ImitateDB: A database for domain and motif mimicry incorporating host and pathogen protein interactions

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Abstract
Molecular mimicry of host proteins by pathogens constitutes a strategy to hijack the host pathways. At present, there is no dedicated resource for mimicked domains and motifs in the host–pathogen interactome. In this work, the experimental host–pathogen (HP) and host–host (HH) protein–protein interactions (PPIs) were collated. The domains and motifs of these proteins were annotated using CD Search and ScanProsite, respectively. Host and pathogen proteins with a shared host interactor and similar domain/motif constitute a mimicry pair exhibiting global structural similarity (domain mimicry pair; DMP) or local sequence motif similarity (motif mimicry pair; MMP). Mimicry pairs are likely to be co-expressed and co-localized. 1,97,607 DMPs and 32,67,568 MMPs were identified in 49,265 experimental HP-PPIs and organized in a web-based resource, ImitateDB (http://imitatedb.slab-nsit.net) that can be easily queried. The results are externally integrated using hyperlinked domain PSSM ID, motif ID, protein ID and PubMed ID. Kinase, UL36, Smc and DEXDc were frequent DMP domains whereas protein kinase C phosphorylation, casein kinase 2 phosphorylation, glycosylation and myristoylation sites were frequent MMP motifs. Novel DMP domains SANT, Tudor, PhoX and MMP motif microbody C-terminal targeting signal, cornichon signature and lipocalin signature were proposed. ImitateDB is a novel resource for identifying mimicry in interacting host and pathogen proteins.

Keywords Host–pathogen protein–protein interaction · Molecular mimicry · Domain · Motif · Infectious diseases

Abbreviations
HP-PPI Host–pathogen protein–protein interaction
HHI Host–host interaction
DMP Domain mimicry pair
MMP Motif mimicry pair
SANT Swi3, Ada2, N-Cor, and TFIIB
CD search Conserved domain search
PSSM Position-specific scoring matrices
COG Cluster of orthologs
PKC Protein kinase C
CK2 Casein kinase II

Introduction
In nature, host–pathogen Protein–protein interactions (HP-PPIs) are ubiquitous and essential for initiation and propagation of infectious diseases (Dean Southwood 2019). Pathogenesis involves interactions between the signalling networks of the host and pathogen. Recent studies regarding HP-PPIs focus on the mechanisms employed by pathogens to hijack and exploit the host immune system for their own survival (Mayer et al. 2019; Nicod et al. 2017). Processes for molecular mimicry have evolved to enable the proteins of pathogens to imitate the host proteins, disrupt their interactions, and disturb the signalling pathways (Guven-Maiorov et al. 2016). Thus, the interacting proteins and pathways of the pathogen may be conceived to be in a continuum with those of the host. The mimicry of host antigenic determinants as a survival mechanism was described initially in parasites (Damian 1964). The ability of the pathogen to...
mimic the host components may be achieved by horizontal gene transfer (Diaz et al. 1997) or convergent evolution (Stebbins and Galan 2000). Molecular mimicry can take four distinct forms as depicted in Table 1 with examples; (a) similarity in both sequence and structure of a full-length protein/functional domain (Sharp et al. 1997; Dar and Sicheri 2002), (b) structural similarity without an apparent sequence similarity (Standfuss 2015; Burg et al. 2015), (c) similarity in the sequence of a short linear motif (Wu et al. 2005), (d) similarity of only the binding site architectures or interface mimicry without apparent sequence homology (Huang et al. 2009). The local similarities between epitopes from the infectious agents and antigens present in the host can also lead to autoimmune diseases (Cusick et al. 2012; Venigalla et al. 2020; McClain et al. 2005).

Hijacking of host networks by the pathogen essentially works by imitation and competition with endogenous host–host interactions (Franzosa and Xia 2011; Yapi-Eser et al. 2021). It has been observed that a majority of the pathogen proteins bind to the same domain on their respective host target that are otherwise bound by host endogenous proteins (Chen and Xia 2021). In addition to employing mimicking host domains, effectors also employ short linear motifs that bind to host domains with similar specificities as host endogenous proteins, albeit sharing little homology with the latter (Samano-Sanchez and Gibson 2020). However, allosteric modes of binding have also been studied as seen in LegK7 protein of Legionella pneumophila (Lee et al. 2020). Some small molecules have been implicated in inhibition of motif mimicry mediated interactions. Anacardic acid, a small inhibitor has been developed against Anaplasma phagocytophilum effector AmpA that hijacks host cell SUMOylation (Beyer et al. 2015). N-(p-Amylcinnamoyl) anthranilic acid is an inhibitor that has been developed against YxxØ-motif found in multiple viruses that exploit host AP2M1 for intracellular trafficking (Yuan et al. 2020). A CAAX peptidomimetic drug has been developed against CAAX motif which is used by L. pneumophila to exploit host prenylation machinery to facilitate targeting of effector proteins to membrane-bound organelles during intracellular infection (Ivanov et al. 2010). These promising developments suggest that host–pathogen interactions can be targeted using small-molecule inhibitors and peptide mimetics as anti-infective strategies.

The existing methods of detection of mimicry are simply based on identifying sequence or structure similarity. A previously available database, namely mimicDB (Ludin et al. 2011) provides information about molecular mimicry proteins or epitopes involved in a limited number of human parasites. Another database miPepBase (Garg et al. 2017) lists the experimentally verified mimicry peptides involved in auto-immune disease. A computational pipeline using pBLAST against the human proteome has also been implemented for the prediction of the molecular mimicry candidates in bacterial pathogens (Doxey and McConkey 2013). An interface mimicry-based method, the HMI-PRED server (Guven-Maiorov et al. 2020) carries out structural prediction of given HP-PPIs. However, it is limited due to the requirement of the structure of the microbial protein involved in mimicry.

Similarity between motifs and domains of the host and pathogen proteins does not necessarily indicate their actual interaction. This is further dependent on the proteins having simultaneous expression and being present in the same cellular compartment. The analysis of the PPIs in yeast and human showed that a large majority of the interactions occur between proteins present in the same subcellular compartment (Schwikowski et al. 2000; Gandhi et al. 2006). Studies

| S. no | Types of molecular mimicry | Examples | PDB structure ID |
|-------|---------------------------|----------|-----------------|
| a     | Similarity in both sequence and structure of a full-length protein or a functional domain | K3L protein of Vaccinia Virus mimics the S1 domain of human eIF-2-α to bind to human PRK (Sharp et al. 1997; Dar and Sicheri 2002) | K3L S1 domain: PDB ID: 1uz eIF-2-α S1 domain: PDB ID: 1kl9 |
| b     | Structural similarity without an apparent sequence similarity | Viral proteins (US28 protein of human cytomegalovirus and vMIP-II protein of Kaposi Sarcoma virus) mimics both the structures and interactions of their host counterparts (CXCR4 and CX3CL1, respectively) although they have a very low sequence similarity (Standfuss 2015; Burg, et al. 2015) | US28-CX3CL1 (PDB ID: 4xt1) vMIP-II-CXCR4 (PDB ID: 4rws) |
| c     | Similarity in the sequence of a short linear motif | The LMP1 protein of Epstein–Barr Virus mimics the motif PxQxT of CD40 to interact with TRAF3 (Wu et al. 2005) | LMP1-TRAF3 (PDB ID: 1zms) TRAF3-CD40 (PDB ID: 1fl1) |
| d     | Similarity of only the binding site architectures (interface mimicry) without sequence homology | Map of E. coli, and SopE of S. typhimurium form interfaces with human Cdc42 that mimic the interface between Cdc42 and human intersectin (Huang et al. 2009) | Cdc42-Map (PDB ID: 3gcg), Cdc42-SopE (PDB ID: 1gzs), Cdc42-Intersectin (PDB ID: 1ki1) |
have also shown that functionally related or interacting proteins from the same pathways share Gene Ontology, and usually constitute a higher co-expression score (Wolfe et al. 2005; Durmus Tekir et al. 2012). Therefore, the resemblance between the experimentally validated host and pathogen interactors of the same host protein may increase the confidence in the identification of molecular mimicry candidates due to colocalization and co-expression of the interacting protein pairs.

A pair of pathogen and host proteins that interact with the same host protein may share a common domain indicating global structural similarity or a common short linear sequence motif indicating local sequence similarity. This pathogen protein may be involved in molecular mimicry of the host protein. These pathogen and host protein pairs have been termed respectively as domain mimicry pair (DMP) and motif mimicry pair (MMP) as shown schematically in Fig. 1a, b. A competitive mode of binding of both interaction partners to the same protein is shown in Fig. 1b while allosteric mode of binding is depicted in Fig. 2. Delineating the DMPs and MMPs provides information about the host interactions that are likely to be disrupted by pathogen protein mimicry.

In this work, we collated the entire set of experimental HP-PPIs from interaction databases to compute their DMPs and MMPs, which were organized in the form of a publicly available database, ImitateDB available online at http://imitatedb.sblab-nsit.net. The ImitateDB resource can help researchers to search for organism-wise mimicry patterns prominent in the host–pathogen interactome. It houses 1,97,607 DMPs and 32,67,568 MMPs. Several novel potential domain and motif mimics have been identified in our dataset. Specific domains or motifs imitated commonly by many pathogens are likely to be responsible for microbial virulence suitable for drug/vaccine targeting. Thus, ImitateDB constitutes a source of information for molecular imitation in HP-PPIs for researchers in the field of infectious diseases and microbiology.

**Materials and methods**

**HP-PPI data collection and cleaning**

The information regarding the HP-PPIs was collected from different databases namely BioGrid 4.4 (Stark et al. 2006), PHISTO (Durmus Tekir et al. 2013), HPIDb 3.0 (Ammari et al. 2016), MINT (Chatr-aryamontri et al. 2007), IntAct 4.2 (Hermjakob et al. 2004), MPIDB (Goll et al. 2008), UniProt (The UniProt 2017), VirHostNet 3.0 (Navratil

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**Fig. 1** Panel (a) Domain Mimicry Pair (DMPs) and Motif Mimicry Pairs in Host–pathogen protein–protein interactions and Host–host interaction network: a pathogen protein(red) interacts with many host proteins(blue) that in turn interacts with many other host proteins(yellow). The pathogen protein(red) and host first interactor protein(yellow) with a common interacting host protein (blue) are compared for similar domains (green) and motifs (purple) to determine DMPs and MMPs respectively. Panel (b) A Schematic of individual DMP: a host first interactor protein (yellow) and pathogen protein (red) that interacts with the same host protein (blue) share the same domain ‘A’ (green). B Schematic of individual MMP: a host first interactor protein (yellow) and pathogen protein (red) that interacts with the same host protein (blue) share the same motif ‘A’ (purple)
et al. 2009), MatrixDB (Launay et al. 2015), I2D 2.9 (Brown and Jurisica 2007), DIP (Xenarios et al. 2000) and InnateDB 5.4 (Lynn et al. 2008). To maintain uniformity in the protein identifiers extracted from different sources, all the identifiers were converted to the corresponding UniProt accession number. Similarly, to maintain uniformity in the syntax/nomenclature of pathogens, all pathogen names were converted into the corresponding NCBI Taxon identifier. The duplicate entries were removed from the data to avoid redundancy. The obsolete entries were either removed or converted into secondary UniProt accession numbers, if available.

**Host–host interaction (HHI) data collection**

The host proteins directly interacting with the pathogen interacting host proteins (as shown in Fig. 1a) are referred to as the host first interactor proteins. Information about the host first interactor proteins was collected using UniProt. These data were further processed using bioDBnet 2.1 (Mudunuri et al. 2009) to filter out the various non-human interactors of the host proteins and retain only the human interactors of the host proteins.

**Domain annotation**

The term domain, as used in DMP refers to a tertiary structure (folding unit) which is a distinct functional and/or structural unit of a protein, is independently stable and much larger unit than a motif. Domain annotation was carried out using the NCBI Batch Conserved domain (CD) Search 3.19 (Marchler-Bauer et al. 2011) a sensitive method that searches multiple sequence alignments converted into position-specific scoring matrices (PSSM) using Reverse Position Specific-BLAST. The default parameters of CD search were used with an expect value of 0.01. The domain information was collected in the form of a unique PSSM ID and Domain short name for every unique domain family of all the proteins.

**Motif annotation**

The term motif, as used in MMP refers to a Prosite pattern. This is a short sequence linear motif corresponding to a short conserved biologically significant region of the sequence. Prosite patterns are represented by sequence signatures, are not independently stable and are much smaller than a domain. The motifs were identified using the Expasy
ScanProsite (Castro et al. 2006) API (Application Programming Interface) with the help of a Python script using the get() function to fetch the motifs for a large number of proteins. ScanProsite is considered a standard benchmark for other databases due to the high quality of its motifs (Ferreira and Azevedo 2007). It covers all the important motifs like active sites, binding sites, disulfide bonds and the promiscuous motifs as well like post-translational modification sites that have a role in mimicry mediated host–pathogen interaction and virulence (Kumar et al. 2020). For this study, ScanProsite was run with the “Exclude Profiles” option to eliminate the domains and scan only against the patterns corresponding to short sequence motifs. The motif information for each protein was collected in the form of ScanProsite motif IDs, motif name and pattern.

Identification of shared DMPs and MMPs

The pathogen proteins and host proteins interacting with the same host protein were compared for shared structural domains (global similarity) or short linear sequence motifs (local similarity). This was done using a python script to find the same domain PSSM-IDs and ScanProsite motif IDs between the pathogen protein and host protein interacting with the same host protein.

Identification of COGs (cluster of orthologs) after determining DMPs and MMPs

The pathogen proteins belonging to different strains of the same organism (especially in case of virus) may be orthologs and may lead to redundancy. To determine the number of unique DMPs and MMPs for every pathogen, the orthologous pathogen proteins involved in DMPs and MMPs were clustered into a single COG using eggNOG 5.0 (Huerta-Cepas et al. 2019).

Database and web interface development

After the completion of data processing and formation of domain and motif mimicry pairs, a database was created using MySQL to house the schema and various tables through MySQL Command line client server. Further, an MVC (Model View Controller) web application was created in Node.js using the Express framework. The front end of the web application was developed using HyperText Markup Language (HTML). Embedded JavaScript Templating was used to render HTML with our own set of variables. Cascading Style Sheets (CSS) with JavaScript and jQuery was employed for implementing the various methods and functions.

Data analysis and visualization

Analysis of the database was done using MySQL, Microsoft Excel, R studio and Tableau. MySQL was used to sort the entities and quantitatively measure the frequency of each entity in the entire data. The graphs and highlight tables depicting the analysis were rendered using Microsoft Excel and Tableau. The high-degree pathogen and host proteins were identified using an R script. Pathway and gene ontology annotation of the host proteins was carried out using PANTHER16.0 (Mi et al. 2021), a tool used for functional enrichment of proteins. The Fisher’s exact test with Bonferroni correction for multiple testing (p < 0.05 values) was used to determine statistical over-representation during enrichment analysis.

Results and discussion

ImitateDB starts with all experimentally determined HP-PPIs. The first interactors of the host proteins were added. These experimentally determined host and pathogen proteins are more likely to be co-expressed and co-localized hence increasing the confidence in the identification of mimicry pairs. The DMPs and MMPs provide information about the matched domains and motifs between the pathogen protein and host protein interacting with the same host protein.

Experimental HP-PPI data

Viruses have the highest number of reported HP-PPIs among the different pathogen categories. 5568 pathogen proteins from 629 organisms interacted with 10,078 host proteins with 61,214 HP-PPIs. Of these, 49,249 reported HP-PPIs were of viral origin. In comparison, reported bacterial HP-PPIs were 10,080 while those from other organisms were even fewer. Further, 11,657 host first interactors having 1,03,120 interactions with the host proteins were retrieved as described in the methodology. Domains and motifs of these first interactors were identified and compared with those present in the pathogen proteins. The total as well as the number
of unique domains (each corresponding to a unique PSSM-ID) and motifs (each corresponding to unique ScanProsite motif ID) annotated in pathogen proteins and host interactor proteins are shown in (Table 2).

**MMPs are more numerous in comparison with DMPs**

Out of the 5568 pathogen proteins from 629 pathogens, a total of 5254 proteins from 611 pathogens had similar domains or motifs as host interactor proteins (Table 2). The DMPs in the entire database were found to be 1,97,607.
whereas the MMPs were found to 32,67,568. The number of DMPs, MMPs, total HP-PPIs, HP-PPIs characterized by mimicked domain and motif for each pathogen category are listed in (Table 3). Viruses showed the highest number of DMPs and MMPs, likely to be due to the preponderance of virus HP-PPIs in the data.

Interestingly, of the total 61,214 HP-PPIs reported, only 1551 were found to be characterized by domain mimicry whereas 49,265 were found to be characterized by mimicked motifs. The total number of HP-PPIs, the fraction of HP-PPIs characterized by mimicked domains and by motifs were compared across pathogen categories and are shown in Supplementary Figure S1. Motif mimicry dominates in number over domain mimicry across all pathogen categories. Previous studies have also reported the extensive use of motif mimicry by viral proteomes (Davey et al. 2011; Duro et al. 2015; Via et al. 2015; Garamszegi et al. 2013). However, due to the short and ambiguous nature of the motifs, some false positives are also expected. Therefore, the detected MMPs need to be carefully examined and validated in future works.

**Domain mimicry**

Table 2 shows the number of pathogen proteins and host interactor proteins involved in domain mimicry or being shared between the pathogen and host interactor proteins. As there were multiple instances of every mimicked domain, we looked for unique domains. There were 4300 unique domains shared by the pathogen and host first interactor proteins. The largest number of DMPs were found for the protein Serine Threonine Protein Kinase US3 (UniProt ID: P04413) from human herpesvirus 1 strain 17 (HHV-1). It forms 61,609 DMPs predominantly consisting of STKc_MST3_like domains (PSSM-ID: 270,786). The top 10 pathogens involved in domain mimicry along with the number of DMPs are shown in Supplementary Table S1.

The top 10 most frequent mimicked domains are shown in Supplementary Figure S2 (a). PHA03247 (large tegument protein UL36 domain family) was the most frequent among DMPs. UL36 is an important domain family that is crucial for virus host interaction and host immune evasion (Newcomb and Brown 2010). UL36 is found to be colocalized with host/viral membrane proteins. It aids in the assembly and cell entry of Herpes Simplex Virus (Schipke et al. 2012). The top 10 most frequently occurring mimicked domains in different pathogen categories are shown in Supplementary Table S2. Of these, the DEAD-like helicase domain superfamily was frequent among viral DMPs and has been previously reported as an emerging class of host domains mimicked by viral pathogens (Meier-Stephenson et al. 2018).

**Motif mimicry**

Table 2 shows the number of pathogen proteins and host interactor proteins involved in motif mimicry along with the number of unique motifs being mimicked or being shared between the pathogen and host interactor proteins. As there were multiple instances of every mimicked motif, we looked for unique motifs. There were only 96 unique motifs shared by pathogen and host first interactor protein. The largest number of MMPs were found for the Polymerase basic protein 2 from influenza A virus strain A/Wilson-Smith/1933 H1N1. It forms 35,385 MMPs predominantly containing of Protein kinase C or PKC_PHOSPHO_SITE motifs (ScanProsite Motif ID: PS00005). The top 10 pathogens by the count of MMPs are listed in Supplementary Table S7. It was observed that Saccharomyces cerevisiae S288c had the maximum count of DMPs and MMPs though the total number of reported HP-PPIs were very low in comparison with virus or bacteria. The genes that regulate cellular processes in humans have equivalents that control cell division in yeasts, thus facilitating alteration of the host cellular machinery (Cazzanelli et al. 2018).
S. cerevisiae is an opportunistic pathogen as it is found to be associated with cutaneous infections, systemic bloodstream infections and infections of essential organs in immunocompromised or critically ill patients (Perez-Torrado and Querol 2015). Escherichia coli K12 is another opportunistic pathogen in our dataset as it is found to switch over its otherwise dormant pathogenic machinery to exert ill effects on the host under specific conditions such as dysbiozed gut microbiome composition, compromised immune system or a lack of gut microbe competition(Bhat et al. 2019). Thus, HP-PPIs, DMPs and MMPs from these organisms are of interest for the role of mimicry proteins in hijacking of human pathways and development of therapeutics against it.

The total count for the top 10 most frequently occurring motifs in the database is shown in Supplementary Figure S2(b), which indicates the predominance of phosphorylation sites for PKC and casein kinase II (CK2). PKC and CK2 family of serine/threonine kinases plays essential roles in hijacking multiple signalling pathways in humans leading to many viral infections (Keating and Striker 2012). Sites for N-myristoylation, amidation, and N-glycosylation were amongst the most frequently mimicked motifs. N-glycosylation site is a frequently occurring motif used by several pathogen proteins (especially viral glycoproteins) to evade the human immune system (Crispin and Doores 2015; Crispin et al. 2018). The envelope proteins of viruses like HIV-1 are heavily glycosylated and can provide camouflage against the human proteins, leading to alteration of immune recognition (Wagh et al. 2018; Seabright et al. 2019). N-myristoylation motifs, post translational modification sites that have prominent roles in cellular signalling pathways, have been found to be mimicked by viral and bacterial proteins (Davey et al. 2011; Maurer-Stroh and Eisenhaber 2004). A comparative view of the top 10 most frequently mimicked motifs amongst the different pathogen categories is shown in Supplementary Table S8. Additionally, several other commonly mimicked motifs in our data are ABC transporter family signature motif, Q motif, ATP/GTP-binding site motif A (P-loop), arginine-rich motif, ubiquitination site and prenyl group binding site. The number of top 20 mimicked motifs for the top 20 pathogens is shown in Supplementary Table S9.

**Mimicry pairs in highly interacting pathogen proteins and host proteins**

Several previous studies have shown that essentiality and pathogen fitness are correlated with high number of interactions (Crua Asensio et al. 2017; Ahmed et al. 2018). Therefore, the number of DMPs and MMPs in the top 10 highly interacting pathogen proteins and host proteins were examined (Supplementary Tables S10 and S11, respectively). The top 10 highly interacting pathogen proteins were of viral origin and predominantly formed MMPs. Among host proteins, a few had a very high number of DMPs. It was observed that nuclear factor NF-kappa-B p105 subunit was a part of 491, while Cellular tumor antigen p53 was a part of 180 DMPs.

**Chemokine and cytokine, cholecystokinin receptor, epidermal growth factor receptor and platelet-derived growth factor signalling pathways are enriched in host proteins of mimicry pairs**

The enriched pathways and processes of the host proteins involved in DMPs and MMPs were annotated. Apart from specific pathways for some autoimmune diseases such as Huntington and Parkinson disease, chemokine and cytokine, cholecystokinin receptor, epidermal growth factor receptor, platelet-derived growth factor signalling pathways, T cell and B-cell activation pathways were enriched among the host proteins constituting the DMPs and MMPs. The enriched pathways along with their corrected p values are listed in supplementary table S12. Similarly, the enriched gene ontologies were determined for the host proteins. The enriched cellular compartments, molecular functions, and biological processes of the host proteins along with their corrected p values are shown in Supplementary tables S13, S14 and S15, respectively.

**Selected novel domain and motif mimicry candidates**

Several novel candidate mimicry domains like SANT, TCP-1 and Tudor in pathogenes were identified from analysis of the ImitateDB data. Some of the novel domain mimics identified in different pathogenes along with their functions are shown in Supplementary Table S12. Microbodies C-terminal targeting signal, lipocalin signature and cornichon signature were novel motif mimic candidates. Selected novel mimicry motifs identified in different pathogenes along with their functions are shown in Supplementary Table S13.

**The ImitateDB web interface**

The web interface for the ImitateDB database provides a user-friendly access to the data and allows the user to search for information about DMPs and MMPs using multiple search options. The web interface has a home page that gives an overview of molecular mimicry and procedure for determination of DMPs/MMPs. The interface provides a separate search page to query for domain and motif to search for DMPs and MMPs, respectively. After choosing between domain or motif, the interface provides the next menu to choose among the different categories of pathogenes, namely virus, bacteria, fungi and others. In each category, the database can be searched by organism, pathogen protein...
ID, host protein ID, interaction detection method, host interactor protein ID, matched domain PSSM ID, domain short name, matched motif ID, motif name, or pattern. For easier searching, selection of the category and subcategory leads to the population of a drop-down menu with available options. Additionally, the user can enter a keyword to retrieve the required data. After this selection, the user needs to enter the correct captcha to fetch the results.

The website also has an instructions manual to help the users to query the database and an interpretation manual to help the users to interpret the results. An expanded view of the search panel in the database is shown in Fig. 4a. The results are displayed in the form of a table that can be downloaded. The results are externally integrated using hyperlinked domain PSSM ID, ScanProsite motif ID, protein ID and PubMed ID. The download feature for bulk files has been restricted due to download constraints. For queries yielding results between 10,000 and 1,00,000 records, the user is provided with the results by email using an in-built mailer (as shown in Fig. 4b), that pops up after clicking the download button. The users are advised to check the spam folder for mails from ImitateDB. For queries yielding results above 1,00,000 records, the user can contact the ImitateDB team to obtain the results.

Literature validation of mimicry using selected examples

The following selected examples from ImitateDB could be validated from the literature as instances of domains/motifs that are mimicked by the pathogen to bind to the host and also serve as the site of interaction:

(a) DMP: ImitateDB determined a DMP consisting of protein K3L (UniProt ID: P20639) of Vaccinia Virus which mimics the S1 domain of human eIF-2-α (UniProt ID: P05198) to interact with the human PRK (UniProt ID: P19525). Competitive binding experiments suggested that PKR recognizes and interacts with K3L and eIF2α by a common mode due to homology between the S1 domain of K3L and eIF2α (Sharp et al. 1997; Dar and Sicheri 2002; Beattie and T.J., Paoletti E 1991).

(b) MMP: The ImitateDB MMP consisting of protein BHRF1 (UniProt ID: P0C6Z1) of Epstein Barr virus (EBV) that mimics the BH2 motif of human Bcl-xl (UniProt ID: Q07817) to interact with the human BAK1 (UniProt ID: Q16611). The BHRF1–Bak complex (PDB ID: 2px1) and Bcl-xl–Bak complex (PDB ID: 1bx1) shows the competitive mode of binding of BHRF1 and Bcl-xl through the BH2 motif on BH3 peptide of BAK (Kvansakul and Hinds 2013).

Other modes of mimicry-mediated binding

There can be instances where the mimicked domain/motif between the interacting host and pathogen protein is not the actual site of interaction. As an example, ImitateDB contains LegAS4 protein (UniProt ID: Q5ZUS4) of L. pneumophila that competes with human histone methyltransferase/H3K9 (UniProt ID: O43463) to bind to human HP1γ (UniProt ID: Q13185), a possible transcriptional repressor of heterochromatin-like complexes. The SET domain of H3K9 is structurally mimicked. However, the binding at HP1γ is not through the SET domain. SET domain mimicry is used by LegAS4 to target human heterochromatin-1 to activate host rDNA.

Fig. 4 a The ImitateDB web interface: expanded view of the search panel of the web interface showing the steps to query the ImitateDB database. b Receive large result files by email: expanded view of the mailer popped up on the ImitateDB interface
transcription as proved through chromatin immunoprecipitation assays (Li et al. 2013). Therefore, in certain cases, the mimicry in the DMP/MMP may be incidental.

Concluding remarks

ImitateDB integrates experimental PPI data with structural/sequence similarity to bring higher confidence to prediction of mimicry between host and pathogen proteins. While this method increases the confidence in prediction for mimicry pairs, the limitation is that the mimicry candidates will only be identified for those organisms and proteins for which the experimental PPIs have been reported. Therefore, the DMPs and MMPs can also be expanded to include predicted PPIs. Apart from this, host and pathogen proteins interact in similar ways as host-endogenous proteins through interface mimicry which is not visible in either domain or motif form.

The curated information in ImitateDB will help in identifying frequent, unique, and novel mimicry domains/motifs among the mimicking host and pathogen proteins. Additionally, MMPs or DMPs allows us to easily identify and model the host protein motif or domain at which the competition for interaction is taking place. The disruption of these HP-PPIs can be regarded as a strategy for developing novel broad-spectrum therapeutics against multiple infectious diseases.

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Author contributions ST: carried out data cleaning, enrichment and organisation, development of the database, analysis, and manuscript preparation. VB: developed the backend and front end of the web interface. TM: carried out data acquisition and cleaning. SB: was involved in conception, design, analysis, and supervision of the study. The manuscript was reviewed by all the authors.

Data availability The authors confirm that the data supporting the findings of this study are available at http://imitatedb.sblab-nsit.net. The python script for the identification of DMP/MMP is available at the following link: https://github.com/sblab/ImitateDB.git. At present, Imitate DB contains information from HP-PPIs up to April 2021. We plan to update this database regularly as new releases of the contributing databases become available. Apart from collating all the HP-PPIs from different databases, we are working towards mining the HP-PPIs from literature for computation of additional DMPs and MMPs. We plan to compute DMPs and MMPs for predicted HP-PPIs. Work is also ongoing for providing information on DMPs/MMPs for Sars-CoV-2.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval Research involving human participants and/or animals. It is declared that no human participants and/or animals are used in this work.

Informed consent Not applicable.

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