Article

Human disordered charged biased proteins: from the proteome to the druggome

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Abstract
The human disordered charged biased proteins (HDCBPs) are involved in complex diseases. The HDCBP-disease network constructed in our earlier showed that HDCBPs share many diseases. Therefore, they are attractive therapeutic targets for drug discovery. In this study, we explore the associations between (HDCBPs), the related diseases, and the drugs. The results show that 20% and 14% of HDCBPs are listed in DRUGBANK and ChemDB respectively. The elaborated HDCBP-Drug-Disease network revealed that most of the therapeutic area indications included cancer, neoplasm, lymphoma, cardiovascular, respiratory and skin diseases. The constructed HDCBP-Drug-Disease network may improve our understanding of complex diseases and related drugs. Moreover, such a network could suggest opportunities of drug repurposing for which efficacy should be investigated in functional validation studies.

Keywords charged biased proteins; diseases; databases; drugs; network; therapeutic targets.

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1 Introduction

Most biological sequences have different sequence compositions. Particularly, these sequences can be compositionally biased (CB) for a subset of residue types. CB regions are sequence stretches that have a large fraction of a small subset of residue types.

In proteins, CB regions are often linked to intrinsic disorder and to cell-structural proteins, fibrous proteins, functional amyloids, prions and a number of inherited neurological diseases in humans (Harbi and Harrison, 2014; Harrison et al., 2003). In addition, many studies have reported a link among disorder and low-complexity regions notably polar or charged repeats (Das et al., 2014; Dosztányi et al., 2006).

The Intrinsically disordered proteins/regions (IDPs/IDRs) are often compositional bias sequences, characterized by long stretches of polar and charged residues. IDPs have been widely studied, showing that

they are often involved in diseases and they are attractive targets for drug development (Choura et al., 2022). Our earlier works revealed that 95% of HDCBPs are associated with multiple diseases, including various cancers and nervous, endocrine, immune, hematological, and respiratory systems diseases (Choura and Rebaï, 2013, 2017, 2019, 2021). Thus, HDCBPs are considered potential drug targets.

Here, we explore the associations between the human disordered charged biased proteins (HDCBPs), the related diseases, and the drugs to build an HDCBP-disease and HDCBP-drug heterogeneous network. Then, we discuss the use of certain HDCBP as therapeutic targets.

2 Methods

2.1 Disease-gene and drug-gene associations

The HDCBP related disease proteins (293 proteins) were downloaded from our earlier works (Choura and Rebaï, 2017, 2019). Among them the highest HDCBPs associated with diseases were selected for further analysis. There were 25 KR proteins and 41 DE proteins (positively and negatively charged respectively).The drug-target data were downloaded from DrugBank and ChEMBL (Wishart et al., 2017; Mendez et al., 2019) using the UniProt mapping tool (The UniProt Consortium, 2021).

2.2 Network construction

The HDCBP-disease and HDCBP-drug networks were built and merged into one network. The network was constructed and visualized by Cytoscape (version 3.5.1).

Cytoscape is an open source software platform for visualizing molecular interaction networks and biological pathways and integrating these networks with annotations. It provides a basic set of features for data integration, analysis, and visualization (Su et al., 2014).

The nodes in the network are diseases and drugs which that are connected if they share a HDCBP.

3 Results

3.1 HDCBP-Drug-Disease network

By integrating different sources including DRUGBANK and ChemDB, it was noticed that 20% (59/290) and 14% (40/290) of HDCBPs are listed in DRUGBANK and ChemDB respectively (Supplementary material: HDCBPs, related drugs and diseases. It contains 2 worksheets: 1) Mapping of all DE and KR proteins to DrugBank and CHEMBL identifiers, and 2) The highest HDCBPs (Top 10), related diseases and drugs). Moreover, the number of DE targets was significantly higher than that of KR targets (29% vs. 5%, Chi-square test, p value < 0.05). The deduced network showing the highest HDCBPs associated with multiple diseases and related drugs is displayed in Fig. 1.

3.2 HDCBP drug targets

We found that some HDCBPs are targeted with more than one drug (Table 1). In addition, a given HDCBP is often involved in multiple diseases.

Among them B-lymphocyte antigen CD19 (CD19), which is associated with many drugs and diseases (Fig. 2).

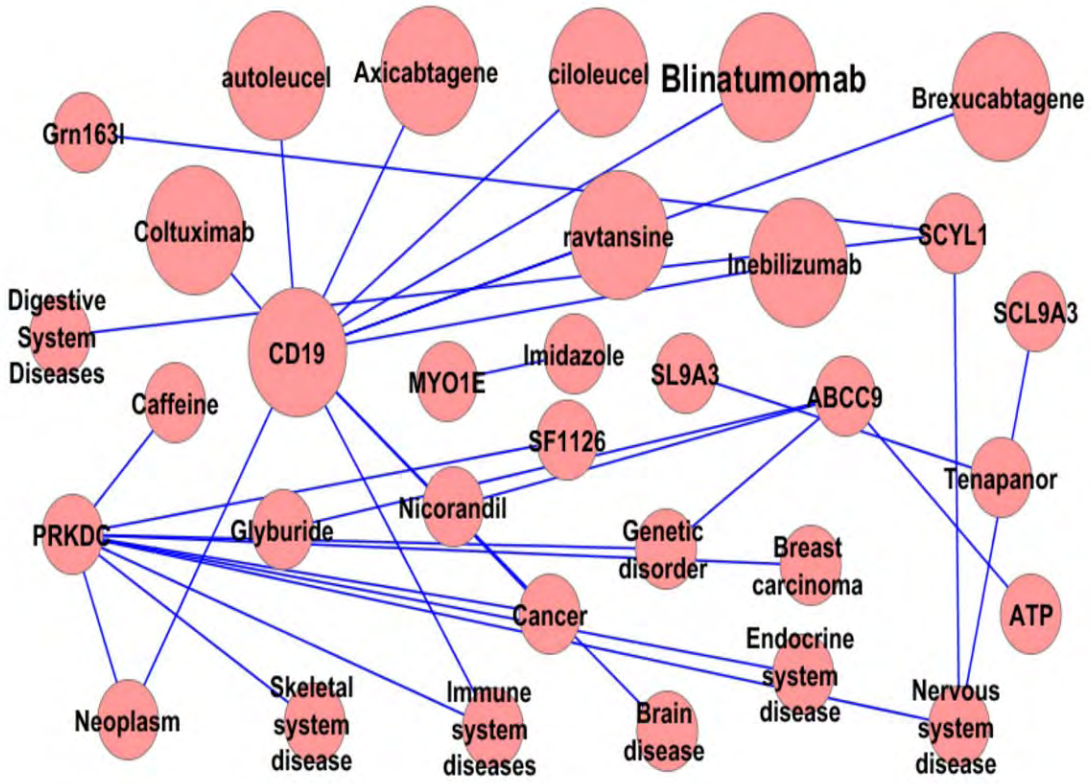

Fig. 1 HDCBP–Drug-Disease network.

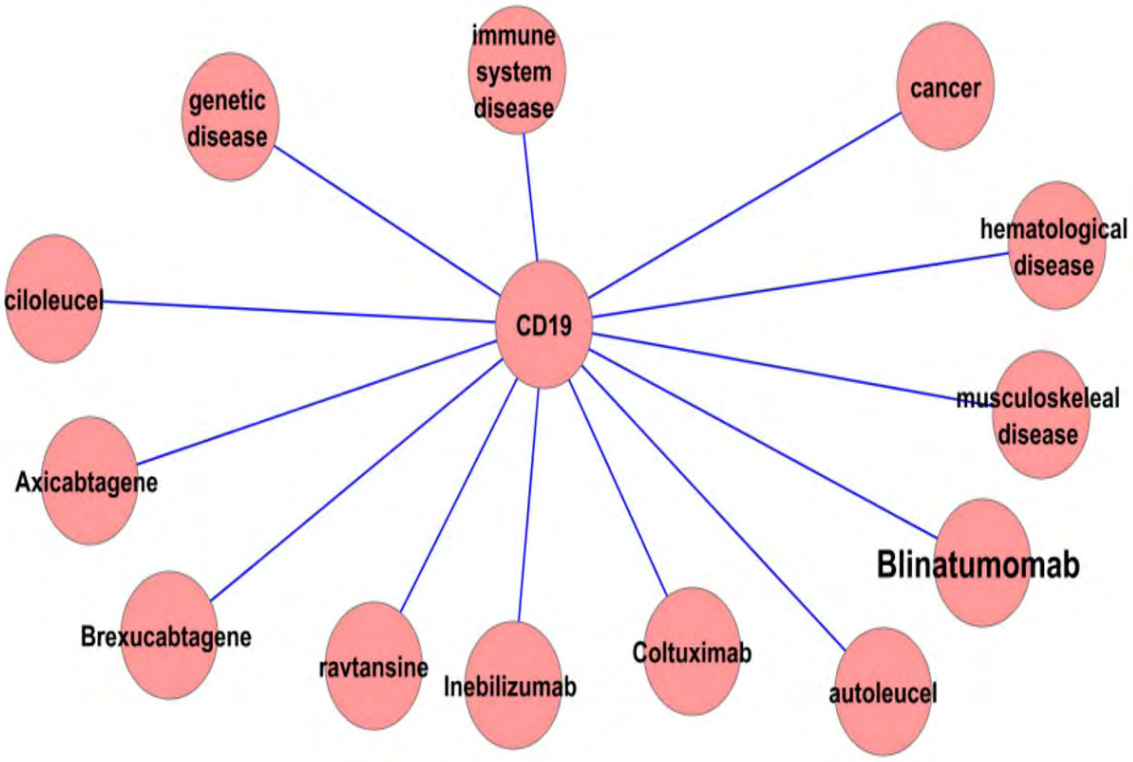

Fig. 2 Network view of associated drugs and diseases with B-lymphocyte antigen CD19 (CD19).

4 Discussion

The objective here is to investigate the association between HDBPs-drugs and diseases. First, we map the HDBPs-drugs subnetwork and merge it with HDBPs-diseases subnetwork previously established (Choura and Rebaï, 2019). The resulted network group HDBPs and related drugs and diseases providing novel drug indications. The analysis using drug target databases shows that 20.35% of HDCBPs are targets of current drugs, while 13, 8% of HDCBPs are predicted as drug targets. In line with the current study, previous analysis showed that 95% of HDCBPs are associated with multiple diseases, including various cancers and nervous, endocrine, immune, hematological, respiratory and skin diseases (Choura and Rebaï, 2019). Moreover, the data show that HDCBPs particularly SCYL1, MYO1E, SL9A3, PRKDC, ABCC9 and CD19 share common diseases and drugs.

Since the drug acts on the same target, it produces different therapeutic effects and could be good target for drug repositioning.

For instance, Inebilizumab is a humanized anti-CD19 cytolytic monoclonal antibody for B-cell depletion in autoimmune conditions. This antibody drug with a maximum clinical trial phase of IV that was first approved in 2020 is indicated for immune system disease and neuromyelitis opticaspectrum disorder (NMOSD) (Frampton et al., 2020). In addition, it has 11 investigational indications notably in multiple sclerosis (Agius et al., 2017).

Another example, in the repositioning of minoxidil which is an adenosine triphosphate-sensitive potassium channel opener, indicated in severe hypertension (Dargie et al., 1977). Also, minoxidilis an effective treatment for hair loss and can be used for hair growth and regeneration (Choi et al., 2018).

5 Conclusion

We explored the association of the HDCBPs with drugs and related diseases. The results show that 20% and 14% of HDCBPs are present in DRUGBANK and ChemDB respectively. The therapeutic areas are mainly cancer, neoplasm, lymphoma, cardiovascular, respiratory and skin diseases. Some examples of HDCBP drug targets have been discussed. Furthermore, the data provided may constitute a promising direction in the development of new drugs and may provide a list of potential drug repositioning candidates for which in-depth studies are needed.

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