CovInter 2.0: Comprehensive Molecular Interactome of Coronavirus Infection ☆

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Abstract

The ongoing evolution of coronaviruses (CoVs) poses a long-term threat to global public health, requiring dissection of virus-host interactions to develop broad-spectrum antivirals. Existing data resources are often limited to specific interaction types, hindering a systematic understanding of the complete viral life cycle. To address this, CovInter 2.0 (https://idrblab.org/COVINTER) has been developed as a comprehensively upgraded database of coronavirus interactomics, which is the first to systematically integrate the six major classes of molecular interactions that drive the viral life cycle, compiling over 61,000 entries. Furthermore, data for 229 potential anti-CoV drugs and their targets have been included, bridging molecular interactions with therapeutic development. The platform features an interactive network visualization tool for intuitive exploration of these complex relationships. As an open-access resource, CovInter 2.0 provides a powerful tool for virology and drug discovery, computational biology, designed to accelerate the identification of novel antiviral targets and the development of next-generation therapeutics.

Introduction

Understanding the molecular mechanisms underlying the infection of coronavirus is critical for developing durable prophylactic and therapeutic strategies. The life cycle of coronavirus comprises several stages, all of which are driven by complicated molecular interactions [1,2]. As shown in the Figure 1, these interactions can be categorized into six types: (a) virus protein – host protein interactions (VPHPI) [3,4], (b) virus RNA – host RNA interactions (VRHRI) [5,6], (c) virus protein – host RNA interactions (VPHRI) [7,8], (d) virus RNA – host protein interactions (VRHPI) [9–11], (e) virus RNA – virus protein interactions (VRVPI) [12,13], and (f) virus protein – virus protein interactions (VPVPI) [4,14]. A comprehensive understanding of the viral lifecycle, which requires collective consideration of these six interaction types [2,13], is essential for elucidating viral pathogenesis [3,6,15], drug discovery [3,16], and therapeutic repurposing [4].

Our previous database, CovInter 1.0 [10], was pioneering in its dedicated focus on VRHPI, which represent a critical interface reflecting both the

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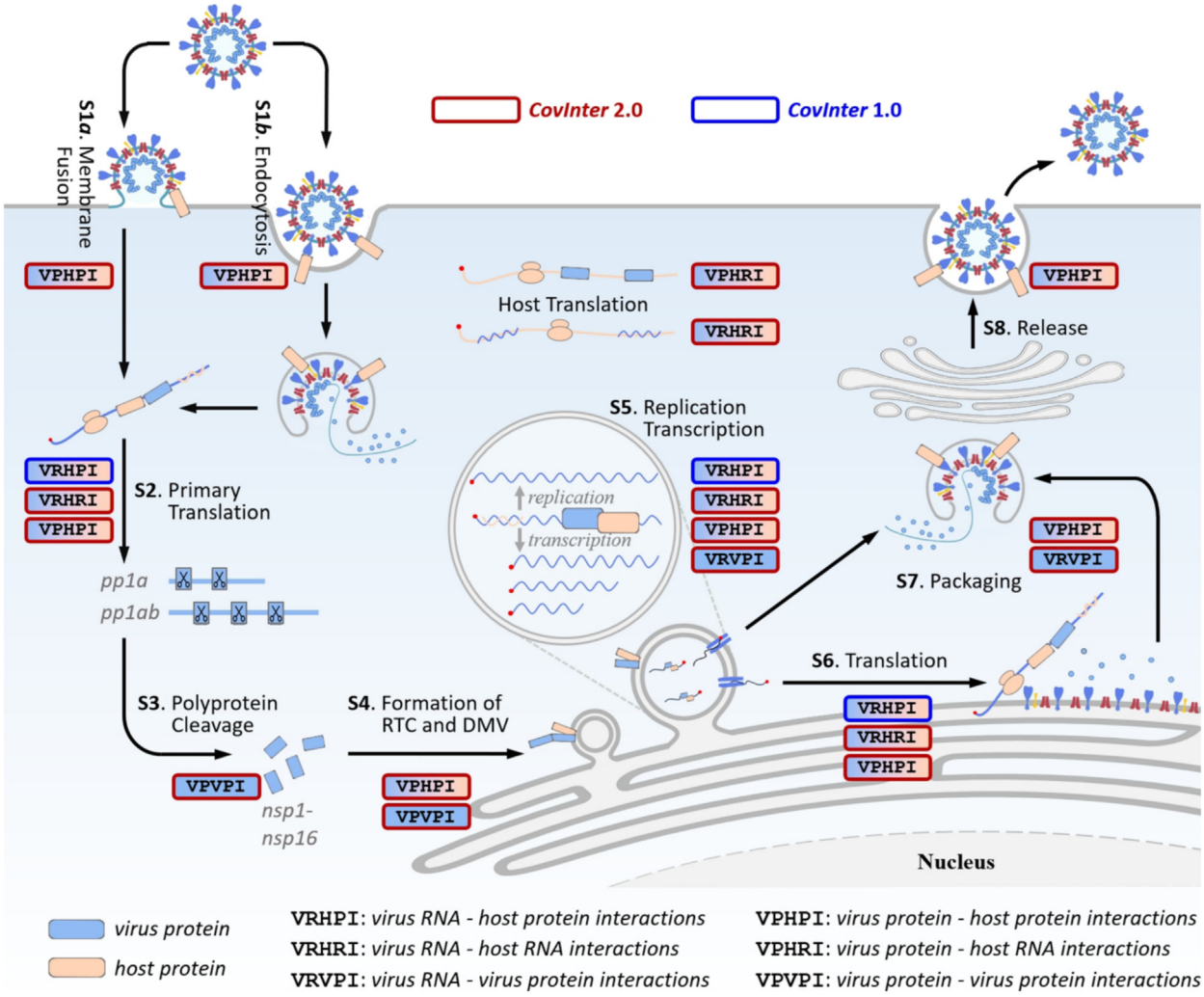

Figure 1. An overview of the coronavirus life cycle and its associated molecular interactions. The schematic diagram illustrates the eight main stages of the coronavirus life cycle: (S1) virus entry, (S2) primary translation, (S3) polyprotein cleavage, (S4) formation of the replication/transcription complex (RTC) & double-membrane vesicles (DMV), (S5) replication & transcription, (S6) translation, (S7) packaging, and (S8) release. These processes are driven by six distinct types of molecular interactions: virus protein-host protein interactions (VPHPI), virus RNA-host RNA interactions (VRHRI), virus protein-host RNA interactions (VPHRI), virus RNA-host protein interactions (VRHPI), virus RNA-virus protein interactions (VRVPI), and virus protein-virus protein interactions (VPVPI). The figure maps these interaction types to their corresponding stages in the viral life cycle. Labels with blue outlines indicate interaction types covered by CovInter 1.0, while those with red outlines highlight the new or expanded coverage in CovInter 2.0, providing a more comprehensive view for studying the mechanisms of viral infection.

virus's attempts to accelerate its translation and replication and the host's efforts to combat viral pathogenicity. However, CovInter 1.0 was limited to VRHPI and thus provided only a partial view of the coronavirus lifecycle. Meanwhile, existing resources remain fragmented—typically restricted to a single interaction type or a narrow functional context [10]. For instance, resources like VirHostNet [17], VirusMINT [18], BioGRID [19] and HVIDB [20] primarily document protein–protein interactions, while VirBase [21] focus on RNA-RNA interactions, and NPInter [22] covers various RNA-related interactions but omits protein–protein interactions. Furthermore, these platforms share a common limitation: they are not specifically focused on coronaviruses, requiring researchers to sift through data from numerous pathogens. Therefore, it is highly demanded to have a database that comprehensively describes the entire molecular interactome of the life cycle in coronaviruses.

To address this, CovInter 2.0 (https://idrblab.org/COVINTER) provides a vastly expanded dataset, created through meticulous data integration and de-duplication. To ensure a fair and direct comparison, we applied the same rigorous de-duplication process to data extracted from other major repositories. The resulting non-redundant counts highlight CovInter 2.0's superiority across

the full spectrum of molecular interactions: It provides 33,939 VPHPI records, vastly outnumbering major repositories like BioGRID (∼29 k), VirHostNet (∼11.6 k), and IntAct (∼10 k); 12,837 VRHPI records, a notable expansion from CovInter 1.0 (∼10.3 k) and far exceeding NPInter (∼1k); 13,763 VRHRI records, significantly surpassing VirBase (∼5.5 k); 618 VPHRI records, which also outpaces source like NPInter (447); 542 VPVPI records, surpassing VirHostNet (312) and BioGRID (442); and 129 VRVPI records, exceeding those in NPInter (111). This comprehensive collection firmly establishes CovInter 2.0 as the most extensive and definitive resource for coronavirus interactome research.

To facilitate mechanistic interpretation and enhance usability, we delineated the coronavirus life cycle into eight major stages based on established descriptions for SARS-CoV, MERS-CoV [23], and SARS-CoV-2 [1,2]**.** Moreover, each interaction type was assigned to its corresponding steps in the coronavirus infection cycle, which included (as illustrated in Figure 1): (*S1*) virus entry, (*S2*) primary translation, (*S3*) polyprotein cleavage, (*S4*) formation of RTC & DMV, (*S5*) replication & transcription, (*S6*) translation, (*S7*) packaging, and (*S8*) release. In addition, CovInter 2.0 integrates clinically relevant antiviral drug information, providing a more comprehensive resource for virology, drug discovery, and computational studies.

As reported, these newly collected data can help to facilitate drug repurposing and target identification by bridging molecular virology with drug discovery [24,25]. For each molecule, an interaction network is constructed with the molecule as the central node, clearly illustrating its connectivity and the frequency of its interactions with its partners within the viral infection process. This significantly enhances the visualization of the data. In essence, this updated database serves as a comprehensive resource for the research community by integrating six interaction types and mapping them to key stages of the viral life cycle.

The latest CovInter platform has been rigorously validated for performance and cross-platform compatibility, functioning seamlessly across major web browsers including Google Chrome, Mozilla Firefox, Safari, and Internet Explorer 10 or later. Following comprehensive testing across multiple geographic regions, CovInter now represents a robust and indispensable resource for virologists, computational biologists, and translational researchers dedicated to elucidating CoV-host interactions and advancing antiviral therapeutic innovation.

Factual content and data retrieval

A comprehensive interactome covering six interaction types

The CovInter database has been substantially upgraded to version 2.0, moving from a specialized to a comprehensive resource for the coronavirus research community. While the previous version focused exclusively on virus RNA-host protein interactions (VRHPI), CovInter 2.0 systematically integrates a full spectrum of six major interaction categories. In addition to an expanded VRHPI dataset, this update introduces five new types: virus protein-host protein interactions (VPHPI), virus RNA-host RNA interactions (VRHRI), virus protein-host RNA interactions (VPHRI), virus RNA-virus protein interactions (VRVPI), and virus protein-virus protein interactions (VPVPI). As a key feature, each of these interactions has been carefully annotated and mapped to the specific stage or stages of the virus life cycle in which they occur (Figure 1), providing a holistic view of the infection process.

The construction of this comprehensive interactome involved a dual-pronged data collection strategy. Alongside extensive manual curation from keyword-based literature searches, coronavirus-related data from numerous established public databases were systematically aggregated, curated, and harmonized. These sources include general molecular interaction repositories (e.g., BioGRID, IntAct) [19,26], specialized virus-host interaction databases (e.g., VirHostNet, VirusMINT, VirusMentha, HVIDB) [17,18,20,27], and resources focused on specific molecule types like RNA (e.g., NPInter, VirBase, VirusCircBase) [21,22,28]. This large-scale integration effort ensures that CovInter 2.0 not only includes the latest findings but also consolidates decades of community-driven data into a single, cohesive, and easily accessible platform.

To ensure that users can conveniently access and browse this data, CovInter 2.0 features a user-friendly interface for displaying molecules and their interactions. A search for a protein of interest returns a results list, from which the “PRO Info” button can be selected. For example, clicking this button for the SARS-CoV-2 Nucleocapsid protein N (ID: vpt0038) leads to the detailed information page shown in Figure 2. This page is organized into two main panels: the first panel (Figure 2A) summarizes the fundamental information of the protein, including its standard nomenclature, viral strain, and a link to its 3D structure visualization. The second, interactive panel (Figure 2B) lists all molecular partners that interact with the protein, including both host and other viral molecules. Clicking on any row in this list (e.g., the host RNA HMGN1) reveals a detailed view (Figure 2C), which provides supporting evidence for the selected interaction, such as experimental methods and literature citations. In addition to these three views, the webpage also features an interactive interaction network diagram that provides a graphical summary of all connections. To allow for a clear

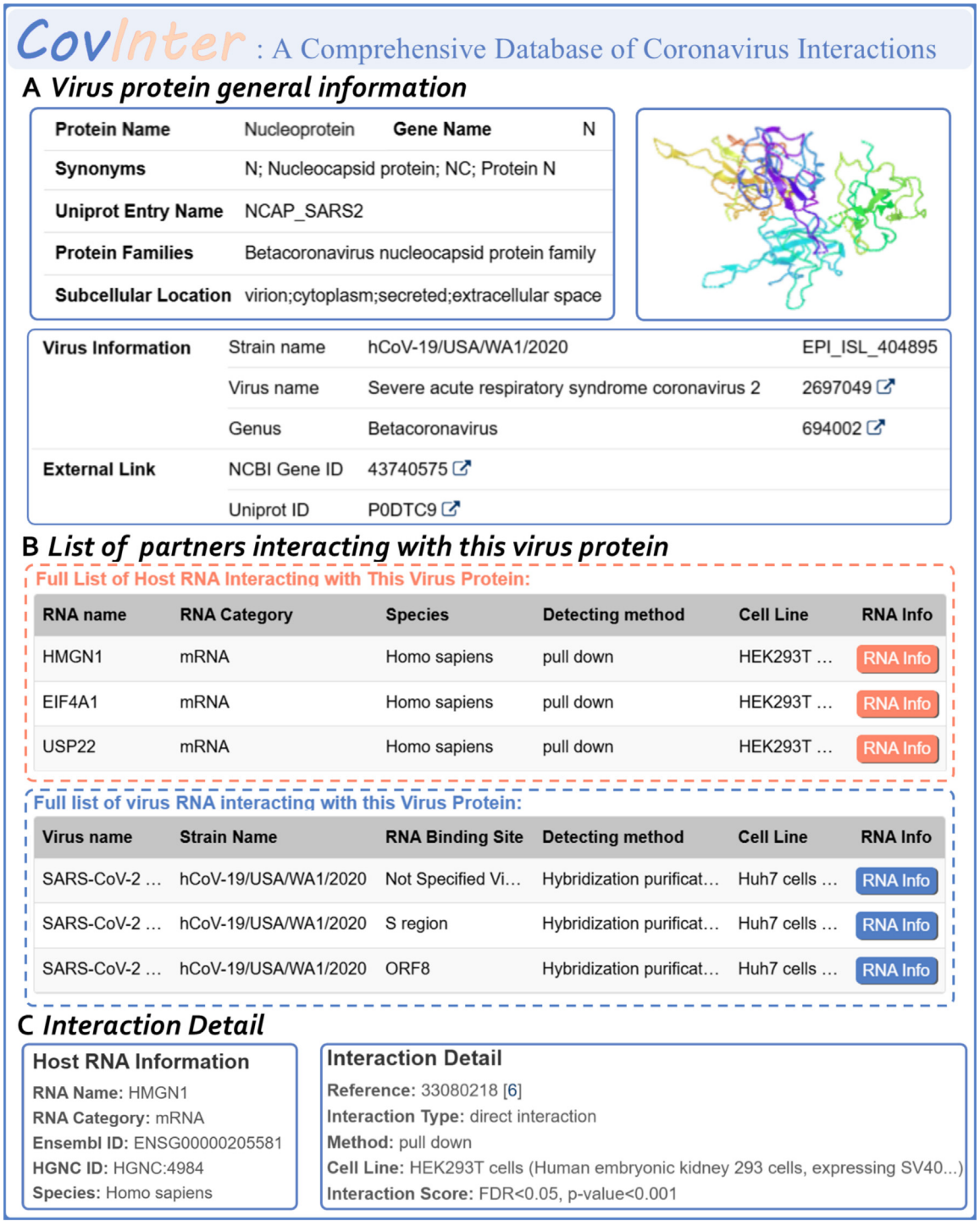

Figure 2. The data presentation interface for a virus protein in CovInter 2.0. The figure illustrates the user interface for querying a selected virus protein, using the SARS-CoV-2 Nucleocapsid (N) protein as an example. (A) The "General Information" panel consolidates core data such as the protein name, origin, and 3D structure. (B) The interactive "List of partners" table catalogs all known molecular interactions. The rightmost button "RNA Info" provides direct links to the information page of the partner molecule. (C) Selecting a specific line from the list (e.g., with the host RNA HMGN1) displays the "Interaction Details" panel, which provides comprehensive experimental evidence, including the detection method, cell line, literature reference, and statistical score. This hierarchical design allows researchers to seamlessly navigate from a high-level overview to specific interaction data, facilitating an intuitive exploration of the complex interactome.

and detailed biological analysis, this network is shown in an enlarged format in Figure 3. This design allows researchers to seamlessly transition from a high-level overview of a protein or RNA to the specific details of its interactions.

The six interaction types are described using two distinct data subsets in detail below

Virus RNA – host protein interactions (VRHPI)

CovInter 1.0 primarily focused on the interactions between virus RNA and host proteins, as these are critical for how the virus hijacks host machinery for translation and replication.

In the 2.0 update, this dataset has been significantly expanded, increasing the number of VRHPI entries from 10,341 to 12,837. This expanded collection now encompasses interactions between 322 virus RNAs and 1825 host proteins.

Virus protein – host protein interactions (VPHPI)

VPHPI are widely distributed throughout the coronavirus life cycle and play essential roles in viral infection. During the S1: entry stage, these interactions facilitate viral attachment, membrane fusion, and cell-to-cell spread. For example, the spike (S) protein initiates entry via binding to ACE2 [2], while TMPRSS2 cleaves and activates the spike glycoprotein, thereby accelerating the fusion process [29,30]. During the S2 and S6: translation stages, virus proteins manipulate host proteins to favor virus protein synthesis. For instance,

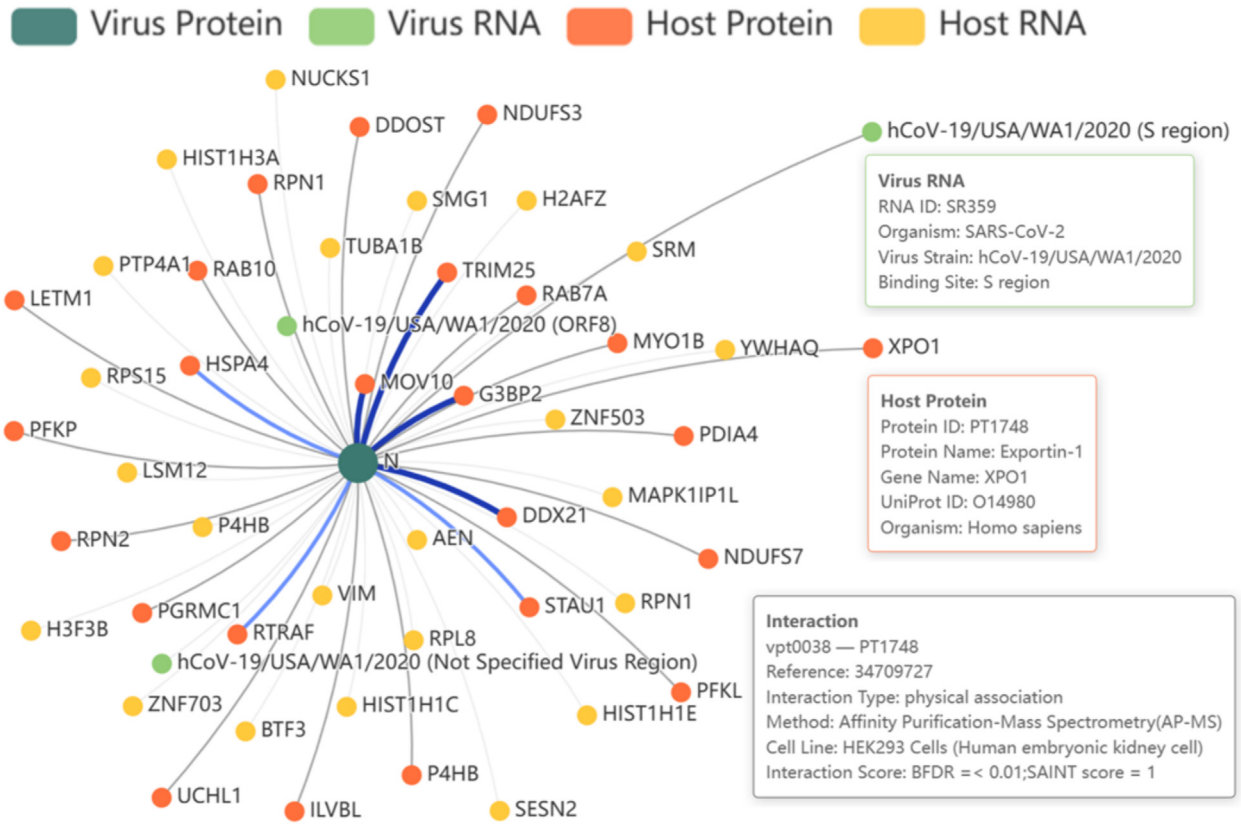

Figure 3. Interaction network of the SARS-CoV-2 Nucleocapsid (N) protein. The figure illustrates the complex interaction network centered on the Nucleocapsid (N) protein (central dark green node), a crucial component for viral RNA packaging and virion assembly. The N protein is shown to interact extensively with a large number of host proteins (orange nodes), such as MOV10, RAB7A and NDUFS3, highlighting its critical role in hijacking and modulating host cellular machinery. The network also details interactions between the N protein and various viral RNA elements (light green nodes), including specific regions like the S region and ORF8 of the hCoV-19/USA/WA1/2020 genome, which are essential for viral replication. Furthermore, interactions with host RNA (yellow nodes), exemplified by RPS15, are also depicted. The pop-up boxes provide examples of the detailed annotations for both nodes and interactions available in the CovInter 2.0 database.

nsp1 interacts with the DNA polymerase α complex (POLA1, POLA2, PRIM1, PRIM2) to suppress host genome replication [31], while nsp5 interacts with DNA damage-related proteins MDC1, BRCA1, and USP11 to inhibit the DNA damage response (DDR) [32], interfere with cell-cycle regulation, and dampen antiviral signaling, thereby promoting viral replication. At the S4: formation of RTC & DMV stage, coronaviruses remodel host membranes to establish replication organelles (DMVs). Host proteins VMP1 and TMEM41B facilitate nsp3/4 complex formation, driving DMV biogenesis [33]. In the S5: replication & transcription stage, METTL3, together with nsp15, contributes to the replication/-transcription complex (RTC) [34]. METTL3 also installs m6A modifications on SARS-CoV-2 RNA, which decreases RIG-I recognition and suppresses innate immune activation [35]. Additionally, the host helicase DDX1 interacts with nsp14 to enhance viral replication [36]. During the S7: Packaging and S8: Release stages, VPHPI may contribute to the maturation of virions, for instance by recruiting furin or furin-like proprotein convertases to cleave the S protein at the S1/S2 boundary, generating the S1 and S2 subunits required for subsequent viral entry [37]. ORF3a also interacts with VAMP7 and STX4 to facilitate viral egress [38].

Overall, VPHPI represents the most extensively studied class of coronavirus interactions, spanning almost the whole viral life cycle. CovInter 2.0 cataloged 33,939 interactions between 463 viral proteins (from 46 coronavirus strains) and 7555 host proteins (from 34 host species). These host proteins include those from *Homo sapiens* and 33 other model organisms, covering 676 protein families such as the DP1 and SFTPD families.

Virus RNA – host RNA interactions (VRHRI)

While many virus RNA-host RNA interactions occur within the S2, S5, and S6 stages to support viral processes, others represent a distinct mechanism that specifically targets and affects host translation. Host miRNAs can bind virus RNA to effectively inhibit viral replication and interfere with virus protein translation [39,40], while viral genomes can hijack host miRNAs to modulate host biological processes, potentially affecting the genes originally targeted by these miRNAs [40]. Studies have shown that SARS-CoV-2 RNA can directly base-pair with the 3′ UTR of host mRNAs, forming RNA duplexes that recruit the RNA-binding protein YBX3. This mechanism selectively stabilizes specific host mRNAs (e.g., NFKBIZ, KMT2E, FOS, and JUN), thereby promoting viral replication and driving imbalanced immune responses, such as cytokine storms [6]. Compared with viral protein-mediated global host gene suppression, RNA-RNA regulation provides higher specificity.

In summary, virus RNA-host RNA interactions represent a selective post-transcriptional regulatory mechanism that fine-tunes host mRNA stability and translation. In CovInter 2.0, 13,763 interactions were recorded between 288 virus RNAs and 8597 host RNAs from 20 coronavirus strains and 3 infected hosts, including *Homo sapiens* and two model organisms (*Sus scrofa* and *Chlorocebus sabaeus*), covering 12 RNA families, including microRNA, snRNA, and mRNA.

Virus protein – host RNA interactions (VPHRI)

Interactions between virus proteins and host RNAs mainly involve virus proteins disrupting the translation machinery of the host. The most well-studied example is the virus protein nsp1, also known as the host shutoff factor. SARS-CoV-2 nsp1 binds to the human 40S ribosomal subunit, including the 43S pre-initiation complex and the non-translating 80S ribosome [41–44]. Its C-terminal domain inserts into the mRNA channel, blocking mRNA binding. nsp1 from SARS-CoV and MERS-CoV appears to perform similar functions [45]. Other virus proteins like nsp8 and nsp9, have been shown to bind 7SL RNA within the signal recognition particle, interfering with the transport of host proteins to the cell membrane [44]. These interactions can dampen the host immune response by suppressing the normal expression of certain host proteins.

CovInter 2.0 identified 618 VPHRI, representing interactions between 15 virus proteins and 450 host RNAs. These interactions come from three coronavirus strains and from two infected hosts (*Homo sapiens* and *Chlorocebus sabaeus*), covering two protein functional families and two RNA families.

Virus RNA – virus protein interactions (VRVPI)

The known interactions between virus RNAs and virus proteins are mainly concentrated in two stages: S5: replication & transcription, and S7: packaging. nsp7, nsp8, and nsp12 assemble into the replication/transcription complex (RTC), which serves as the core machinery for viral genome replication and transcription [46]. nsp13 functions as a helicase to unwind the highly structured SARS-CoV-2 genome [47]. The N-terminal 3–5′ exoribonuclease (ExoN) domain of nsp14, together with its cofactor nsp10, establishes the virus RNA proofreading mechanism that maintains genome stability [48,49]. During the packaging stage, the nucleocapsid (N) protein binds viral genomic RNA (gRNA) to form compact ribonucleoprotein (RNP) complexes. In addition, proteins M, S, and ORF9b have also been identified as contributing to the assembly of complete virions [12].

CovInter 2.0 documents a total of 129 VRVPI, showing interactions between 75 virus RNAs and 27 virus proteins from 8 coronavirus strains. Further mining of these interactions could help identify potential therapeutic targets and provide deeper insights into how coronaviruses

manipulate their RNA-protein networks during infection.

Virus protein – virus protein interactions (VPVPI)

During the viral infection process, coronavirus proteins also interact with one another. The initially translated polyproteins pp1a and pp1ab are processed in stage S3: polyprotein cleavage, generating nonstructural proteins (nsp1–nsp16). This cleavage is mainly catalyzed by the papain-like protease (PLpro) in nsp3 [50] and the chymotrypsin-like or main protease (Mpro) in nsp5 [51]. Subsequently, the co-expression and interaction of nsp3 and nsp4 induce the formation of double-membrane vesicles (DMVs). Nsp7, Nsp8, and Nsp12 further assemble into the replication/transcription complex (RTC), which drives viral RNA synthesis [46]. The N-terminal 3–5′ exoribonuclease (ExoN) domain of nsp14, in association with its cofactor nsp10, establishes the virus RNA proofreading mechanism [49], thereby preparing the environment for replication and transcription. In addition, accessory proteins such as ORF3a and ORF7a interact with structural proteins M, E, and S during the packaging stage to facilitate virion assembly [52].

Compared with virus-host interactions, direct interactions among virus proteins are relatively less common. Data curation indicates that most biologically meaningful VPVPI occur during polyprotein processing, RTC assembly, and virion packaging. Many other interactions are experimentally reported but remain poorly understood, requiring further investigation. In the CovInter database, a total of 542 VPVPI are documented, describing the interactions among 131 virus proteins from 12 coronavirus strains.

Interactive network visualization. To provide a more intuitive representation of these complex relationships, the platform now introduces a new interactive network visualization feature. This tool can dynamically generate a complete interaction network for any selected molecule (e.g., a virus protein, host protein, or RNA), clearly illustrating all its known interaction partners and their respective types (Figure 3).

Conclusion and perspectives

The development of CovInter 2.0 represents a significant milestone in integrating data resources for coronavirus research. By systematically curating and integrating six critical types of molecular interactions, the database provides an unprecedentedly comprehensive framework for dissecting the entire life cycle of coronaviruses, from entry to release. CovInter 2.0 is designed to not only empower researchers to accurately identify novel antiviral drug targets—targeting both host and viral factors—but also provide crucial insights into viral pathogenesis, immune evasion strategies, and the development of more effective therapeutic interventions.

To ensure broad accessibility and usability, the CovInter platform has undergone rigorous performance and cross-platform compatibility testing, ensuring seamless operation on all major web browsers (including Google Chrome, Mozilla Firefox, Safari, and Internet Explorer 10 or later). Validated across multiple geographic regions, CovInter 2.0 is positioned to serve as a powerful and reliable resource. It is poised to empower virologists, computational biologists, and translational researchers, thereby accelerating the understanding of scientific community in CoV-host interactions and advancing the innovation of next-generation antiviral therapies.

CRediT authorship contribution statement

Weimin Lu: Writing – original draft, Software, Data curation. **Yintao Zhang:** Software, Data curation. **Kuerbannisha Amahong:** Data curation, Conceptualization. **Sisi Zhu:** Data curation. **Xiuwen Li:** Data curation. **Ying Zhou:** Writing – review & editing. **Feng Zhu:** Supervision, Project administration, Conceptualization. **Lin Tao:** Supervision, Project administration, Conceptualization.

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DATA AVAILABILITY

Data will be made available on request.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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