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Identification of histone deacetylase10 (HDAC10) protein interaction network and its implications on cancer

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Abstract

Genes mediate and control the cellular pathways but changes in their expression dysregulates its mechanism and cause diseases. So, one of the major challenges in cancer research is the determination and mapping of involvement of molecular pathways. There has been large interest in developing pathway and network analysis to determine driver genes and regulators responsible for the disease. Bioinformatics methods deals big data to explore biologically relevant interactions and pathways.Studies shows that, histone deacetylases (HDACs) exists as biomarkers in cancers. The objective of this study is to investigate the protein-protein interaction (PPI) network and pathways of HDAC10 protein. Using multiple computational approaches, we have systematically analyzed the functional partners of HDAC10 proteins, associated pathways and their biological functions. During the investigation, BioGrid showed 36 hub proteins which are significant and dominant in mediating cellular functions. This observation leads us to evaluate further role of interactors in biological functions using intAct and PANTHER database and show that TXNDC5 is the protein which exhibits highest number of interactions with HDAC10. We also present important signalling pathways for HDAC10 includingp53, mapkas well aswntsignalling which are previously implicated with cancers. These results can further assist in better understanding the widerange of disease mechanism and signalling associated with HDAC10 and the binding affinity studies may help to develop novel therapeutic elements for HDAC10 mediated diseases.

Keywords:*HDAC10, protein-protein interaction, cancer pathways, gene ontology.*

1. Introduction

The complexity of mechanism of cancer and the availability of large datasets have made the necessity of research in pathway studies and approaches. Cancer is a disease which involves the mutations of many genes eventually involves the uncontrolled division of cells. In normal cells, many genes control the cell growth and division process while cells attain the mode of rapid division, invasion and metastasis in cancer. There is a growing interest in the identification of genetic mechanism that contributes to the risk of developing complex diseases. Thus, pathway analysis is an important concept among this which deal mainly the gene ontology (GO) analysis. However, the pathway analysis is more complex and detailed, it needs the complete understanding of association between a set of functional genes and the disease phenotype.

The rapid techniques and advancement of sequencing methods helps the researchers to understand the expression of the genome and proteome level studies. Alternative splicing and single nucleotide polymorphisms (SNPs) studies have significant impact in cancer research. Similarly,

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bioinformatics studies have greater applications to deal various pathways and interactors that confer disease risks and mechanism associated in the genes, even when there is a large data set under consideration.

Pathway databases such as BioGrid(Stark et al. 2006), IntAct(Kerrien et al. 2007), String-DB (Szklarczyk et al. 2017) etc.. aims to identify the genetic network of highly complex diseases, which result from the merging of multiple related genes. Hence, our study mainly focuses on the analysis of HDAC10 protein interaction and their pathways. Its genetic aberration has been associated with progression of various human cancers (Hai et al. 2017; Oehme et al. 2013; Yang et al. 2016). HDAC10 gene is located on 22q13.33 as shown in Figure 1. This paper also aims to describe a method of reassigning functions for HDAC10 based on the available databases by constructing protein interaction networks and GO functions inorder to improve the methodology to detect causal pathways and cancer disease mechanisms.

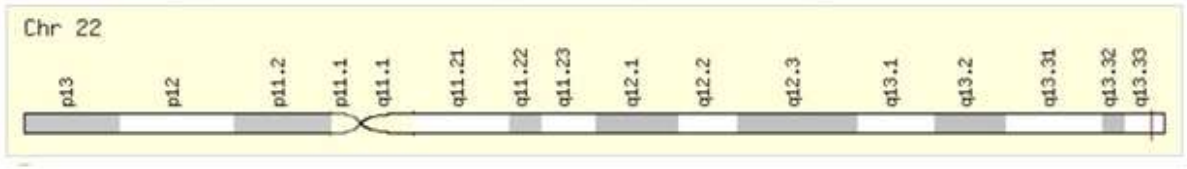

Figure 1: Genomic view of HDAC10 gene, which shows Cytogenetic band: 22q13.33.

2. Materials and methods

2.1 HDAC10 sequence retrieval from UniprotKB

The query sequence of HDAC-10 with the accession id Q969S8 was retrieved from UniprotKB resource. UniprotKB consists of protein sequence data and its related annotations (Apweiler et al. 2004). The complete sequence consists of 669 amino acid residues.

2.2 Interacting proteins of HDAC10 from BioGrid database

To determine the experimentally identified interactors of HDAC10 (human, Q969S8), we have submitted the sequence information to the BioGRID database (Biological General Repository for Interaction Datasets, http://thebiogrid.org/). The list of interactions was interpreted for further gene ontology studies.

2.3 Mapping the biochemical interaction pathways of HDAC10 using IntAct database

Inorder to determine the interactions maps and pathways, the query protein HDAC10 (human, Q969S8), was submitted to IntAct Molecular Interaction database (https://www.ebi.ac.uk/intact/).IntAct is an open source java-based database and toolkit which provides the interactions of a user entered protein. All interactions in IntAct are derived from literature data or the submission from individual researchers (Hermjakob et al. 2004).

2.4 Determination of HDAC10 protein families and subfamilies based on function using PANTHER

In order to select HDAC10 protein families and subfamilies on divergence of function, we analysed the interactor proteins using PANTHER (Protein ANalysis THrough Evolutionary Relationships), which is available at http://www.pantherdb.org. This webpage allows the user to enter gene ids for functional classification and statistical analysis. Clicking the 'Submit' button displays the result. A detailed summary of gene list is also displayed for further selection and analysis by users.

3. Results and discussion

3.1 HDAC10 interactors from BioGrid

The BioGrid database was queried for HDAC10 (human, Q969S8) and protein-protein interactions were retrieved. The results reveal a set of curated genetic and protein interactions as shown in Figure 2. The figure visualized the associated interactions using an embedded interactive network viewer and retrieved the image. BioGRID curates the biomedical literature for major model organism species, including humans, emphasis on biological processes and human diseases (Chatr-aryamontri et al. 2017). The interaction network shows 36 hub genes which have 43 physical interactions (23 and 20 low throughput studies) through these interacting genes. We noticed a specific drug-target interaction of a chemical compound namely panobinostat which is used to treat HDAC10 mediated diseases.

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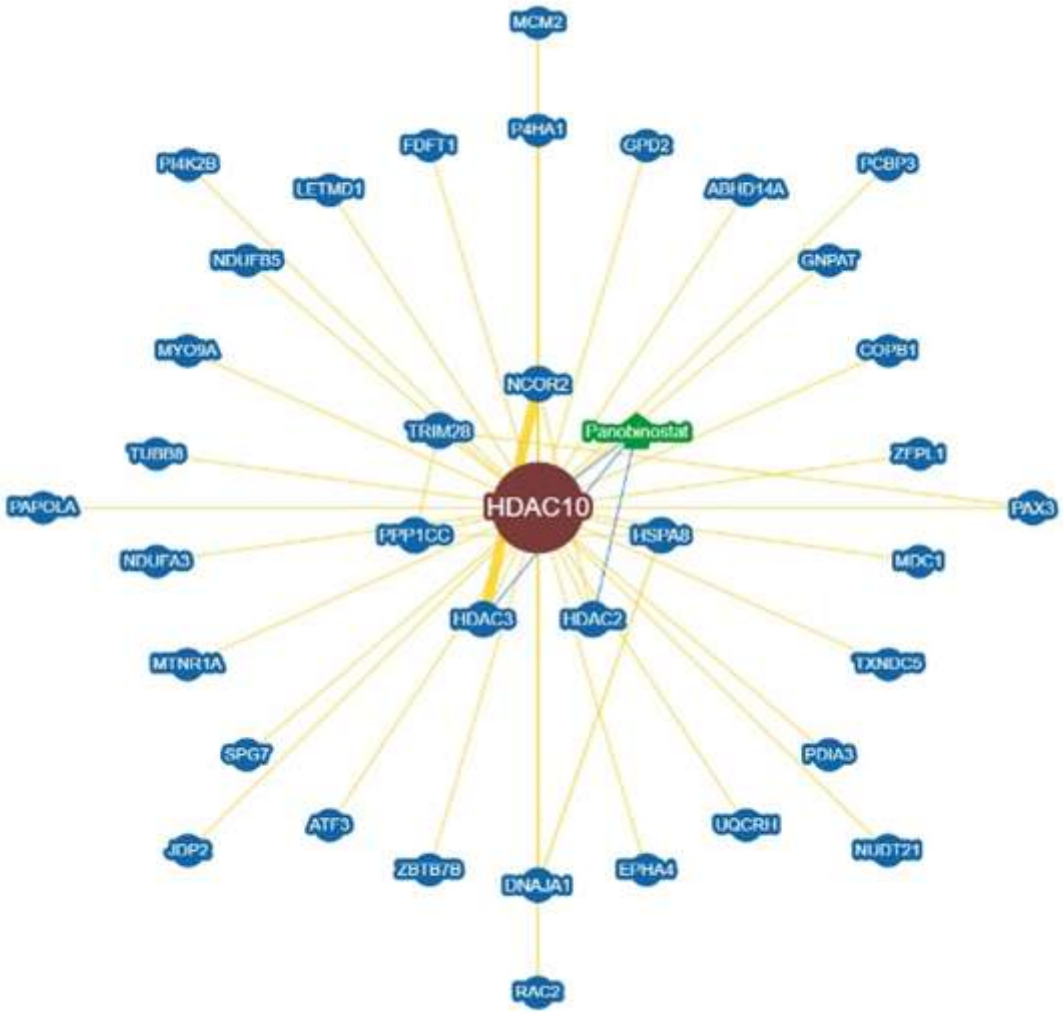

Figure2: HDAC10 interacting proteins were determined using BioGrid shows 36 hub genes as interactors with 43 interactions.

Thus, it is confirming that, protein interaction studies also enable researchers to carry out drug–target interaction.

From the GO point of view, the results categorised into three aspects such as GO process, GO function and GO component as shown in Table 1. We have analysed GO features and Notch signalling was found to be the prominent pathway involved in interaction. Further, we investigated the molecular interactions between the interactors. Interactors share many of the structural features such as enzyme binding, protein binding including histone deacetylase activity that mediates chromatin modification, regulation of transcription etc. plus, highly conserved domains that mediate interactions .

with cytoplasmic and signalling proteins indicating that the activation of HDAC10 regulates its interaction with many intra and inter cellular proteins. GO molecular components results shows that, these enzymes are located in cytoplasm, nucleoplasm, and nucleus. Ubiquitination is an important point of regulation found in the signaling pathways. It is therefore possible that ubiquitination regulates HDAC10 activity. Studies shows that, HDACs express in specific tissues and organs in the organism and plays a crucial role in development and differentiation processes (Maribel 2014). Our study reconstructed known GO term assignments with high precision and putative GO assignments for HDAC10 protein which provides evidence of its novel protein associations.

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Table 1: Implications of GO features of HDAC10 obtained from BioGrid

GO biological process	GO molecular function	GO molecular component
• Notch Signaling Pathway • Chromatin Modification • Histone Deacetylation • Negative Regulation of Transcription from RNA Polymerase II Promoter • Negative Regulation of Transcription, DNA-Templated • Protein Deacetylation • Regulation of Transcription, DNA-Templated	• Enzyme binding • Histone deacetylase activity • Histone deacetylase binding • Protein binding • Protein deacetylase activity	• Cytoplasm • Histone Deacetylase Complex • Nucleoplasm • Nucleus

3.2 HDAC10 interactors from IntAct and functional analysis using PANTHER

The IntAct analysis revealed interactions with 11 proteins associated with HDAC10 and TXNDC5 shows the highest number with 98 protein interactions as shown in Table 2. TXNDC5 (Thioredoxin Domain Containing 5) is a gene that have isomerase and protein disulphide isomerase activity (Galligan and Petersen 2012). Studies shows that thioredoxin interacting protein (TXNIP) is regulated by HDAC10 protein, a class II member (Lee et al. 2010). The identified HDAC10 protein interaction network is found to be predominantly expressed with thioredoxin protein enriched for pathways involved in gene regulation process. Based on the gene function prediction using homology, protein families and subfamilies are annotated with ontology terms. In PANTHER, each subfamily is associated with ontology terms that describe the functions of its constituent proteins with components in biochemical pathways (Mi et al. 2016). Detailed information about the enriched GO terms and pathway details are explained in Table 2 and Figure 3.

For each set of interactions, the number of experiment information is indicated, and a link allows the viewing of its biological functions. The annotations and biological function details can be displayed in different format either charts or html text page. From our study, a set of biological functions were displayed as graphical view as PIE chart (Figure 3).

Table 2: Interactors of HDAC10 obtained from intAct and PANTHER

S.No	Interacting gene	Interaction AC in EBI	Number of interactors from PANTHER
1.	HDAC3	EBI-297792	21
2.	HDAC2	EBI-297477	31
3.	NCOR2	EBI-297505	21
4.	MTNR1A	EBI-11576993**imex** : IM-24624-118	17
5.	P4HA1	EBI-6598258**imex** : IM-18733-10	15
6.	RAC2	EBI-6598258**imex** : IM-18733-10	74
7.	PDIA3	EBI-6598258**imex** : IM-18733-10	38
8.	DNAJA1	EBI-6598258**imex** : IM-18733-10	25
9.	FDFT1	EBI-6598258**imex** : IM-18733-10	96
10.	COPB1	EBI-6598258**imex** : IM-18733-10	57
11	TXNDC5	EBI-6598258**imex** : IM-18733-10	98

We checked annotations of all interacting proteins that changed in their expression and mechanism of action and located them in PANTHER. This database involves a set of biological interactions of which most of them have revealed the nature of protein coding genes and binding affinity data. Of these enriched GO terms, four important and prominent pathways were determined as binding partners with HDAC10 such as p53 pathway, mapk pathway and wntsignalling pathway. P53 is a nuclear transcription factor and more than 50 % of cancers have loss of p53 gene function (Ozaki and Nakagawara 2011) and mitogen-activated protein kinase (MAPK) pathways are very common in cancers (Dhillon et al. 2007). Wntsignalling is one of prominent pathway which affects maintenance of cancer stem cells, metastasis and immune control (Zhan, Rindtorff, and Boutros 2016). Our analysis and results suggest that, the association of HDAC10 serves as a key regulator in cancer mechanism and ubiquitination is the of the major PTM modifications leads to cancers. Further studies are required for a comprehensive understanding of the molecular mechanisms that involves the complexity of HDAC10 mediated cancers.

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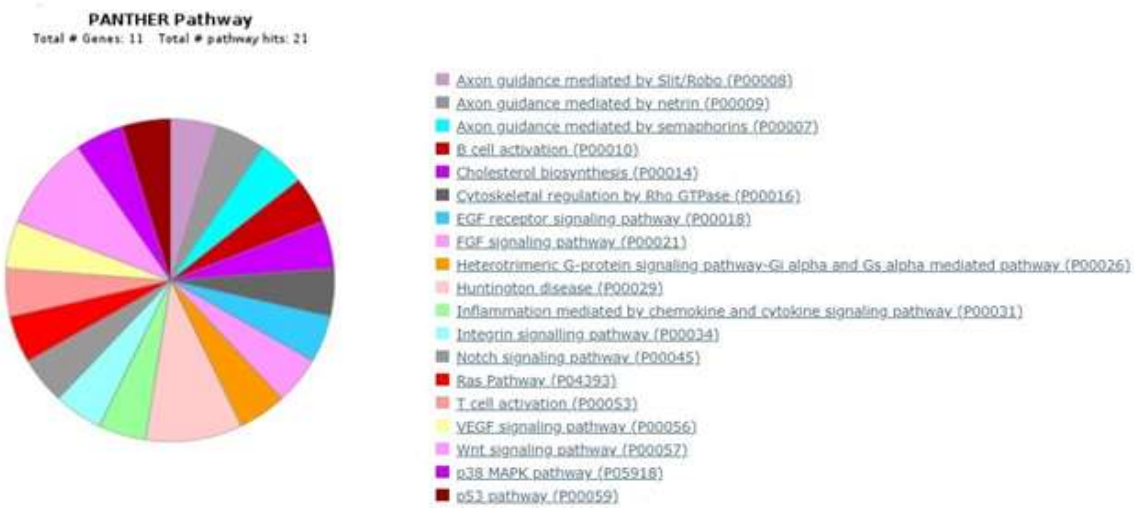

Figure 3: PIE chart representation of biological process annotations of HDAC10 protein based on PANTHER database. Different categories in color shows biological process of gene and pathway hits.

4. Conclusion

In this study, the networks and pathways of HDAC10 have explored using two bioinformatics databases. also, an attempt has been made to overview the various pathways in HDAC10 protein. In our analysis, the number of the mapped protein interactions obtained for HDAC10 were higher than those in the literature-based database. BioGrid and IntAct provided satisfactory details of HDAC10 target interactions and its biological pathways with a user-friendly graphics. We identified thioredoxin protein shows the highest number of 98 interactions with HDAC10. PANTHER analysis reassigns the biological information and confirms that cellular signalling pathways have direct implications in cancer progression. In addition, we considered this study may provide a prototype for reassigning the biological function of the important biological targets and determining the protein protein interactions. We anticipate that, the analysis of pathway and target interactions can provide important clues to improve the process of drug design and development.

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Conflict of interest

None

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