A Systems Biology Driven Approach to Map the EP300 Interactors Using Comprehensive Protein Interaction Network

Shivananda Kandagalla[1(✉)], Maria Grishina[1], Vladimir Potemkin[1(✉)], Sharath Belenahalli Shekarappa[2], and Pavan Gollapalli[3]

[1] Laboratory of Computational Modeling of Drugs, Higher Medical and Biological School, South Ural State University, Chelyabinsk 454080, Russia
kandagallas@gmail.com, potemkinva@susu.ru

[2] Department of PG Studies and Research in Biotechnology and Bioinformatics, Kuvempu University, JnanaSahyadri, Shankaraghatta, Shivamogga 577451, Karnataka, India

[3] Central Research Lab, K.S. Medical Academy, Nitte University (Deemed To Be University), Deralakatte, Mangalore 575018, Karnataka, India

Abstract. EP300 is one of the putative tumor-suppressor genes and is mutated/deleted, under expressed/overexpressed in several types of cancer. The role of EP300 and its interactions during cancer is crucial to explore its reprogramming events that lead to malignant phenotype and acquisition of drug resistance. In this context, all the experimentally valid EP300 interactors were collected from the primary protein-protein interaction (PPI) databases and followed by tracing their subcellular location using the UniProtKB database. Further, all the EP300 interactors were categorized based on their subcellular location and functionally annotated with the DAVID gene ontology tool. Subsequently, the interactome of EP300 with its interactors was constructed and identified TP53, CREBBP, JUN, HDAC1, CTNNB1, MYC, PCNA, HDAC2, FOS, and KAT2B as the top first neighbors of EP300. Together, the present analysis gives a comprehensive overview on EP300 interactors located in different subcellular locations.

Keywords: EP300 · Interactome · Cytoscape

1 Introduction

EP300(p300) is a ubiquitously expressed transcriptional coactivator and a member of the EP300/CBP family of type 3 major lysine (K) acetyltransferases (KAT3), present in all mammals and found in many multicellular organisms, such as flies, worms, and plants. In humans, 31 exons in chromosome 22 (locus 22q13) codes for the p300 gene, and gene size spans approximately 90 kb. Overexpression and inappropriate activation of EP300 are associated with malignancy, tumor size, poor differentiation, tumor progression, and poor prognosis [1–3]. Increased expression of EP300 has been observed in advanced human malignancies, such as liver, prostate cancers, primary human breast cancers, etc., [4].Recent reports highlight EP300 as a central regulator of angiogenesis, hypoxia,

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and EMT pathway in esophageal squamous carcinoma [5]. The increased expression of cancer stem cell markers, tumorsphere formation was observed in EP300-depleted cells and diminished in EP300-overexpressing cells [6]. Apart from cancer, EP300 is a key player in Rubinstein − Taybi syndrome (RTS or RSTS) disease [7].

EP300 shares high sequence homology with CBP (CREBBR or KAT3A), and less with other acetyltransferases [8]. Both proteins have almost 86% amino acid residue identity in the catalytic domain and significant sequence homology was found in several types of protein-protein interacting motifs, and other non-catalytic domains [9]. In EP300, the acetyltransferase domain spans from residues 1284 to 1673, and IBiD (Interferon Binding Domain) located at the C-terminal side. The IBiD contains an NCBD (Nuclear Coactivator Binding Domain) and glutamine-rich domain, followed by a proline-containing PxP motif. There are three cysteine/histidine-rich domains (C/H) like C/H1, C/H2 (which is part of the catalytic domain), and C/H3. The C/H1 and C/H3 domains contain transcriptional adaptor zinc fingers (TAZ1 and TAZ2), and additionally, C/H3 domain contains a ZZ zinc finger. The C/H2 domain contains a plant homeodomain (PHD) and the domains such as interferon binding homology domain (IHD), KIX domain, and bromodomain is located between the C/H1 and C/H2 domains [10, 11].

EP300 functions as acetyltransferase by facilitating transcription through acetylation of histones, transcription factors, sequence-specific DNA binding factors, and basal transcriptional machinery. During intracellular or extracellular signaling the cell must turn different subsets of genes to regulate different cellular functions accomplished by acetylation of histone proteins during transcription. Most of the cellular signaling pathway such as cAMP signaling pathway, HIF-1 signaling pathway, FoxO signaling pathway, cell cycle, Wnt signaling pathway, Notch signaling pathway, TGF-beta signaling pathway, adherens junction signaling, Jak-STAT signaling pathway, DNA damage pathways, and other pathways use EP300 as downstream effector protein [12, 13]. EP300 responds to those signaling pathways differently, which mainly depends on the cell environment and its phosphorylation state. Various proteins such as PKC, cyclin E/CDK-2, CaMKIV, IKK, and AKT phosphorylate EP300 at different sites which ultimately impact on its acetyltransferase activity. Along with, self-modification (auto-acetylation) of EP300 also influences on the acetyltransferase activity. EP300 contain methylation sites near the KIX domain and lysine SUMOylation site near the bromodomain. EP300 also has acetylation site (17 lysine residues) in the regulatory loop of acetyltransferase domain and their acetylation is essential for its acetyltransferase activity, and for binding with other proteins. In addition, EP300 through protein interacting domains binds to the different proteins and thereby it regulates wide variety of signaling pathways [14, 15]. All these reports clearly show that EP300 regulates signaling pathways by interacting with multiple proteins and targeting these interactions during disease conditions could be a good solution. In this concern, all the experimentally valid datasets of EP300 interactors were collected from primary protein interaction databases, followed by tracing their subcellular locations and functional annotations. Finally, the interactome of EP300 with its interactors was developed and first-degree interactors were identified.

2 Materials and Method

2.1 Collection of EP300 Interactors

The experimentally detected proteins having the interaction with EP300 were extracted from the public databases such as, IntAct [16], BioGRID [17], APID [18], PINA [19], Mentha [20], HitPredict [21], WiKi-Pi [22], PIPs [23], PPI-finder [24] and PrePPI [25]. Non-human interactors of EP300 were excluded from the study. Using the UniProt Knowledge base (UniProtKB) Id mapping, the gene symbols and protein symbols were identified [26].

2.2 Protein Class and Subcellular Location Analysis

The subcellular location of EP300 interactors was explored using the UniProtKB database based on the record "Subcellular location". UniProtKB database act as a central hub in identifying functional information of proteins with accurate annotations, and also it includes widely accepted biological ontologies, classifications and cross-references, and clear indications of the quality of annotation in the form of evidence attribution of experimental and computational data (https://www.uniprot.org/help/uniprotkb). The PANTHER classification system was used to identify the protein classes of EP300 interactors. The PANTHER (Protein Analysis THrough Evolutionary Relationships) database contains comprehensive information on the evolution and function of protein-coding genes from 104 completely sequenced genomes. PANTHER classification tools allow users to classify new protein sequences and to analyze gene lists obtained from large scale genomics experiments [27, 28].

2.3 Functional Annotation and Pathway Enrichment Analysis

The EP300 interactors located in the different subcellular location were functionally annotated with gene ontology (GO) terms in the PANTHER database and the pathway enrichment analysis was performed in the DAVID database (The Database for Annotation, Visualization, and Integrated Discovery) against PANTHER and KEGG pathways with a p-value < 0.05 [29].

2.4 Construction of EP300 Interactome

The primary protein interaction data of EP300 interactors were extracted from STRING database v10.5 [31] with a high confidence score of 0.9. The interactions in the STRING database are derived from different sources: text mining, experiments, co-expression, neighborhood, gene fusion, and co-occurrence. The high confidence interaction of score above 0.9 indicates, all the interactions are validated in all the above-mentioned sources. The low confidence (score 0.7) interactions were considered for N4BP2, MSTO1, MYB, HOXD10, and KLF16 interactors. The interactome of EP300 with its interactors was constructed using Cytoscape 3.4.0 [30] based on the subcellular location and the first-degree interactors of EP300 were identified from the core interactome.

3 Results and Discussion

A total of 854 predicted or experimentally validated EP300 interactors were obtained from public databases as illustrated in the methods section. The predicted EP300 interactors in many of the above primary databases are mainly from indirect clues such as data mining, Bayesian prediction, structural information, and more information can be found in [32]. It is difficult to maintain the accuracy of predicted results from the indirect clue and Zhang QC et al. [25] reported that the interactions from indirect methods are often more indicative of functional associations between two proteins than of direct physical interactions. Hence, the interactors only with experimental evidence were selected to maintain accuracy and other computational predictions without experimental validations were excluded for the analysis. A total of 540 EP300 interactors were included for further analysis and a complete list is provided in the supplementary file [37].

3.1 Analysis of Subcellular Location and Protein Class

The subcellular location analysis shows that EP300 interactors were located in different cell locations, and further based on location we categorized EP300 interactors into three broad classes: (i) cytoplasm; (ii) nucleus; (iii) both in cytoplasm and nucleus. Among 540 EP300 interactors, 202 interactors present in both cytoplasm and nucleus, 72 interactors present in the cytoplasm, 263 interactors in the nucleus, and the remaining interactors subcellular location is not available in the UniprotKB database (excluded for further analysis). Cytoplasm location includes apical cell membrane, cell membrane, cytoskeleton, focal adhesion, mitochondrion outer mem-brane, etc., and nucleus location is found to include chromosome, centromere, nucleus matrix, PML body, etc. Further analysis of the protein class of these EP300 interactors shows that they are mainly associated with the protein class nucleic acid binding and transcription factors. Other enriched top protein classes are transferase, hydrolase, enzyme modulator, receptor, etc., are shown in subsequent figures (Fig. 1D; 2D; 3D). All these results give a comprehensive overview of EP300 interactors protein classes and their subcellular locations.

3.2 Functional Enrichment Analysis of EP300 Interactors

The functional enrichment analysis of EP300 interactors present in the different subcellular locations was done separately. The analysis shows that EP300 interactors present in the cytoplasm enriched in various biological and molecular functions. As shown in Fig. 1A, the interactors present in the cytoplasm are mainly participating in response to the extracellular stimulus, positive regulation of apoptosis, positive regulation of programmed cell death, positive regulation of cell death, and regulation of apoptosis. Further, these EP300 interactors are mainly enriched in the molecular function of ribonucleotide binding, nucleoside binding, and ATP binding process (Fig. 1B). The EP300 interactors present in the nucleus mainly participate in the regulation of transcription, regulation of transcription (DNA-dependent), regulation of transcription from RNA polymerase II promoter, and regulation of RNA metabolic process(Fig. 2A). DNA binding, transcription regulator activity, and transcription factor activity are the top enriched GO molecular function are shown in Fig. 2B.

Finally, the analysis of EP300 interactors present in both cytoplasm and nucleus revealed that most of the interactors are participate in the regulation of transcription, positive regulation of macromolecule metabolic process, and regulation of RNA metabolic process (Fig. 3B). The transcriptional regulator activity, transcription factor binding, transcriptional activator activity, and transcription factor activity are the top enriched molecular function (Fig. 3B). Together, this analysis provides the functional significance of EP300 interactors present in the different subcellular locations. Interactors present in the cytoplasm were mainly involved in the biological process such as extracellular stimulus, positive regulation of apoptosis, positive regulation of programmed cell death, positive regulation of cell death, etc. Whereas interactors present in both cytoplasm and nucleus were engaged in almost similar biological processes.

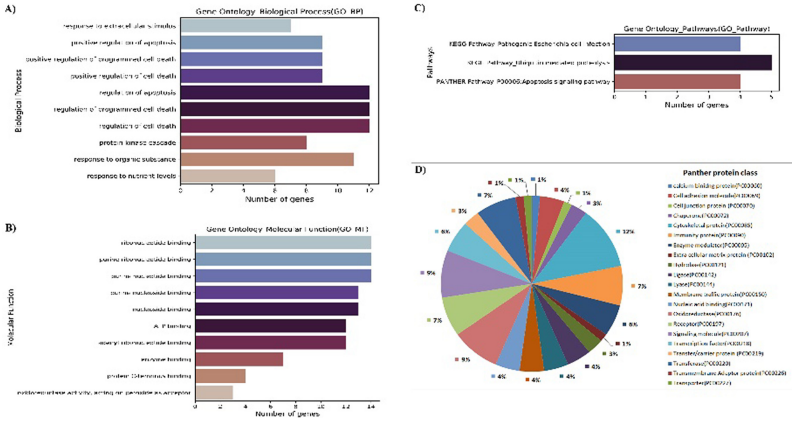

Fig. 1. Functional enrichment of EP300 interactors present in the Cytoplasm: Top annotated EP300 interactors involved in A) Biological Process, B) Molecular function, C) Pathways (KEGG and PANTHER), D) PANTHER protein class.

3.3 Pathway Enrichment Analysis of EP300 Interactors

The EP300 interactors present in the cytoplasm were enriched during pathogenic Escherichia coli infection and ubiquitin-mediated proteolysis based on KEGG pathway analysis. The PANTHER pathway results suggest that EP300 interactors are mainly associated with the apoptosis signaling pathway (Fig. 1C). The EP300 interactors present in nucleus were enriched in the cell cycle, DNA replication in KEGG pathways and the p53, p53 pathway feedback loop 2, oxidative response, and Wnt signaling are the top PANTHER enriched pathways (Fig. 2C).

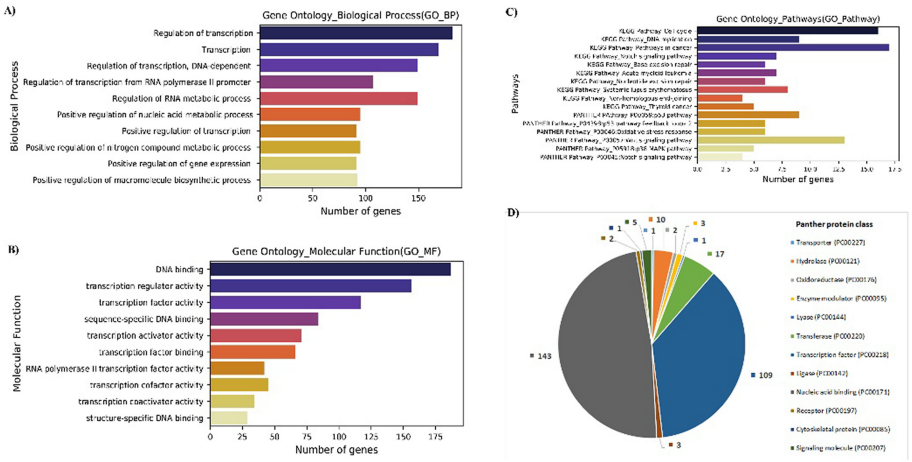

Fig. 2. Functional enrichment of EP300 interactors present in the Nucleus: Top annotated EP300 interactors involved in A) Biological Process, B) Molecular function, C) Pathways (KEGG and PANTHER), D) PANTHER protein class.

Finally, EP300 interactors present in both cytoplasm and nucleus are enriched during pathways in cancer, chronic myeloid leukemia, prostate cancer, acute myeloid leukemia, pancreatic cancer, cell cycle, and ErbB signaling pathway are among the top enriched KEGG pathways. The PDGF signaling pathway, JAK/STAT signaling pathway, B cell activation, T cell activation, p53 pathway, EGF receptor signaling pathway, p53 pathway feedback loops 2 and TGF-beta signaling pathway are among the top enriched PANTHER pathways (Fig. 3C). Collectively these analysis provides the details on EP300 interactors associated pathways. From the results, it can be seen that apart from normal pathways, EP300 interactors also enriched in associated disease related pathways such as cancer, infection, etc. Further analysis of EP300 interactors associated with disease related pathways gives broad insights on the role of EP300 and also, it provides a new avenue in developing new drugs.

3.4 EP300 Interactome and Identification of First-Degree Nodes

The interactome of EP300 with its interactors was constructed to check the influence of EP300 based on the analysis of the first-degree nodes. First, the network of EP300 interactors present in the nucleus was constructed and the network consists of 1165 nodes and 6046 edges (Fig. 4A). Further first-degree nodes of EP300 were identified and these nodes have direct contact with EP300 and any alteration in these nodes changes the signaling pattern. A total of 135 nodes form the direct connection with EP300 and the top nodes based on the degree are TP53, CREBBP, HIST2H2BE, HDAC1, JUN, HIST2H2AC, H2AFZ, and MYC. Next, interactome of EP300 interactors present in the cytoplasm were constructed and the network has 635 nodes with 2331 edges (Fig. 4A). Further identified first-degree nodes of the EP300 in the network and with 18 nodes

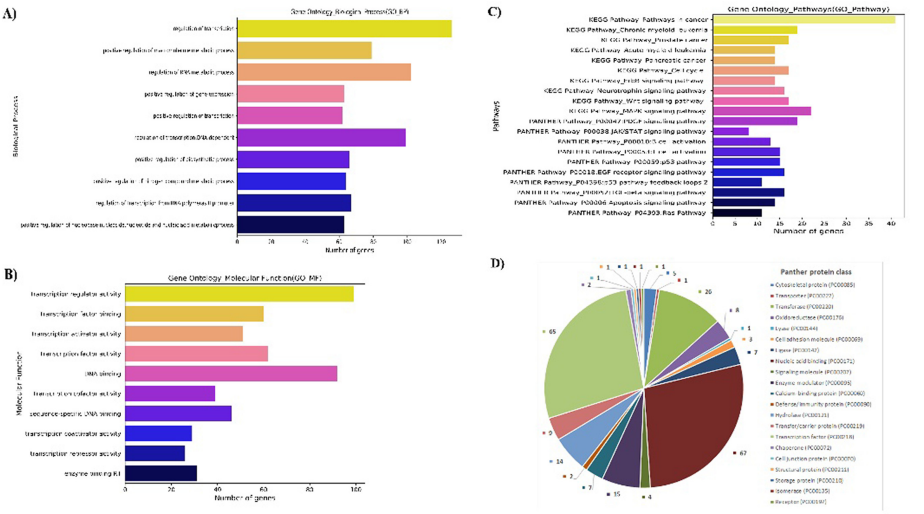

Fig. 3. Functional enrichment of EP300 interactors present in the both Cytoplasm and Nucleus: Top annotated EP300 interactors involved in A) Biological Process, B) Molecular function, C) Pathways (KEGG and PANTHER), D) PANTHER protein class.

EP300 has a direct connection. The UBA52, NR3C1, GRIP1, SREBF1, and JUN are the top nodes based on the degree. Further, the network of EP300 interactors present in the cytoplasm and nucleus were constructed and the network has 1214 nodes with 5443 edges (Fig. 4A). Total 89 nodes have a direct connection with EP300 and among TP53, JUN, AKT1, CREBBP, HDAC2, HDAC1, and MYC are top nodes based on degree (complete list is provided in the supplementary file [37]).

Altogether, the final interactome consists of 2388 nodes with 12577 edges. Among 2388 nodes Ep300 form the direct interaction with only 186 nodes (Fig. 4C) and among TP53, CREBBP, JUN, HDAC1, CTNNB1, MYC, PCNA, HDAC2, FOS and KAT2B are the top interactors. Previously several reports show the significance of EP300 interactions with TP53, CREBBP, JUN, CTNNB1, and MYC in several pathophysiological conditions [33–36], and still, their role is not clearly understood. Further, *in vitro* validation of these interactors is required to understand the role of EP300 in different cancer conditions and which ultimately helps in developing the novel inhibitor also, these interactors act as potential biomarkers.

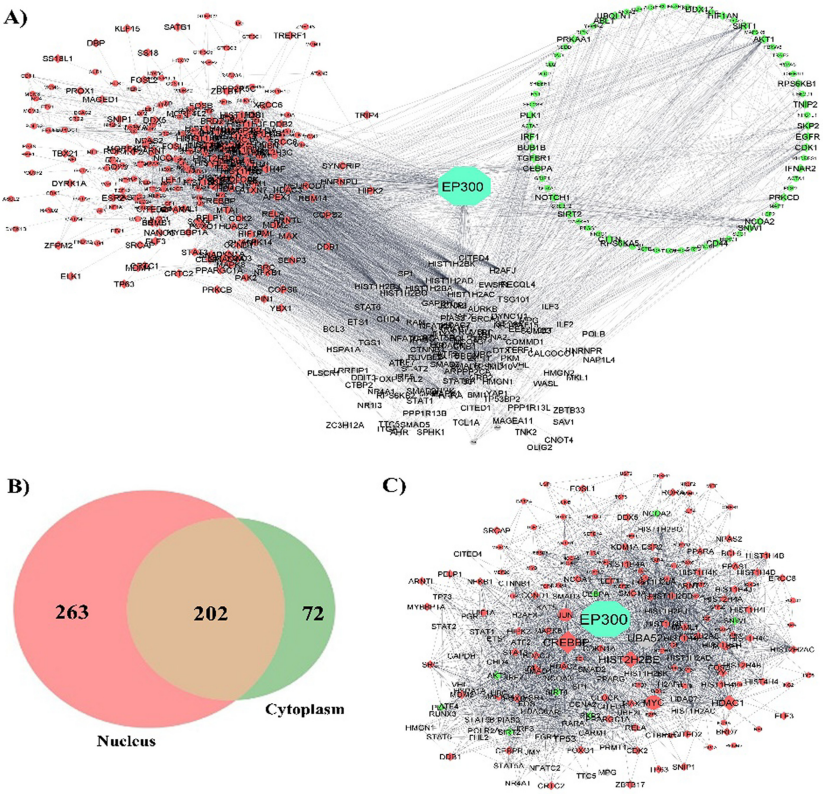

Fig. 4. Interactome of EP300 with it interactors, A) The PPI network of EP300 interactors present in nucleus are colored in red, green nodes corresponds to cytoplasm, and grey node corresponds to both nucleus and cytoplasm. B) Venn diagram showing number of EP300 interacting partners present in different subcellular location. C) First neighbors of EP300 in the interactome.

4 Conclusion

The evaluation of EP300 interactors present in different subcellular locations provides a broad sense to the role of EP300 in complex disease or cellular events. The functional and pathways enrichment analysis of EP300 interactors clearly shows their involvement in several pathological conditions and mainly in cancer. Among the EP300 interactors, TP53, CREBBP, JUN, HDAC1, CTNNB1, MYC, PCNA, HDAC2, FOS, and KAT2B are the top first-degree nodes, and these interactors are the key players with which EP300 interact and perform its functions. Further, *in vitro* validation of these interactors with EP300 is required in different cancer conditions. Altogether, the present analysis gives the complete overview on EP300 interactors presents different subcellular locations.

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Conflict of Interest. All authors declared that they have no competing interest.

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