IN FOCUS

The Landscape of Human Cancer Proteins Targeted by SARS-CoV-2

Beril Tutuncuoglu[1,2,3,4,5], Merve Cakir[1,2,3,4,5], Jyoti Batra[1,2,3,4], Mehdi Bouhaddou[1,2,3,4,5], Manon Eckhardt[1,2,3,4], David E. Gordon[1,2,3,4], and Nevan J. Krogan[1,2,3,4,5]

Summary: The mapping of SARS-CoV-2 human protein–protein interactions by Gordon and colleagues revealed druggable targets that are hijacked by the virus. Here, we highlight several oncogenic pathways identified at the host–virus interface of SARS-CoV-2 to enable cancer biologists to apply their knowledge for rapid drug repurposing to treat COVID-19, and help inform the response to potential long-term complications of the disease.

INTRODUCTION

The global pandemic caused by SARS-CoV-2, starting in 2019, places a heavy burden on public health systems and causes widespread suffering. Analysis aimed to identify common pathways hijacked by the virus and other diseases has the potential for rapid repurposing of clinically available drugs to treat COVID-19, while informing us of potential long-term complications of coronavirus infection. Knowledge about pathways implicated across different diseases will facilitate this task by allowing invaluable input from experts in other fields, such as cancer biologists and physicians.

In order to replicate, viruses have evolved ways to target and manipulate key molecular mechanisms with a minimal number of proteins. Studying the specific pathways that are commonly hijacked by viruses might provide information on functional hubs of cellular protein interaction networks. For example, viruses can manipulate the cell cycle, recruit host DNA-damage machinery to replication sites, hijack host translation machinery, interfere with apoptosis by suppressing signaling pathways, and reprogram host epigenetic markers to antagonize immune responses. Besides being essential for optimal functioning of a cell, these same critical pathways are perturbed in cancer cells. Both cancer cells and pathogens exploit similar molecular mechanisms to manipulate apoptosis and evade host immunity. The evidence for shared viral targets and cancer drivers comes from reported cases where a history of infection with certain RNA or DNA viruses is associated with oncogenesis by activating cellular oncogenes or repressing tumor suppressors. On the basis of this, systemwide integration of protein–protein interactions that drive viral pathogenesis and tumorigenesis are promising to identify critical nodes that drive deregulation of cellular mechanisms.

Prompted by the urgency of the SARS-CoV-2 pandemic, hundreds of researchers came together and formed the QBI Coronavirus Research Group (QCRG) at the University of California, San Francisco, and neighboring institutions. As a concerted effort of the QCRG, we mapped a network of virus–host protein–protein interactions by purification of 26 of the 29 SARS-CoV-2 proteins, followed by mass spectrometry analysis (1). This analysis revealed 332 human proteins that are targeted by SARS-CoV-2. In addition, we identified 69 FDA-approved drugs or compounds in clinical trials and preclinical development that could be repurposed for inhibition of identified virus–host protein–protein interactions. Here, we summarize the common pathways of various cancers with those that are targeted by SARS-CoV-2, as identified by QCRG. Among the identified human proteins, we annotated 46 proteins that are either known or candidate cancer genes by Cancer Gene Census (2) and Network of Cancer Genes (3). Among the identified compounds, 23 of them are used or investigated in clinical trials for cancer treatment (Fig. 1; Supplementary Table S1). Here, we highlight the specific factors that were previously shown to be involved in cancer pathology in these pathways.

CELL CYCLE AND DNA DAMAGE

Dysregulation of cell-cycle control is one of the hallmarks of cancer, as cancer cells continue to proliferate through alteration of processes that provide sustained growth signaling and enable evasion of cell-cycle arrest and apoptosis. As survival of viruses relies on the ability to replicate in host cells, it is not surprising that they also interfere with the host cell-cycle machinery. Viruses can arrest or promote cell-cycle progression. For example, Simian Virus 40 enhances progression into S-phase to promote replication of the viral DNA genome (4). In contrast, infection with the avian coronavirus Infectious Bronchitis Virus (IBV) induces G_2–M phase arrest to enhance progeny virus production (5). In the SARS-CoV-2 interactome, we identified a variety of proteins with roles related to cell-cycle progression, especially proteins associated with the centrosome, mitotic spindle, and regulation of cytokinesis (1). As expected, these interactions occur with viral proteins involved

[1]Department of Cellular and Molecular Pharmacology, University of California, San Francisco, California. [2]The J. David Gladstone Institutes, San Francisco, California. [3]Quantitative Biosciences Institute, University of California, San Francisco, California. [4]QBI COVID-19 Research Group (QCRG), San Francisco, California. [5]The Cancer Cell Map Initiative (CCMI), University of California, San Francisco, California, and University of California, San Diego, La Jolla, California.

Note: Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

Corresponding Author: Nevan J. Krogan, University of California, San Francisco, 1700 4th Street, Room 308D, San Francisco, CA 94158. Phone: 415-476-2980; E-mail: nevan.krogan@ucsf.edu

Cancer Discov 2020;10:916–21

doi: 10.1158/2159-8290.CD-20-0559

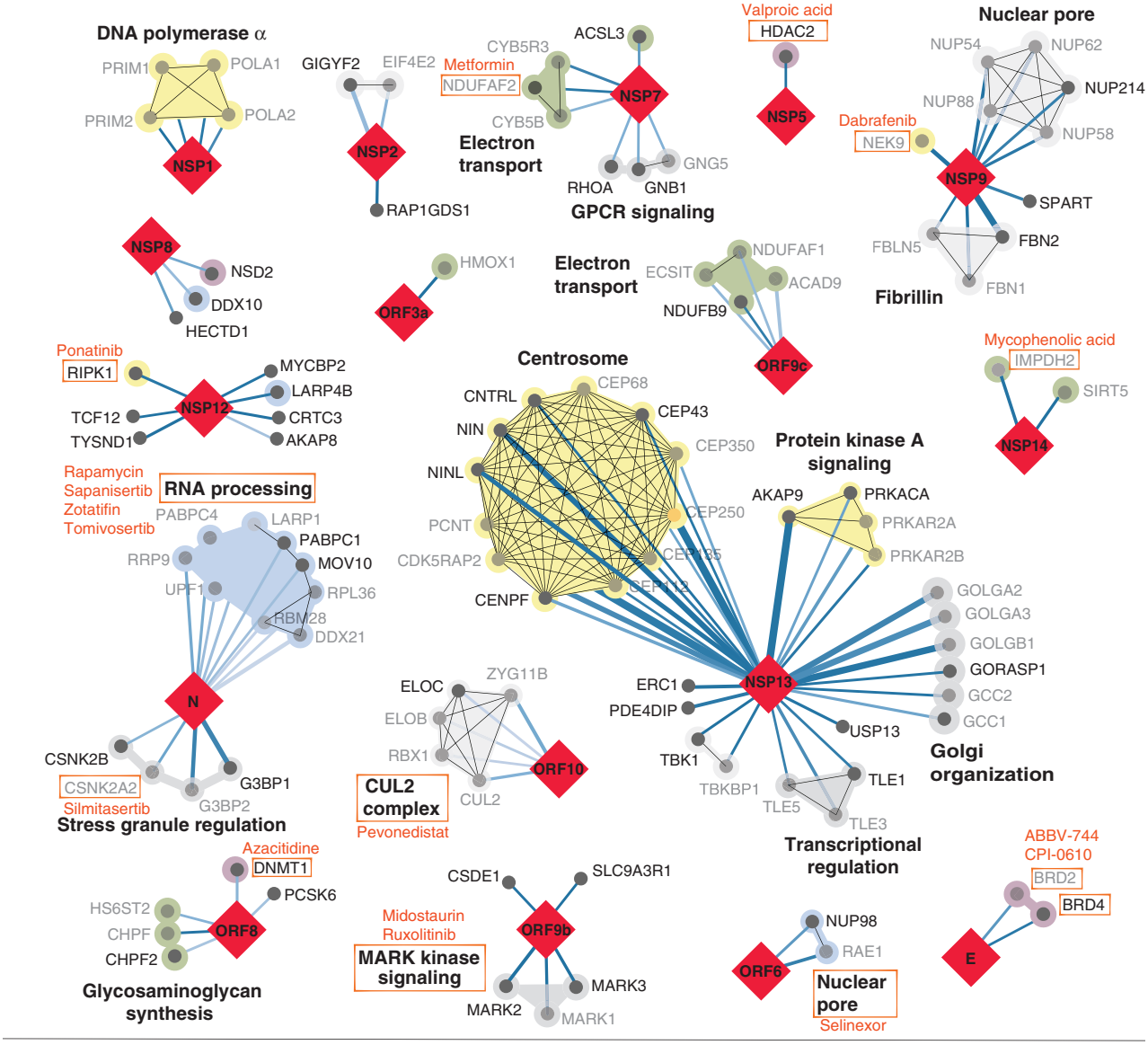

Figure 1. Cancer genes interacting with SARS-CoV-2. Known and candidate cancer genes are selected from the interactome of 26 SARS-CoV-2 proteins using Cancer Gene Census and Network of Cancer Genes databases (black) and literature review (gray). Proteins that are in the same protein complexes or processes with potential cancer genes are shaded. Currently cancer drugs that are currently used or in clinical trials Mist Score and Spectral Count of protein–protein interactions are based on the values obtained from the SARS-CoV-2–human protein–protein interaction map (1). See Supplementary Table S1 for the full list of drugs.

in replication of the viral genome: NSP7 is an essential cofactor of the RNA-dependent RNA polymerase, NSP9 binds single-stranded RNA, and NSP13 is a helicase/triphosphatase. Among these are 12 centrosome-associated proteins, protein A-kinase (PKA) signaling components as well as proteins with roles in the regulation of mitotic progression and cytokinesis (Fig. 1, yellow highlights). Cell-cycle machinery is a common target for cancer treatment, and our chemoinformatic analyses revealed that certain anticancer agents that are already approved or undergoing clinical trials can be effective against these proteins. Dabrafenib, a medication for the treatment of BRAF-associated cancers, is predicted to inhibit NEK9, an interactor of NSP9. In addition, the activity of RIPK1, an NSP12 interactor which is associated with apoptosis, necroptosis, and inflammatory pathways, is predicted to be inhibited by ponatinib and pazopanib. However, it is important to keep in mind that some of these proteins promote cell survival or death depending on the context. For example, *in vitro* studies

in the African green monkey kidney epithelial Vero E6 cell line revealed that ponatinib treatment results in decreased cell viability in higher doses and may result in slightly increased infection to the cells (1). This result is somewhat expected considering the critical function of RIPK1 in the antiviral immune response. Therefore, it is critical to determine the consequences of the interaction with viral proteins before exploring repurposing possibilities.

Several DNA and RNA viruses exploit host DNA damage repair mechanisms to promote viral replication by recruiting DNA damage proteins to viral replication centers or inhibiting apoptosis by suppressing downstream signaling of repair pathways via nucleocytoplasmic shuttling of some host factors. As such, another interesting connection is observed with DNA polymerase alpha complex, where the SARS-CoV-2 protein NSP1 interacts with all four members of the complex (1). This complex is essential for initiating DNA replication on both the leading and lagging strands, and couples DNA replication with DNA damage response and cell-cycle progression. The avian coronavirus IBV was previously shown to induce cell-cycle arrest by activation of ATR-dependent DNA damage repair pathways and induction of replication stress (5). Moreover, inhibitors of ATR signaling repressed the replication of IBV. The activation of the DNA damage signaling pathway as a result of replication stress is akin to the oncogene-induced phenomenon observed in cancer cells. For example, in cancer cells with defective G_1 checkpoint as a result of *TP53* mutation or loss of *RB1*, ATR-mediated signaling is upregulated. Similarly, SARS-CoV induces cell-cycle arrest in the G_1 phase via the retinoblastoma pathway, suggesting ATR inhibitors, which result in an increase of replication stress and eventual genome instability, are a potential line of treatment for COVID-19 (6).

METABOLISM

Cancer cells tend to reprogram their energy production, relying increasingly on glycolysis instead of oxidative phosphorylation. Coupled with rewiring in other metabolic pathways, these changes contribute to the production of nucleotides, amino acids, and lipids that are required to sustain continued proliferation. Similarly, viral infection induces metabolic rewiring in host cells to facilitate their replication. Mitochondrial metabolism is one of the major players in maintaining cellular homeostasis, and a key element for the immune system. Several SARS-CoV-2 viral proteins were found to interact with proteins involved in metabolic processes (Fig. 1, green highlights). Among these are a variety of mitochondrial proteins, including members of the electron transport chain (ETC) such as members and assembly factors of Complex I and Complex III, as well as an ATP synthase subunit. Interactions with the members of Complex I are especially interesting, as metformin is known to inhibit this complex. Treatment of SARS-CoV-2–infected cells with metformin resulted in a modest decrease in viral load, suggesting SARS-CoV-2 hijacks this complex to replicate in the cell (1). ETC is one of the sources of reactive oxygen species (ROS), and oxidative stress and ROS are involved in the pathogenesis of viral infections as well as a variety of lung diseases, including lung fibrosis, acute respiratory distress syndrome, and cancer (7). Our network revealed interactions with this pathway, for example, an interaction between ORF3a and HMOX1, as well as NSP14 and SIRT5. Interestingly, NFE2L2 binds to *HMOX1* promoter and activates its expression. The activity of NFE2L2 is, in turn, regulated by KEAP1 under oxidative stress. Both *NFE2L2* and *KEAP1* are frequently mutated in patients with lung cancer, underlining the importance of this pathway in tumor biology (8). In addition, the NSP14 interactor SIRT5 was shown to regulate NFE2L2 at the transcriptional level, and elevated levels of SIRT5 in lung cancer contribute to tumor progression and drug resistance (9). Taken together, SARS-CoV-2 might use these interactions to perturb the fundamental processes that regulate mitochondrial metabolism and oxidative stress, including pathways that are known to be critical for tumor development.

We have also identified proteins with roles in lipid metabolism, glycosylation, and amino acid metabolism, suggesting a broader scale of metabolic changes that could occur upon SARS-CoV-2 infection (1). ACSL3 is of particular interest as it was shown to be a critical contributor to the fatty-acid metabolism changes occurring during KRAS-driven lung tumorigenesis through its role in acyl-CoA metabolism (10). We additionally identified druggable enzymes associated with nucleotide metabolism, such as mycophenolic acid, which targets IMPDH2, which contributes to *de novo* synthesis of guanine. Future studies further detailing the connections between metabolism and SARS-CoV-2 can lead to the identification of additional therapeutic opportunities.

EPIGENETICS AND CHROMATIN

Viruses have evolved functions to reprogram the host epigenome to antagonize host immune responses and establish a latent state, thereby creating an environment favorable for replication. Epigenetic changes induced by histone methyltransferases and deacetylases were shown to be important for both viral infection and cancer progression. For instance, Epstein–Barr virus (EBV)-encoded latent membrane protein 2A induces increased transcription of DNA methyltransferase 1, resulting in promoter hypermethylation of the tumor suppressor gene *PTEN*, and therefore plays an important role in the development and maintenance of EBV-associated cancer (11). In the SARS-CoV-2 interactome, we find several interactions with epigenetic modifiers or chromatin (Fig. 1, purple highlights). For example, the histone methyltransferase NSD2 interacts with NSP8, and the histone deacetylase HDAC2 is the only high-confidence interactor of NSP5. Several oncogenic pathways connect NSD2 and HDAC2. NSD2 catalyzes the monomethylation and dimethylation of histone H3 Lys36 (H3K36), and NSD2 overexpression and increased catalytic activity induce transcriptional changes that are common in cancer, including multiple myeloma, acute lymphoblastic leukemia, and solid tumors (12). In several lung cancer cell lines, overexpression of NSD2 results in enrichment of RAS-driven, oncogenic responses (12). Interestingly, along with genes involved in tumor invasion and metastasis, HDAC2 was also found to be an NSD2 target gene. HDAC2 is a coactivator of the tumor suppressor p53, resulting in accumulation of DNA damage response signatures in a *TP53*-dependent manner (13). In addition to their role in cancer, both NSD2 and

HDAC2 are involved in NFκB activation by proinflammatory cytokines and play pivotal roles in inflammation by regulating release of proinflammatory cytokines. Among the compounds identified to target host–virus interface, valproic acid inhibits HDAC2, and azacitidine is an inhibitor of DNMT1, another DNA methyltransferase identified to interact with the viral protein ORF8. Valproic acid and azacitidine are FDA-approved compounds that show antitumor activity in multiple cancers (Supplementary Table S1).

NSD2 also interacts with the bromodomain and extra-terminal (BET) family protein BRD4. BRD4 and BRD2 were identified to interact with protein E, an envelope protein of SARS-CoV-2. BET proteins are highly conserved epigenetic readers and transcriptional regulators, recruited to regions with acetylated regions in the chromatin called superenhancers. BRD4 acetyltransferase activity is induced upon respiratory syncytial virus (RSV) infection, leading to expression of NFκB-dependent inflammatory genes and immediate early innate immune genes in response to RIG1 and TLR3 signaling pathways (14). Therefore, it has a role in antiviral signaling as well as in mediating virus-induced inflammation. BRD4 and BRD2 are suppressors of HIV transcription in latently infected cells. As such, inhibitors of BET proteins were shown to reverse HIV latency in cell lines and in some primary cell models. Interestingly, a potential model for the interaction of protein E of SARS-CoV-2 with host BET proteins would suggest the virus inhibits the function of these proteins by sequestration out of the nucleus. As antiviral agents, BET inhibitors might disrupt the interaction of protein E with BET proteins. Yet, *in vitro* studies with the SARS-CoV-2–infected cells indicate BET inhibitors had either no or an activating effect on viral infection, suggesting more mechanistic studies are needed (1). Besides their involvement in viral infection, BRD4 and BRD2 are implicated in carcinogenesis by mediating hyperactivation of oncogenes, such as *MYC*. BET inhibitors are suggested to be therapeutic agents for a wide range of cancers. For example, small-molecule BET inhibitors exert selective regulation of MYC-directed transcription. There are multiple FDA-approved and clinical-stage compounds targeting BET proteins. Among them, ABBV-744 and CPI-0610 are being investigated in clinical trials for acute myeloid leukemia. Epigenetic changes are common in cancer and can have broad effects on the transcriptional landscape of the cells. Mechanistic understanding of these changes might enable quicker repurposing of anticancer drugs for COVID-19 treatment.

TRANSLATION AND RNA PROCESSING

Viruses keep evolving strategies to commandeer and hijack the cellular translation apparatus by implicating different mechanisms that include cap snatching (e.g., influenza virus), manipulation of key translation factors (e.g., poliovirus, vesicular stomatitis virus, adenovirus), shutting off host translation (e.g., SARS) or impairing host mRNA processing, stability, and nuclear export. Notably, the NSP1 protein of SARS-CoV is known to associate with 40S ribosomes and selectively induce endonucleolytic cleavage of host mRNAs (15). Accordingly, we also detected interactions of SARS-CoV-2 proteins with the cellular translation and RNA processing machineries (Fig. 1, blue highlights). We observed the interaction of SARS-CoV-2 protein N with several host factors previously shown to bind mRNA 5′cap structure and be involved in mRNA stabilization. Among them, LARP1 serves as a phosphorylation-sensitive switch for repression or activation of the translation of a group of mRNAs defined by a 5′ terminal oligopyrimidine (TOP) motif (16). *TOP* mRNAs encode factors responsible for translation and ribosome biogenesis, and thus are in the core of cell growth and proliferation. LARP1 is upregulated in cancers especially associated with viral infections and was shown to promote tumorigenesis. Among the interactors and regulators of LARP1, mTOR signaling is commonly perturbed in cancer (16). mTOR regulates the *TOP* mRNA translation by a group of substrates, including LARP1, which bind eIF4E. In addition, LARP4B and its interaction partner PABPC1, which are predicted to have stimulatory roles in translation, were identified to interact with viral NSP12 and protein N, respectively. LARP4B, LARP1, and PABPC1 have been associated with malignancy, yet the exact mechanisms remain elusive. Rapamycin is an FDA-approved compound that disrupts the binding of LARP1 to mTORC1 and is already used for the treatment of multiple cancers. Another small-molecule inhibitor of mTOR, sapanisertib, is currently in clinical trials for breast cancer, lung cancer, and several other advanced solid tumors. Neither rapamycin nor sapanisertib resulted in antiviral activity as monotherapeutic agents *in vitro* (1). In addition, zotatifin and tomivosertib, inhibitors of host translation, are currently in clinical trials for solid tumors. Consistent with the dependency of viral replication on host translation, zotatifin was inhibitory to SARS-CoV-2 infection *in vitro* (1).

SARS-CoV ORF6 protein was previously shown to sequester nuclear import factors on the endoplasmic reticulum (ER)/Golgi membrane, thus blocking the expression of genes that establish antiviral response (17). Interestingly, SARS-CoV-2 ORF6 was identified to interact with NUP98 and its interaction partner RAE1. Binding of the viral protein to this complex likely blocks cellular mRNA export. As a proto-oncogene, the chromosomal rearrangements of the NUP98 gene in human leukemia results in formation of fusion proteins with poorly understood functions. Yet, recurrent chromosomal translocations are likely important for transformation of cells to malignancies. Several of the leukemogenic fusion partners of NUP98 are also part of the interactome of SARS-CoV-2. For example, DDX10, a DEAD box RNA helicase that is involved in ribosome assembly, interacts with the viral protein NSP8. DDX10 forms a characteristic fusion with NUP98. Interestingly, DDX10 is characterized as a tumor suppressor that is silenced in ovarian cancer, and this downregulation is associated with cell proliferation through the NFκB pathway (18). Selinexor is an anticancer drug that inhibits nuclear export. Participants with severe COVID-19 infection are currently being recruited for a clinical trial to evaluate the efficacy of selinexor for COVID-19.

OTHER DRUG REPURPOSING OPPORTUNITIES

The collaborative efforts of QCRG revealed the subset of the human proteome that is targeted by SARS-CoV-2. This analysis identified centrosome-associated proteins, nuclear pore proteins, as well as proteins involved in ER quality control,

RNA processing, respiratory electron transport, and RAB signaling as major targets of SARS-CoV-2. In light of this study, the large catalog of drugs that are effective in the treatment of various cancer types provide potential drug repurposing opportunities. Besides the drugs discussed under various pathway categories above, additional drugs that are already used or investigated for cancer treatment are also suggested inhibitors of human proteins targeted by SARS-CoV-2. Midostaurin and ruxolitinib target the serine/threonine kinases MARK2 and MARK3, which are involved in microtubule stability and regulation of cell polarity. Interestingly, both of these drugs resulted in increased infection *in vitro* (1). Daunorubicin and verapamil, both of which resulted in increased SARS-CoV-2 infection *in vitro*, target the transporter protein ABCC1. Consistent with the role of HSP90 as a host-chaperone that is universally required for viral protein homeostasis, treatment with the HSP90 inhibitor onalespib resulted in a modest inhibition of viral load in Vero E6 cells (1). Pevonedistat, a NEDD8 inhibitor, is in clinical trials for multiple cancer treatments. In addition, silmitasertib inhibits the serine/threonine protein kinase CSNK2A2, which is involved in regulation of stress granules. Interestingly, hydroxychloroquine is in clinical trials for the treatment of pancreatic and prostate cancers, and brivudine was investigated for the treatment of colorectal cancer.

It is important to emphasize that the suggested compounds target a variety of pathways and, therefore, they can restrict, enhance, or have no effect on viral replication (Supplementary Table S1). Pathway dependency of drug responses is also evident in our analysis of the efficacy of the stated compounds for inhibition of SARS-CoV-2 infection in the Vero E6 cell line, where treatment with drugs in the same pathways had similar responses. The list of pathways targeted by the virus may also inform combinatorial drug treatment opportunities. Further mechanistic analysis of these results in functional contexts is of utmost importance and requires the input of scientists from different fields.

CONCLUSION

Viruses have a minimal genome size and thus rely on host machinery to perform the essential events facilitating their replication. Therefore, it is no surprise that they often target numerous cellular pathways or protein complexes to their advantage, including cell-cycle checkpoints, metabolic pathways, epigenetic regulators, mRNA translation pathways. These same pathways are also co-opted by tumor cells to proliferate and invade other tissues. Depending on their genomes (RNA or DNA), as well as replication strategy, viruses employ a number of mechanisms to interfere with the cell-cycle regulatory components, which are critical determinants of cancer progression. Disruption of epigenetic processes and global changes in the epigenetic landscape are important hallmarks of cancer, which result in altered gene function and progression of cancer. Similarly, virus infection induces epigenetic and metabolic reprogramming to evade immune evasion and carry out their life cycle.

Proteomic approaches allow the rapid analysis of a plethora of cellular proteins implicated in signaling pathways that may be targeted during virus infection. Comparing these virus-induced deregulated pathways with signaling events altered in cancer cells bears both fundamental and translational significance. It has been observed that metabolic phenotypes triggered upon viral infection often mirror metabolic alterations in cancer cells. For example, fatty acid synthase inhibitors have been shown to inhibit viral infection in cases of Dengue virus, West Nile virus, influenza virus, poliovirus, and RSV, and are also potential anticancer drugs that are currently being tested in clinical trials. Therefore, it is of high relevance to acertain whether coronaviruses and cancer cells disturb the host pathways in a similar way, which can potentially inform us on treatments and potential long-term consequences of SARS-CoV-2, as well as the other recently emerged coronaviruses MERS-CoV and SARS-CoV. However, to explore the possibilities for expanded use of clinically approved drugs, the optimal drug dosages, safety, and side effects need to be assessed. Furthermore, high concentrations of these drugs increase the possibility of off-target activities that could be beneficial in different indications to target a specific pathway; therefore, careful *in vitro* and *in vivo* studies are required to determine the clinically effective concentration that can be achieved in patients with low toxicity. Systemic analysis integrating protein–protein interactions and functional interactions with tumor genome data is needed for detailed, mechanistic understanding of commonly altered pathways in SARS-CoV-2. Such collaborative efforts of scientists from various fields have the potential to expand the number of identified drugs or immunotherapies that can be used for the treatment of COVID-19.

Disclosure of Potential Conflicts of Interest

N.J. Krogan reports receiving commercial research grants from Vir Biotechnology and F. Hoffmann-La Roche. No potential conflicts of interest were disclosed by the other authors.

Acknowledgements

We would like to thank Kevan M. Shokat for critical reading of this manuscript. This research was funded by grants from the NIH (P50AI150476, U19AI135990, U19AI135972, R01AI143292, R01AI120694, P01A1063302, and R01AI122747, U54CA209891, to N.J. Krogan; F32CA239336, to B. Tutuncuoglu; and F32CA239333, to M. Bouhaddou).

Published first May 22, 2020.

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