; \( p<0.05 \) [38]).

Seven out of 39 diseases have high relative risks among HPV patients (Figure 3F), of which four are previously unknown. Among these four diseases, neoplasm of peritoneum, benign neoplasm of skin, and diseases of sebaceous glands satisfied only two of the three criteria (Text S1). Fanconi anemia, the fourth disease on the list, satisfied all three in that (i) Fanconi anemia shows high relative risk with HPV; (ii) \( \text{FANC} \), a gene in the disease network mutated in Fanconi anemia, is up-regulated in the E6 exogenous expression IMR90 cell data, and (iii) \( \text{FANC} \) is significantly up-regulated in low density bone marrow cells of Fanconi anemia patients (GEO dataset: GSE16334; two-tailed t-test; \( p=0.00069 \) [38]). In addition, HPV E6 was hypothesized to induce expression of \( \text{FANCD2} \) through an E2F-dependent pathway [39,40], a finding that is also supported by our analysis (Text S1). Our analysis predicts a novel potential link between HPV and Fanconi anemia, through the E6→TP53→\( \text{FANC} \) pathway, which had not been previously established. \( \text{FANC} \) has been reported to be expressed at higher levels upon activation of TP53 [41] but since E6 targets TP53 for degradation it is unlikely that the observed upregulation of FANC expression in E6 expressing cells is solely modulated by p53. An additional connection to Fanconi anemia may be through interaction with BRCA1 [42] (Figure 2F). In addition to a physical interaction of E6 and E7 with BRCA1, BRCA1 expression is upregulated in E6 expressing cell lines (Table S14 in Text S1). BRCA1 has been shown to have a potential role in Fanconi anemia through its role in the colocalization of FANCD2 protein [43,44].

The clinical connection between Fanconi anemia and HPV associated tumors has been subject to debate. Not debatable is that FA patients have a much-increased risk in developing squamous cell carcinomas (SCCs) at anatomical sites infected by HPV. Our analysis does not necessarily mean that SCCs in Fanconi patients are caused by HPV, but that they arise by similar molecular mechanisms. The well-documented interplay between E7 and FA and our discovery of a possible connection between E6, FANC and BRCA1 support this hypothesis. Moreover, we observe a relative risk of 3.7 among female HPV patients (mostly cervical cancer patients) toward Fanconi anemia using the US-wide Medicare data, which further supports the identified molecular level relationship between Fanconi anemia and HPV (Methods and Text S1).

Discussion

Given the large number of functional interactions present in human cells and the many possible paths among cellular components, uncovering the precise impact of a virus upon the host interactome is an enormously complicated task. Here we provide evidence that a large proportion of the effect of a virus can be accounted for locally in the network space, which allowed us to develop and test a general methodology designed to elucidate the consequences of viral impacts on the host interactome network, and to prioritize candidate diseases for potential viral implications.

A predictive methodology should ideally take into account cell tropism. Tissue-specific gene expression data can be merged with our analysis (Text S1). We used tissue-specific expression data from BIOGPS [45] to narrow down the number of genes and their associated diseases from the diseasome map. If a gene in the neighborhood of the viral targets is not expressed or is not present in the tissue of interest, we removed the gene from the network. In this way, we obtain a tissue-specific viral network. By applying tissue specificity, the number of associated diseases for EBV was reduced from 128 to 89, and for HPV from 141 to 105, without losing any of the virally-implicated diseases (Text S1 for analysis details; Tables S15, S16 in Text S1 for the list of genes and diseases).

The strategy developed here is not unique to EBV and HPV16. Although the strategy should work better for carcinogenic pathogens, given how well-studied proteins involved in cancer are, it is equally applicable to any pathogen for which protein interactions between the pathogen and the host proteome have been mapped. While still limited by the incompleteness of genome- and proteome-scale datasets [19], the usefulness of the method is likely to grow alongside the ongoing expansion of high-throughput functional genomics databases and gene-disease associations.

Methods

Virus-host protein-protein interactions

Yeast two-hybrid screens (Y2H) between EBV and HPV16 viral proteins and \( \sim 12,200 \) human proteins encoded by a library of full length human open reading frame (ORFs) clones in Human ORFeome v3.1 [46,47] encompassing \( \sim 10,200 \) human genes were carried out as before [17,48]. The EBV-human library Y2H screen tested 86 out of 89 EBV proteins as fusions to the DNA binding domain of Gal4 (Gal4-DB) against ORFeome v3.1 proteins fused to the activation domain of Gal4 (Gal4-AD), while the HPV-human library Y2H screen testing HPV16 proteins E4, E5, E6 and E7 was carried out in reciprocal fashion with HPV proteins as both Gal4-DB and Gal4-AD fusions against the corresponding human Gal4-AD and Gal4-DB fusions, respectively.
Differentially expressed genes in virally implicated disease tissues

Raw data of the gene expression datasets used (GSE2350, GSE2392 and GSE15156) was obtained from Gene Expression Omnibus (GEO) [49], normalized and log-transformed by RMA algorithm [50], and expression changes were calculated as the ratio of expression levels between virus-infected tissues and normal tissues.

Exogenous expression of HPV viral proteins in human cell lines

To obtain the disease associated genes that are differentially expressed in viral protein induced cell populations, HPV16 E6 and E7 oncogenes were independently transfected into primary human fibroblast (IMR90) and keratinocyte (HFK) cell populations. Affymetrix Human Gene 1.0 ST and Human Genome U133 Plus 2.0 arrays, respectively, were used to measure gene expression profiles for five or more replicate samples in each of the cell types. Array data were normalized by RMA, batch effects were removed using ComBat, and the limma package in R/Bioconductor was used to identify differential expression.

Comorbidity analysis and relative risk calculation

Relative risk (RR) was calculated as the ratio between the observed co-occurrence and probabilistically-inferred (assuming independence) co-occurrence of two diseases, based on the patient medical history data from United States (U.S.) Medicare, which contains the clinical diagnosis record of each hospital visit (in ICD-9 codes) of 13 million U.S. patients at age 65 or older [33]. Patients with viral infections were defined with the following diagnostic codes in U.S. Medicare database: 200 (B cell lymphoma) or 147 (nasopharyngeal carcinoma) for EBV infections; 078.1, 079.4, 180 or 795.0 for HPV infections.

Statistical tests

The statistical significance of the average shortest path between virally implicated genes and viruses associated with a given virally implicated disease was calculated by randomly sampling human diseases from OMIM (full table of disease in Dataset S2). The number of virally implicated diseases associated with the proteins in the neighborhoods of random host targets was calculated by picking random proteins from the interactome space (n = 7,832). For both measurements, P values were calculated based on empirical data with 10,000 random configurations. For the analysis of GEO microarray data we used two-tailed t-test statistics.

Supporting Information

Dataset S1 Full list of interactions and gene-disease associations in viral disease networks, including the sources of data. (Sheet 1) EBV disease network, (Sheet 2) HPV16 disease network. VH-PPI: virus-host protein-protein interaction, PPI: host protein-protein interaction, PDI: host protein-DNA interaction, MCE: metabolite enzyme-coupled interactions calculated using KEGG, or BIGG databases, or flux coupling analysis. (XLS)

Dataset S2 OMIM genes and diseases and their corresponding ICD-9 codes. (XLS)

Dataset S3 Relative risk analysis. (Sheet 1, 3) relative risk between EBV- and HPV-implicated diseases and candidate diseases in the disease network. (Sheet 2, 4) relative risk between EBV- and HPV-implicated diseases and all mappable diseases which constitute the random control. (XLS)

Dataset S4 Full list of diseases prioritized by the flow algorithm for (Sheet 1) EBV (Sheet 2) HPV. Diseases are sorted according to maximum scores. (XLS)

Text S1 Supporting information, tables and figures are provided in this document. (PDF)

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Author Contributions

Concepted and designed the experiments: NG HY MP ORR JAM EK FPR JRC JAD JQ DEH KM MV ALB. Performed the experiments: AD DB RF ORR AB BZ KWH KH MG AC RR. Analyzed the data: NG HY MAC BS NS. Contributed reagents/materials/analysis tools: DSL MAC PB NAC JQ KM. Wrote the paper: NG HY MAC MEK DEH KM MV ALB.

References


Viral-Host Networks Reflect Disease Etiology

Figure 3. Viral disease networks. A,C, The neighborhoods of viral targets in the host interactome, along with their disease associations, represent “viral disease networks”. Diseases associated with genes in the neighborhood of EBV (A) or HPV16 (C) targets that are not yet characterized with viral implications are shown as grey nodes. Node size is proportional to the degree of a node (number of neighbors it has) in the viral disease network. B,D, Diseases associated with genes in the neighborhoods of randomly generated viral targets of EBV (B) or HPV16 (D) are significantly sparser than the neighborhoods of actual viral targets. E, Benchmarking the prioritization using relative risk with virally infected patients showed that the higher-ranked diseases in the prioritization are more often associated with viral infection. F, Differentially expressed genes in E6 or E7 induced IMR90 and HFK cell populations with their associated diseases. If a gene is regulated by a specific viral protein target, it is also almost always differentially expressed in the cell population where that specific viral protein is induced. For example, EDN1 is regulated by FOS, an E7 target, and EDN1 is differentially expressed in E7 induced cell populations. Large grey nodes: diseases with high relative risk among HPV patients. doi:10.1371/journal.pcbi.1002531.g003


