A Network Biology Approach to Investigating Multiple Drug Resistance (MDR)

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Abstract

Cancer is one of the leading causes of death worldwide in the 21st century. Several therapeutic strategies, including chemotherapy, radiotherapy, and immunotherapy, have been developed for cancer treatment. However, one of the major causes of treatment failure is the development of multiple drug resistance (MDR). Several mechanisms have been implicated in MDR, including alterations in metabolic pathways, overexpression of ATP-binding cassette (ABC) transporters, and other molecular alterations.

In this study, we analyzed microarray datasets comparing drug-resistant cancer cells with drug-sensitive counterparts to identify differentially expressed genes (DEGs). Protein–protein interaction (PPI) networks were subsequently constructed and analyzed using the STRING database. Based on topological network parameters, ten hub genes were identified, and their associated biological pathways were investigated using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. Finally, Venn diagram analysis was performed to identify common upregulated and downregulated genes across the analyzed datasets that may represent potential therapeutic targets.

Our analysis revealed that ABCB1, a key transporter involved in MDR, interacts with several genes, including FN1, MMP2, KDR, and members of the SLC gene family. Furthermore, P3H2, RPH3AL, NCF1, and NCF2 were consistently identified as commonly upregulated genes across the three analyzed datasets. These findings provide insights into the molecular mechanisms underlying MDR and may contribute to the identification of potential biomarkers and therapeutic targets for overcoming drug resistance in cancer.

Keywords: Multiple drug resistance (MDR); Network biology; Protein–protein interaction (PPI); Differentially expressed genes (DEGs); Hub genes; ABCB1; Bioinformatics

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Introduction

Cancer is second cause of death in developed and developing countries (Ferlay *et al*., 2021). There are several approaches toward the cancer treatment, like radiotherapy, immunotherapy, and chemotherapy. One of the reasons for failure of treatments is multiple drug resistance (MDR). MDR can be inherent or acquired. There are many factors to make a sensitive cancer cell to resistant one. Overexpression of MDR genes, cellular reprograming, oncogenic and metabolic change, or combination of these mechanisms (Baguley, 2010). Upregulation of ABC transporters is responsible for many types of resistance cells. Overexpression of ABC transporters leads to efflux of drug out of cell. So, concentration of chemotherapeutics doesn't reach to pharmacologic level to kill carcinogenic cells (Dean *et al*., 2001). About 48 ABC transporter identified in human. They can be found in liver, pancreas, kidney, blood brain barrier, gastrointestinal tract, and etc. The major subtype of them is ABCB1 (p-glycoprotein), ABCC1 (MRP1), ABCG2 (BCRP). In physiological condition ABC transporters are responsible to remove xenobiotic and toxic endogen compounds from cells, and maintain the hemostasis. P-gp play a crucial role in cell permeability (Begicevic and Falasca, 2017). One way to conquer drug resistance is design a specific inhibitors of ABC transporters like Tariquidar (Fox and Bates, 2007). But in chemotherapy condition inhibition of these transporters increases side effects of toxic anticancer agents because most antineoplastic drugs have a low molecular weight and require a high concentration to be effective (Vaidya *et al*., 2022).

Another way to become resistance is change in metabolism pathways. Many chemotherapeutic agents became active or inactive in metabolic ways like (cyp450), and (Glutathione 5 Transferase). Change in regulation or mutation of these enzymes can lead to drug resistance. Overexpression of anti-apoptosis genes like Bcl2 is another way to become resist to chemotherapy (Portt *et al*., 2011).

The aim of this study is to identify hub gene in resistant cancer cells as a potential biomarker and new target for cancer and adjuvant treatment. We used three microarray datasets that were downloaded from GEO database (https://www.ncbi.nlm.nih.gov/geo) to find differentially expressed gene (DEGs). Then we used $STRING_{v.12}$ software (Mering *et al*., 2003) to find protein-protein interaction (PPI). By further analysis we selected 10 hub genes in each dataset. Kyoto Encyclopedia of Genes and Genomes (KEEG) used to analysis of signaling pathways of them. By Venn diagram, we found common genes in databases.

Material and method

All dataset that was on GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array platform and compare a sensitive human cancer cell by drug resistant one. GSE119087 (which compared gene expression in

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vincristine-sensitive parental ovarian tumor cell line with resistant one) (Dabydeen *et al*., 2019), GSE24460 (Parental MCF-7 cell line versus Doxorubicin Resistant MCF-7 ones) (Calcagno *et al*., 2010), GSM7732765 (which reports mRNA profiles of human breast cancer cell lines, MCF7 parental, and MCF7-derived tamoxifen resistant cell lines (Ahn *et al*., 2024))datasets were used for this study. Cell files downloaded from GEO (https://www.ncbi.nlm.nih.gov/geo).

We used R software 4.0.1 and Bioconductor package (Gentleman *et al*., 2004) for analysis of downloaded CELL file. We used Affy package in Bioconductor to read CELL file. Simpleaffy (Wilson and Miller, 2005) was used to quality assessment. The Limma (Ritchie *et al*., 2015) package in Bioconductor was used for differential expression analysis. MAS.5 (Pepper *et al*., 2007)method was utilized for quintile normalization of data. Gene annotated using hgu133plus2.db in Bioconductor package. The P.value was set less than 0.1 in comparison between down-regulated and up-regulate genes. Then about 150 most down-regulated and up-regulated genes selected to obtain protein-protein interaction (PPI) network by $STRING_{v.12}$ software (Mering *et al*., 2003). Minimum interaction score set 0.4 to predict PPI network. Then interaction network analyzed by $Cytoscape_{v3.10.1}$ and $Gephi_{v0.10}$ software. Subsequently by CytoHubb plugin in $Cytoscape_{v3.10.1}$ 10 most hub-genes selected based on degree, closeness and betweenness, in order to explore their biological pathway in KEGG (https://www.genome.jp/kegg) database. Then Venn diagram used to obtain common genes in three datasets (GSE119087, GSM7732765, GSE24460). Identification of potential biomarker has been done by literature review.

Results

Protein-protein interaction network.

Figures 1 and 2 shows PPI network in up-regulated and down-regulated in GSE119087. In up-regulated PPI network MMP-9 is shown to be a hub gene and previous studies showed this (Yang *et al*., 2003; Shen *et al*., 2017). TLR4 is a possible cancer target (Jian *et al*., 2020; Sun *et al*., 2018). CXCL8 is a tumorigenesis factor in the literature review (Asokan and Bandapalli, 2021; Mishra *et al*., 2021; Yi *et al*., 2022). COL1A1 and another collagens family are upregulated in resistant cell and it has been said that many types of collagens like are upregulated in resistant cancers too (R. Januchowski *et al*., 2016; Liu *et al*., 2018; Zhang *et al*., 2018; Yao *et al*., 2022). CDH2 upregulated in MCF7 drug resistant cells (Gao *et al*., 2018; Gao *et al*., 2022). ALDH1A is shown as a tumor suppressor and downregulated in this study (Yue *et al*., 2022). FN1 is a biomarker and is a hub gene in the dataset (Bao *et al*., 2021; Zhang *et al*., 2022). Figures 3 and 4 shows interaction of ABC transporters in down-regulated and up-regulated protein network. ABCB1 that is one of important transporters in MDR mechanism is in interaction with FN1, MMP-2, KDR, and SLC families. In downregulated genes ABCC2 is in relation with some of SLC and CYP families.

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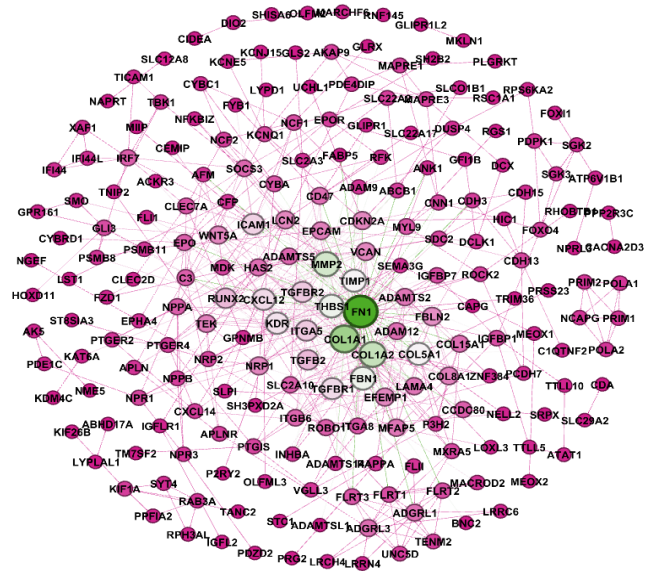

Figure 1*:* up-regulated genes in GSE119087 study. Green to red means more hub to les hub gene.

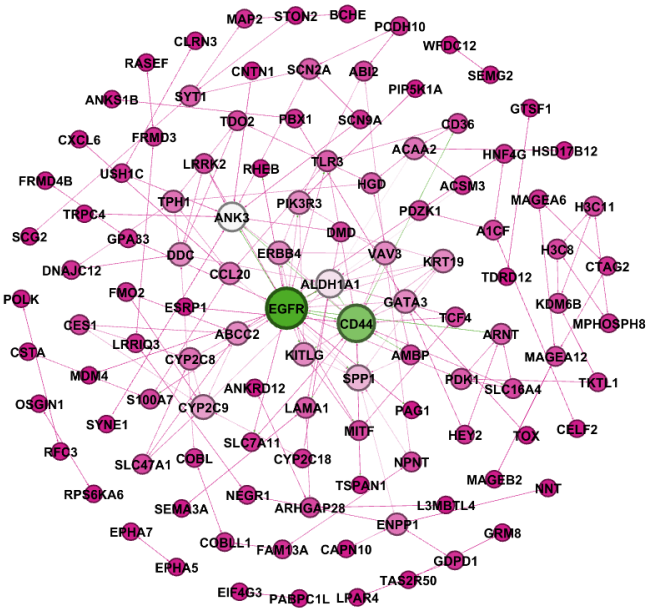

Figure 2*:* down-regulated genes in GSE119087 study. Green to red means more hub to les hub gene.

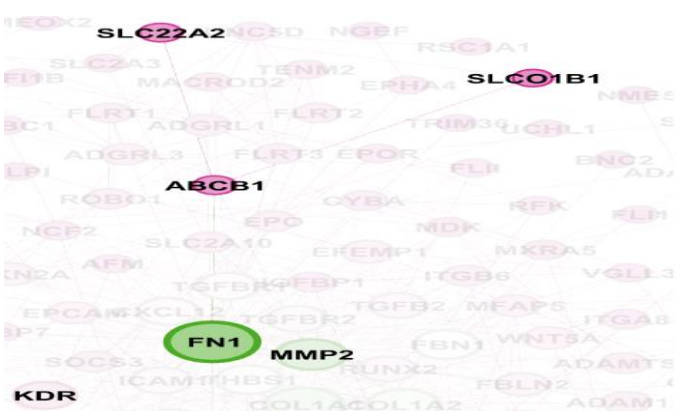

Figure 3*:* interaction of ABCB1 in up-regulated genes.

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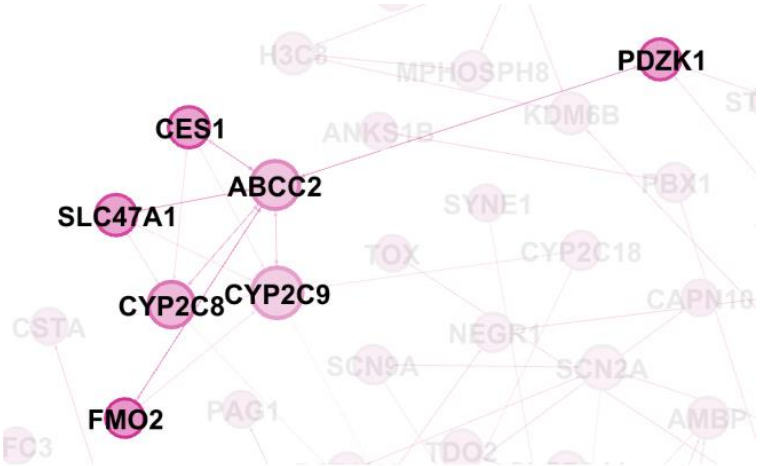

Figure 4: interaction of ABCC2 on down-regulated genes.

Figures 5 and 6 shows PPI network in up-regulated and down-regulated in GSE24460 protein interaction dataset. MMP-9, COL1A1, CDH2, are hub and important genes in PPI. ICAM-1 is another important gene that regulate in drug resistance (Schröder *et al*., 2011). ESR (Kim *et al*., 2011; Dustin *et al*., 2019) and PGR (Ghali *et al*., 2020) is down-regulated in this study and many previous studies before. CDH2 which has been reported to overexpressed in resistant cancers before.

Figures 7 and 8 show interaction of ABC transporters in down-regulated and up-regulated protein-protein network of this study. ABCB1 interacted with MMP-9, GLT-9, CDH2. ABCC3 and ABCG1 are down-regulated genes in this study.

Figures 9 and 10 shows PPI network in up-regulated and down-regulated in GSM7732765 protein-protein interaction dataset. CLC8, SOX2 (Novak *et al*., 2020), FOS (Moorehead and Singh, 2000; Mahner *et al*., 2008), PTGR2 up-regulated in the dataset, that is in correlation with previous studies . In down regulation network some IFIs genes families can be found and some previous studies accentuated this (Ohsugi *et al*., 2017; Naranjo *et al*., 2021). OS1 suppresses tumor growth in previous studies (Lee *et al*., 2019).

Venn diagram

In the Venn diagram it's obvious that 4 genes are common in all datasets. GSE119087 and GSE24460 has 23 genes in common. GSE119087 and GSM7732765 with GSE24460 and GSE119087 has 21 and 17 genes in common respectively. In the Venn diagram of down regulated genes 5 common genes can be found in GSE24460 dataset that are common by two other ones.

Pathway analysis

Many up-regulated genes are in Age-RAGE signaling pathway in diabetic, Chagas disease, lipid and atherosclerosis, cellular senescence and gastric cancer. Down-regulated hub genes are in proteoglycans in cancer, focal adhesion and thyroid cancer.

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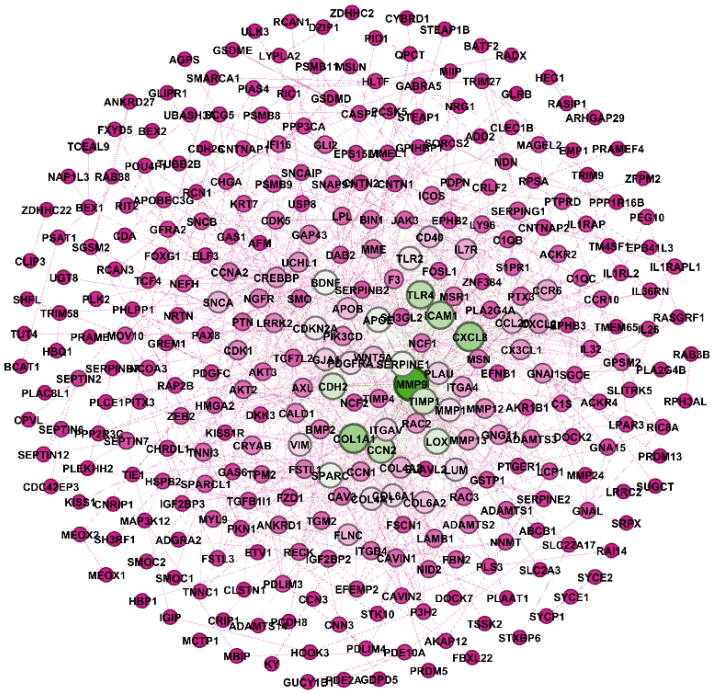

Figure 5*: U*p-regulated genes in GSE24460 study. Green to red means more hub to les hub gene.

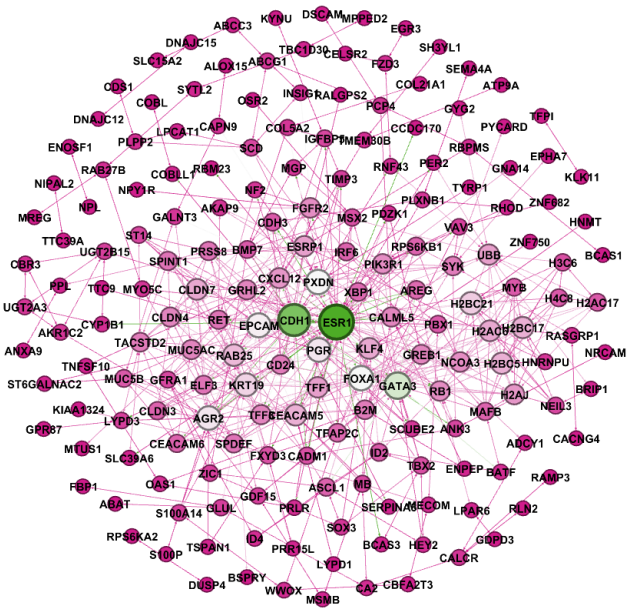

Figure 6*:* down-regulated genes in GSE24460 study. Green to red means more hub to les hub gene

Figure 7*:* ABCB1 interaction in up-regulated genes

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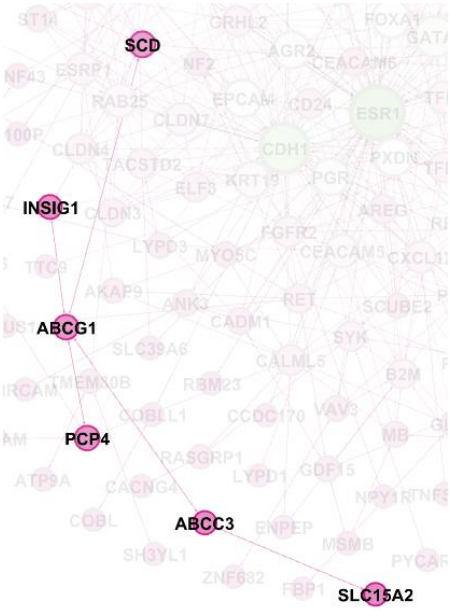

Figure 8: ABCC3 and ABCG1 interaction in down-regulated genes.

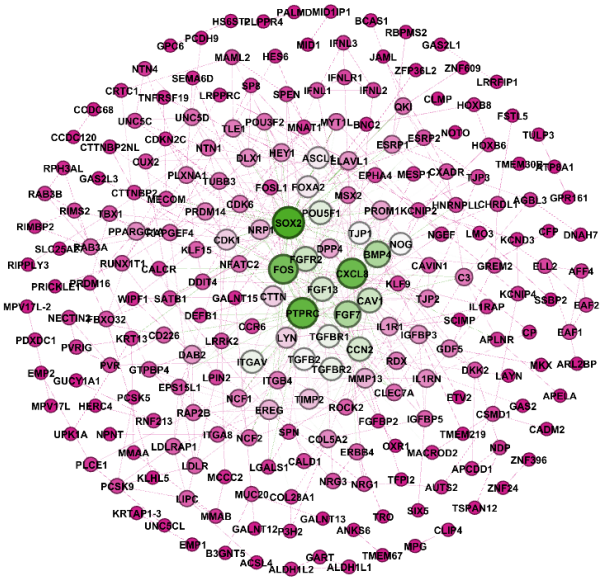

Figure 9*:* up-regulated genes of GSM7732765 dataset. Green to red means more hub to les hub gene.

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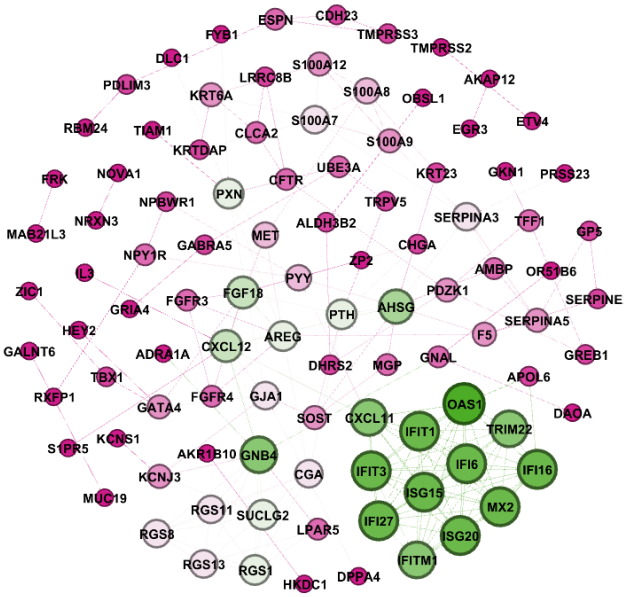

Figure 10: up-regulated genes of GSM7732765 dataset. Green to red means more hub to les hub gene.

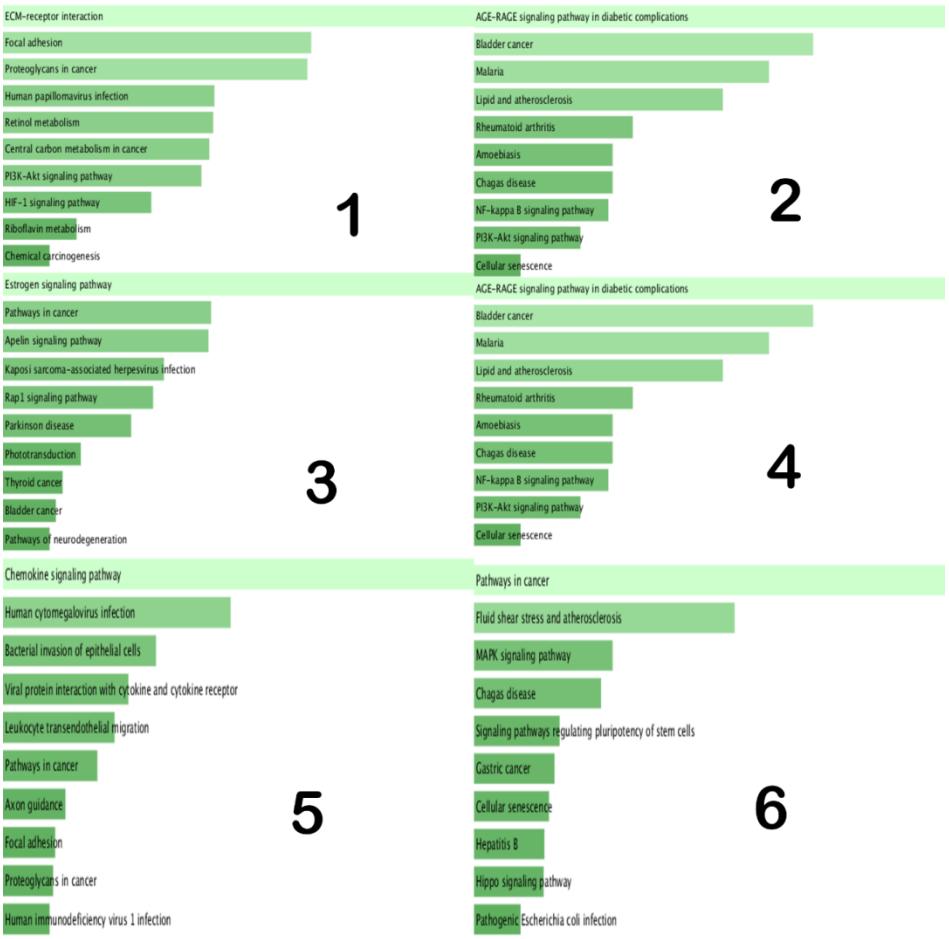

Figure 11: KEEG signaling pathway of hub genes. 1 and 2 down-regulated and up-regulated hub genes of GSE119087 dataset. 3 and 4 down-regulated and up-regulated hub genes of GSE24460 dataset. 5 and 6 are related to GSM7732765 dataset, up-regulated and down regulated respectively.

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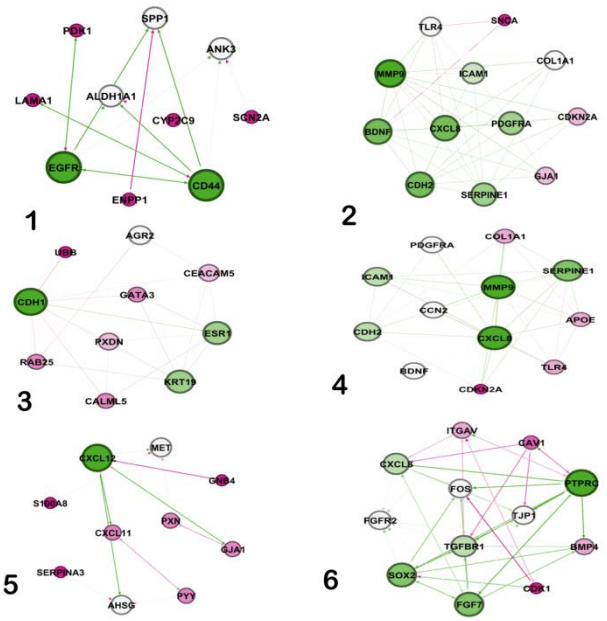

Figure 12*:* PPI network of about 10 hubest genes of datasets. 1 and 2 down-regulated and up-regulated hub genes of GSE119087 dataset. 3 and 4 down-regulated and up-regulated hub genes of GSE24460 dataset. 5 and 6 are related to GSM7732765 dataset, up-regulated and down-regulated respectively.

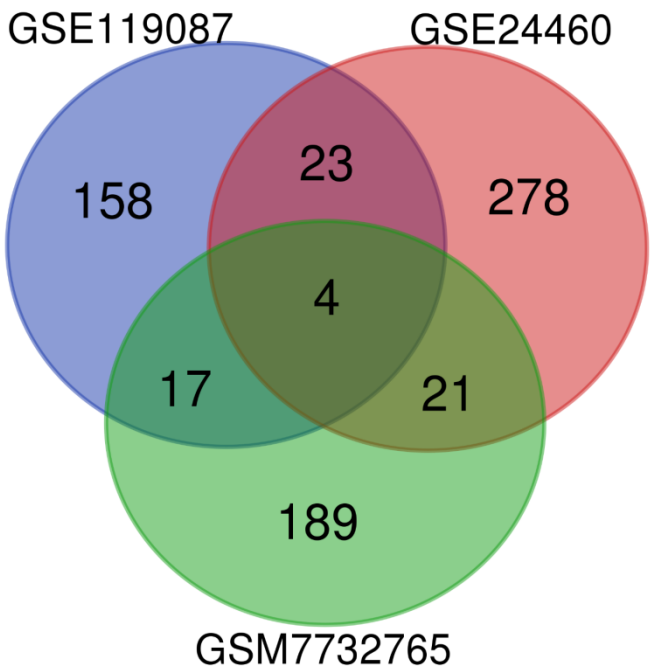

Figure 13: venn diagram of up-regulated genes.

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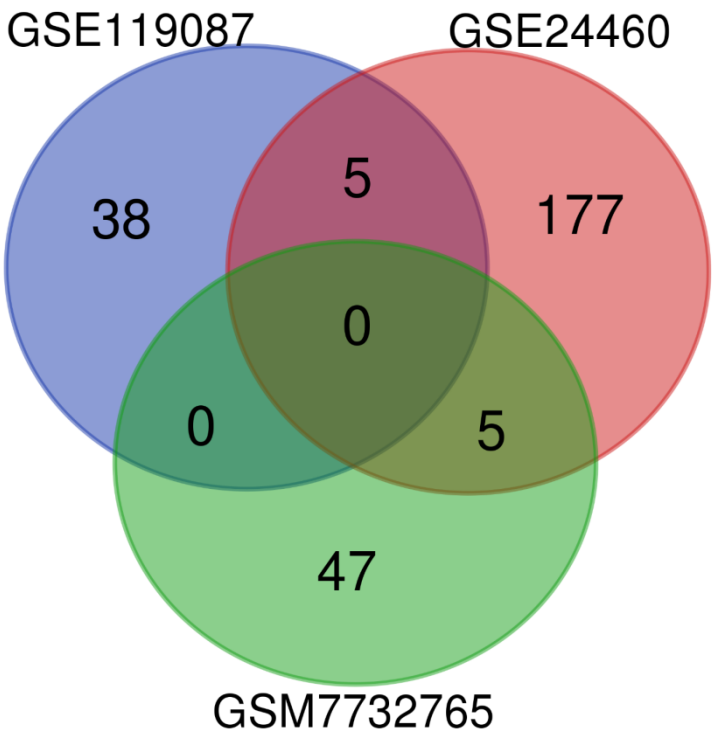

Figure 13: Venn diagram of down-regulated genes.

Discussion

PPI interactions shows that COL family are significant gene and can be a biomarker in resistant cancer. ABCB1 that is one of transmembrane protein and overexpressed in resistant cancers is in the interaction with FN1, MMP2 and some SLCs families. SLCs like ABCtrasporters are responsible in cell detoxification. In chemotherapy condition targeting of ABCteransporters has many side effects, so SLC, FN1, MMP2, CDH2 could be an alternative target to conquer drug resistance. ABCC2 downregulated in GSM183338 dataset and has connection with CYP family. Down regulation of CYPs may be related to metabolic mechanism of drug resistance. In another study ABCB1 up-regulated and is in connection to GSTP1 that is another protein in cell detoxification. Down regulation of ESR1, PGR, ALDH1A, can be a biomarker for cancer resistance. Moreover, ABCG2 and ABCC3 downregulated in GSE119087 study. As it is shown in Table 1, 4 genes are common upregulated in three studies (P3H2, RPH3AL, NCF1, NCF2). Targeting of these genes may lead to cover wide variety of resistance, and they have a high therapeutic value. In down-regulated genes we have found 10 genes that are common in datasets. It's probable that their mutation causes a cancer cell to resist against drugs, like ANK3.

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Table 1*:* common genes in venn diagram of up-regulated genes.

Names	Total	Elements
GSE119087 GSE24460 GSM7732765	4	P3H2, RPH3AL, NCF1, NCF2
GSE119087 GSE24460	23	SLC22A17, SMO, PSMB11, MEOX1, UCHL1, SLC2A3, MEOX2, ICAM1, ADAMTS2, SRPX, MIIP, GLIPR1, MYL9, ZNF384, PPP2R3C, ADAMTS14, WNT5A, FZD1, AFM, PSMB8, PSMB8, CDKN2A, CYBRD1, CDA
GSE119087 GSM7732765	17	TGFB2, NRP1, NGEF, ROCK2, GPR161, C3, CLEC7A, RAB3A, APLNR, EPHA4, ITGA8, TGFBR2, UNC5D, TGFBR1, TGFBR1, CFP, MACROD2, BNC2
GSE24460 GSM7732765	21	PLCE1, CHRDL1, MMP13, DAB2, CCR6, ITGB4, RAB3B, CDK1, LRRK2, CAVIN1, CXCL8, EMP1, CCN2, ITGAV, PCSK5, CALD1, IL1RAP, EPS15L1, NRG1, FOSL1, RAP2B

Table 1: common genes in venn diagram of down-regulated genes.

Names	Total	Elements
GSE119087 GSE24460	5	KRT19, PBX1, PDZK1, ANK3, VAV3
GSE24460 GSM7732765	5	ZIC1, HEY2, NPY1R, GREB1, TFF1

Table 3: List of abbreviation.

MMP-2	Ubiquitinous metalloproteinase
TLR-4	Toll like receptor
CXCL 8	C-X-C motif chemokine 8
COL1A1	Type I collagen is a member of group I collagen
ALDH1	Aldehyde Dehydrogenase 1 Family Member A1
FN1	Fibronectin 1
KDR	Kinase inserts domain receptor
CDH2	Cadherin-2
GLT-9	Glutamate Transporter-9
CLC8	Charcot-Leyden Crystal Galectin 8
SOX2	SRY-Box Transcription Factor 2
FOS	Fos Proto-Oncogene, AP-1 Transcription Factor Subunit
PTGR2	Prostaglandin Reductase 2
ESR1	Estrogen Receptor
PGR	Progesterone Receptor
ABC	ATP Binding Cassette
ANK3	Ankyrin 3
ICAM-1	Intercellular Adhesion Molecule 1
SLC	Anion exchange transporter
IFI	Interferon alpha-inducible protein

Conclusion

This study shows that P3H2, RPH3AL, NCF1, NCF2 up regulated in all datasets, so we should consider their importance in drug resistance. SLCs detoxification role may be another mechanism of multiple drug resistance. Another genes that should consider are collagens genes that have been

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expressed in other resistant cancer cells (Radosław Januchowski *et al*., 2016).

Conflict of interest

The author declares that don't have any conflict of interests.

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