A literature mining-based approach for identification of cellular pathways associated with chemoresistance in cancer

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Abstract

Chemoresistance is a major obstacle to the successful treatment of many human cancer types. Increasing evidence has revealed that chemoresistance involves many genes and multiple complex biological mechanisms including cancer stem cells, drug efflux mechanism, autophagy and epithelial–mesenchymal transition. Many studies have been conducted to investigate the possible molecular mechanisms of chemoresistance. However, understanding of the biological mechanisms in chemoresistance still remains limited. We surveyed the literature on chemoresistance-related genes and pathways of multiple cancer types. We then used a curated pathway database to investigate significant chemoresistance-related biological pathways. In addition, to investigate the importance of chemoresistance-related markers in protein–protein interaction networks identified using the curated database, we used a gene-ranking algorithm designed based on a graph-based scoring function in our previous study. Our comprehensive survey and analysis provide a systems biology-based overview of the underlying mechanisms of chemoresistance.

Key words: chemotherapy; chemoresistance; cancer; systems biology; pathway; gene

Introduction

Resistance to chemotherapy, which can develop over time, is one of the major obstacles to successful cancer treatment in many human cancers [1–7]. It is known that chemoresistance is multifactorial in nature and involves numerous genes and multiple complex signaling pathways [8, 9]. In recent years, growing attention has been paid to cellular systems in cancer stem cells (CSCs) with the capability of self-renewal and differentiation into other tumor cell subtypes [10]. CSCs are considered to be associated with chemoresistance, tumor recurrence and metastasis [11]. Many reports have shown that other biological mechanisms including ATP-binding cassette (ABC) membrane transporter activity, epithelial–mesenchymal transition (EMT) process, autophagy and altered DNA damage response in CSCs

are also significantly involved in chemoresistance [12]. However, despite such extensive studies, the underlying biological mechanisms that contribute to chemoresistance have not been entirely understood [13–16]. To better understand the role of genes and pathways involved in chemoresistance, we performed a comprehensive literature review. This review summarizes the associated biological mechanisms in the context of chemoresistance and reports chemoresistance-related genes and pathways of the published chemoresistance-related research. We demonstrate the results of our analysis performed on these genes using a manually curated pathway analysis platform (MetaCore version 6.21; Thomson Reuters Inc., Carlsbad, CA) [17], resulting in the identification of key biological pathways and highly connected protein–protein networks.

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Table 1. Chemoresistance-related genes identified by literature review

Cancer	N	Genes
Breast	91	ABCB1, ABCC1, ABCG2, AKT1, ALDH1A1, ANXA2, ATP6V0C, AURKA, AURKB, AXL, BCL2, BCL2L1, BIRC5, BMP6, BRCA1, BSG, CASP3, CAV1, CD44, CSF1, CTBP1, CTBP2, CTNNB1, CXCL1, CXCL2, CXCR7, DEPTOR, DUSP1, EIF4E, EIF5A2, EP300, ERBB2, ESR1, FGF1, FOXQ1, GH1, GHR, GSTP1, HIF1A, HSPB1, HSPG2, IGF1, IL17A, IL8, IMP3, JUN, KIF14, KRT19, KRT8, LAPTM4B, LCMT2, LGALS7, LKB1, MAPK1, MAPK3, MAPT, MMP1, MSH2, MTDH, NDST1, NOTCH1, PDGFRA, PDGFRB, PEA15, PGK1, PIK3CA, PRDX2, PRKCE, PTEN, PTGS2, RARRES1, SIRT1, SLC4A7, SLC9A1, SMAD3, SNAI1, SPHK2, SPP1, SRC, STAT3, TAZ, TGFB1, TNF, TP53, UBE2I, ULK1, YBX1, YWHAE, YWHAZ, NF- κ B ^a , MT proteins ^a
Colon	52	ABCB1, ABCC2, ABCC3, ABCF1, ABCG2, AKT1, AKT2, ALDH1A1, AURKA, BCL2, BCL2L1, CA12, CD44, CDX1, CRY2, DKK1, DKK4, DTL, EGFR, HDAC4, HIF1A, IGF1, IGFBP3, IKKB, KIN, LGR5, LYN, MCL1, MMP7, MMP9, NR1H4, NR1I2, NR4A2, PAK6, POSTN, PPARGC1A, PSAT1, PTEN, PYY, REPS2, SCGB2A1, SDC1, SIRT1, SNAI1, SP1, TFAP2E, TNFSF13, TP53, TYMS, UCP2, VEGFA, NF- κ B ^a
Head and neck	38	ABCB1, ABCC2, ABCG2, ATP7B, BCL2, BDNF, BIRC5, BMI1, BSG, C2orf40, CA9, CASP8, CD44, EGFR, ERCC1, ERCC4, FAM168A, GDF10, GSTP1, HAX1, HEC4, HSPA5, HSPB1, HTATIP2, IGF1, NANOG, NEFL, NOS2, NTRK2, POU5F1, PPM1D, PROM1, STAT3, TGFA, TGFB3, TRIP13, TWIST1, ZEB1
Lung	66	ABCB1, ABCC2, ABCC5, AIFM1, ANXA1, ANXA2, ANXA4, BAX, BCL2, BIRC5, BIRC6, BRCA1, BSG, CASP3, CASP9, CD44, CD9, CDKN1A, CXCR4, DKK3, DUSP1, E2F3, EIF3A, ERBB2, ERCC2, EZH2, FOXM1, GSTP1, HDAC1, HDAC4, HER2, HOXA1, HSP90B1, HSPA5, HSPB1, KDR, KEAP1, KRAS, LCMT2, LGALS1, MAPK14, MCL1, MEOX2, MET, MSH2, NFE2L2, PTGS2, RUNX3, S100A11, SCGN, SKP2, SLC05A1, SND1, SPHK2, SPP1, STAT3, TLR7, TLR8, TP53, TUBB3, TWIST1, VDAC1, XPA, XRCC1, ZEB1, NF- κ B ^a
Ovarian	122	ABCB1, ABCB3, ABCC1, ABCC2, ABCC3, ACTN4, ACVR1C, AKR1C1, AKT1, AKT2, ANXA11, ANXA4, APAF1, ARID1A, ATP7B, AURKA, AURKB, BAX, BCL2, BCL2L1, CASP3, CASP9, CD44, CDCP1, CDKN1B, CFLAR, CHI3L1, CLEC3B, CLU, CSN1S1, CXCR4, CYCS, DAXX, DICER1, DNMT1, DUSP6, EDNRA, EGFR, ENG, EPB41L1, ERBB2, ERCC1, ERCC4, EZH2, FASN, FOXP1, GLI2, GSC, GSTP1, HDAC1, HK2, HSP90AA1, HTRA2, IGF1, IL6, JAG1, KDM5B, KDR, KIT, KLK4, KLK5, KLK6, KLK7, KRAS, LAPTM4B, LCMT2, LGALS1, MAD2L1, MAPK1, MAPK14, MAPK3, MAPK8, MIEN1, MKI67, MSLN, MSMB, MTDH, MVP, MYD88, NFE2L2, NOTCH1, PAK7, PHB, PML, POSTN, PPARG, PPARGC1A, PPM1D, PRPF4, PRSS8, PTEN, PTGS2, PTK2, RGS10, RGS17, RSF1, SFRP5, SLC28A1, SNAI1, SNAI2, SPHK2, STAT1, STAT3, SULF1, TEAD1, TEAD3, TEAD4, TFAM, TGFB1, TLR4, TNFSF10, TOP2A, TP53, TP73, TRIM27, VEGFB, WNT5A, XIAP, YAP1, ZMYND10, NF- κ B ^a , HSP70 ^a
Pancreatic	79	ABCB1, ABCC2, ABCC5, ABCG2, AKT1, ALCAM, APAF1, BAD, BCL2, BCL2L1, BIRC5, BMI1, BNIP3, BRG1, BTRC, CASP8, CASP9, CBL, CCND1, CCNG2, CD44, CEACAM6, CXCR4, DCK, DLL4, DNMT1, EGFR, ERBB2, ETS1, EZH2, F2R, FASLG, GLI1, HES1, HIF1A, HMGA1, HOXA5, IGF1R, IL1B, IL6, ILK, ISG15, KRT18, L1CAM, LHX2, MACC1, MAP3K7, MAPK8, MDK, MET, MUC1, MUC4, NEU1, NOTCH1, NOTCH2, NRP1, PARK7, PLAUG, PROM1, PTGS2, PTK2, RRM1, RRM2, S100A4, SFN, SHH, SIRT1, SLC29A1, SMO, SNAI1, SRC, STAT1, TNFSF10, TP53, TP63, TUBB3, WNT5A, XIAP, NF- κ B ^a
Prostate	28	ABCB1, ABCC1, ANXA3, AURKA, AURKB, BSG, CD44, CDH1, CLU, DAB2IP, EGF, EGR1, ETS1, GATA2, GDF15, HSP27, IGF2, IGFBP2, IL6, KEAP1, MMP9, NFE2L2, NOTCH1, NR2C2, REST, SIRT1, TGFA, TLR4
Stomach	41	ABCB1, ABCC1, ABCG2, AGBL2, AKT1, ATG5, BAX, BCL2, BCL2L1, BMI1, CAV1, CD44, CDH1, DDB2, DPYD, ERCC1, FOXM1, HIF1A, IL-33, IL6, JUN, LGR5, MAPK1, MAPK3, MYC, NOTCH1, NR4A2, PEBP1, PROM1, PTEN, RHOA, SOX2, STAT3, TFAP2E, TP53, TRIM24, TYMP, TYMS, WNT6, NF- κ B ^a , MT proteins ^a

^aA family of proteins.

Key biological mechanisms associated with chemoresistance

Cancer stem cells

There is increasing evidence that a subpopulation of cells within most tumors called CSCs or tumor initiating cells arises from transformation of normal stem cells [18–22]. CSCs can self-renew and generate other tumor cell types [10]. CSCs are believed to play a significant role in tumorigenesis, progression, metastasis, recurrence and resistance to various kinds of therapies within a heterogeneous tumor mass [10, 11, 23–26]. Therefore, it is important to elucidate the characteristics of CSCs and to identify key biomarkers or pathways of CSCs to develop CSC-related therapies [27]. A number of CSC markers have been identified including ABCG2, ALDH1A1, CD9, CD44, CD133, NANOG, POU5F1 and SOX2, and it has been reported that these markers are associated with chemoresistance [28]. However, the underlying molecular mechanism of chemoresistance associated with CSCs remains still largely unknown [29, 30].

Epithelial mesenchymal transition

EMT is an important biological process by which epithelial cells lose their cell polarity and acquire a migratory mesenchymal phenotype [31]. Accumulated evidence has shown that EMT is implicated in metastasis and chemoresistance in cancer [32, 33]. More specifically, it has been observed that induction of EMT by EMT inducers such as TWIST1, ZEB1 and FOXQ1 promotes tumor invasion and chemoresistance via loss of cell polarity and loss of cell–cell adhesion [33]. EMT-related markers including E-cadherin (CDH1), Snail (SNAI1), ZEB1 and N-cadherin (CDH2) showed significant difference of expression in residual tumors after chemotherapy for esophageal cancer compared with chemo-naïve tumors [34]. In particular, a reduced expression of E-cadherin and an increased expression of Snail in residual tumors were associated with poor response to chemotherapy and shortened survival time. This suggests that there is an association between EMT-related markers and chemoresistance. In other studies, in colorectal cancer [35] and ovarian cancer [36], Snail enhanced the effect of EMT and chemoresistance. Cheng et al. showed that EMT induced by

Figure 1. Venn diagrams depicting the number of shared and unique genes (A) among breast, ovarian, and pancreatic cancers and (B) among breast, ovarian, and lung cancers using the gene list shown in Table 1 (a family of proteins was counted as 1). For both the Venn diagrams, the left-top and right-top circles indicate breast cancer and ovarian cancer, respectively. A colour version of this figure is available at BIB online: <http://bib.oxfordjournals.org>.

hypoxia can contribute to treatment failure and chemoresistance by activation of hypoxia-inducible factor-1 α (HIF-1 α /HIF1A) and nuclear factor- κ B (NF- κ B) in pancreatic cancer, suggesting that inactivation of HIF-1 α and NF- κ B may be a potential therapeutic strategy to overcome hypoxia-induced chemoresistance [37].

Autophagy

Autophagy is a cellular process that involves the degradation and digestion of long-lived or malfunctioning proteins as well as damaged organelles [38, 39]. The role of autophagy in cancer cell death and survival remains controversial [40, 41]. Although deficient autophagy is associated with tumorigenesis, autophagy also contributes to cancer cell survival, protecting cells from stressful conditions such as hypoxia or cytotoxic therapies, thereby resulting in resistance to common anti-cancer therapies [38]. It was found that overexpression of autophagy-related gene 5 (ATG5), which is one of the key regulators of autophagic cell death, was positively correlated with ABCC1 expression. Both ABCC1 and ATG5 were shown to be significantly associated with chemoresistance in gastric cancer [42]. In another study, CDX1 was found to have a protective effect on colon CSCs, leading to chemoresistance through activation of autophagy [43]. Dean *et al.* summarized each chemoresistance-related ABC transporter gene and its corresponding chemotherapeutic drugs effluxed by the transporter [44].

ABC transporters

ABC transporters play a critical role in the development of chemoresistance in cancer cells [10]. They form a superfamily of membrane proteins, consisting of 48 known proteins, including multidrug resistance protein 1 (P-glycoprotein/MDR1/ABCB1),

multidrug resistance-associated protein 1 (MRP1/ABCC1) and breast cancer resistance protein (BCRP/ABCG2) [45]. P-glycoprotein is a key protein involving drug efflux and multidrug resistance in many cancers [46–49]. ABC transporters normally protect cells from excessive extracellular and intracellular concentrations of xenobiotics and toxins [12]. An intriguing property of stem cells is that they express high levels of ABC transporters [44]. Elevated expression levels of ABC transporters in CSCs pump chemotherapy drugs out of the cells and accordingly decrease the intracellular accumulation of drugs, thereby contributing to multidrug resistance [50]. Novel chemotherapeutic strategies are being developed through targeted interventions of ABC transporter-related pathways [10, 51]. Investigators have designed numerous strategies to modulate ABC transporter intrinsic activity [52, 53] or regulate the expression levels of these proteins [54].

Computational systems biology

Computational systems biology is an emerging field that focuses on the modeling of complex biological components for a system-level understanding of molecular and cellular systems using mathematical and computational techniques [55, 56]. However, the development of computational approaches that identify meaningful biological insights from large-scale data is a major challenge [57, 58]. Complex biological components including genes, proteins and transcription factors are often represented as networks in which the connected edges indicate interactions or associations. Beyond simple graph representations, Bayesian modeling in biological networks has been used extensively, as reviewed by Wilkinson [59]. Materi and Wishart summarized computational systems biology approaches that have been used to provide novel insights into tumor genesis, growth, apoptosis, vascularization and therapy [60]. In our previous study, we used a computational systems biology approach based on graph theory to investigate the importance of biomarkers and to identify radiation response-related pathways and hub genes based on literature review [61]. Computational systems biology approaches have also been used to identify potential drug target enzymes in sphingolipid metabolism using metabolic control and pathway analysis [62], and to identify cancer chemoresistance-associated pathways from integrated biological interaction networks collected from public databases [13]. An integrative network inference approach using Bayesian modeling was proposed to infer genetic and metabolic pathways associated with chemoresistance in a way that a gene interaction network and a metabolic network, separately generated using gene expression and metabolite data, are merged into a larger network to predict correlations between genes and metabolizing enzymes [63].

In this study, we mined the scientific literature to identify chemoresistance-related genes, and then used the MetaCore system to construct protein–protein interaction networks and to identify biological pathways. In addition, to investigate the importance of chemoresistance-related markers in protein–protein interaction networks identified using the curated database, we used our gene-ranking algorithm designed in our previous study [61]. Although some microRNAs have been implicated in drug resistance, we limit ourselves to gene products.

Literature mining results

We performed a comprehensive literature review to identify chemoresistance-related genes from published papers.

Figure 2. Connected protein–protein interaction networks constructed using (A) a MetaCore platform tool, and (B) a power graph analysis tool with a list of chemoresistance-related genes of pancreatic cancer.

Peer-reviewed papers published until May 2015 were searched by using PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) or GoPubMed (<http://www.gopubmed.com/web/gopubmed/>) search engine with the following query: (chemo-resistance[Title] OR chemoresistance[Title] OR chemotherapy resistance[Title]) AND (cancer[Title] OR adenocarcinoma[Title] OR carcinoma[Title] OR neoplasms[Title] OR tumor[Title]). Our search resulted in 894 articles, of which 462 were relevant to the aim of study. The inclusion criteria are as follows: (1) studies on chemoresistance-related biomarkers (genes or proteins), and (2) studies on eight cancers (breast, colon, head and neck, lung, ovarian, pancreatic, prostate and stomach). Through the literature review, several types of chemoresistance-related biomarkers including genes, proteins, kinases and protein complexes were identified. To unify the nomenclature of biomarkers differently used across studies, we converted all biomarker terms into their corresponding official gene symbols. As a result, 334 unique genes and four families of proteins were identified. Among them, many biomarkers showed an association between chemoresistance and biological processes including CSCs (CSC markers: ALDH1A1, CD9, CD44, CD133, NANOG, POU5F1 and SOX2), EMT (EMT inducers: TWIST1,

FOXQ1, SNAI1 and ZEB1), autophagy (ATG5) and ABC transporters (ABCB1, ABCC1 and ABCG2) as mentioned earlier. Table 1 summarizes chemoresistance-related genes for each cancer. Supplementary data provide the information as well. Ovarian, breast and pancreatic cancers had relatively many biomarkers with 122, 91 and 79, respectively. For these three cancers, 11 biomarkers including ABCB1, AKT1, BCL2, BCL2L1, CD44, ERBB2, NF- κ B, NOTCH1, PTGS2, SNAI1 and TP53 were commonly identified. Figure 1A shows a Venn diagram depicting the number of shared and unique chemoresistance genes among breast, ovarian and pancreatic cancers. Figure 1B shows a Venn diagram for breast, ovarian and lung cancers. Even though in lung cancer, a smaller number of genes was identified with 66 compared with pancreatic cancer, 12 genes were common among the three cancers.

To investigate the most significant biological processes and protein–protein interaction networks based on the list of genes identified through literature review (Table 1), we uploaded the gene symbols into the MetaCore platform. To identify the interaction networks, we used an option of ‘direct interactions’ that allows the platform to search for direct interactions between genes, proteins, transcription factors and compounds from the

Figure 2. Continued

MetaCore database built by the MetaCore scientists with their data curation process, resulting in directly connected protein-protein interaction networks. Figure 2A illustrates a directly connected protein-protein interaction network identified using 79 biomarkers of pancreatic cancer. It is worth noting that this network consisted of 72 proteins, showing that the input genes are highly connected to each other. As expected, genes with similar functions are often clustered in the same pathway or biological process [64]. Similar results were found for other cancers (data not shown). As can be seen in Figure 2A, the network is centered around p53 (TP53), with the most interactions with other proteins, implying its important role in chemoresistance. Figure 2B illustrates a simplified network of Figure 2A obtained, using a power graph analysis tool that uses two abstractions: power nodes and power edges shown as thick circles and lines, respectively. A power edge indicates that all nodes inside a power node on one side are connected with all nodes on the other side. For more information for power graph analysis, see [65]. From the directly connected network constructed using the MetaCore software for each cancer, the number of interactions of each gene was counted. Table 2 shows the top 10 genes with the most interactions for ovarian, breast and pancreatic cancers when genes in Table 1 were used for that cancer type. In a directly connected network constructed using all the biomarkers in Table 1, TP53 had the most interactions with other genes with 93 outgoing edges and 64 incoming edges. In ovarian and pancreatic cancers, TP53 also had the most

interactions with 64 and 52 edges, respectively, whereas in breast cancer, the JUN gene had the most interactions with 57 edges, demonstrating its key role in chemoresistance. Note that if one gene has interactions with another gene bidirectionally, it was counted for both outgoing and incoming edges.

To investigate the biological importance of genes in the protein-protein interaction networks, we used a graph-based scoring function that we proposed in our previous paper [61]. This approach calculates a global gene score using the Floyd-Warshall algorithm based on a power law and using the number of papers that showed the interaction evidence between two proteins as a weighting value on the interaction. Table 3 shows the top 10 genes for ovarian, breast and pancreatic cancers. Interestingly, TP53 was first ranked in all the three cancers. However, overall there was a difference in genes compared with those in Table 2 that were ranked based on the number of gene interactions. Using the MetaCore software, significant biological processes were identified for ovarian, breast and pancreatic cancers (Table 4). In all the three cancers, signal transduction NOTCH signaling and development EMT regulation processes were highly ranked.

Numerous studies have identified chemoresistance-related genes or proteins in different cancer types. In bladder cancer, HOXC9, PSEN1, SRSF2, PLA1 and HIC2 were found to be associated with chemoresistance [7, 15, 66]. Overexpression of ADAM10 regulated malignant cell growth and invasion, suggesting that ADAM10 could be a candidate therapeutic

Table 2. Ranking of genes based on the number of interactions from directly connected networks constructed by the MetaCore platform when the gene list shown in Table 1 was used

When all genes shown in Table 1 were used				
Ranking	Gene	Number of outgoing edges	Number of incoming edges	Total
1	TP53	93	64	157
2	SP1	124	31	155
3	JUN	98	33	131
4	ESR1	77	50	127
5	MYC	70	41	111
6	STAT3	62	42	104
7	EP300	78	19	97
8	CTNNB1	59	36	95
9	HIF1A	63	26	89
10	HDAC1	70	16	86
Ovarian cancer				
1	TP53	35	29	64
2	STAT3	22	18	40
3	HDAC1	30	5	35
4	HSP90AA1	22	7	29
5	EZH2	21	6	27
6	MAPK14	17	8	25
7	EGFR	11	13	24
8	PPARG	12	12	24
9	CASP3	17	6	23
10	NOTCH1	11	12	23
Breast cancer				
1	JUN	43	14	57
2	TP53	33	23	56
3	ESR1	35	19	54
4	STAT3	25	18	43
5	CTNNB1	19	19	38
6	HIF1A	23	15	38
7	AKT1	19	14	33
8	EP300	24	9	33
9	SMAD3	9	15	24
10	BRCA1	10	12	22
Pancreatic cancer				
1	TP53	29	23	52
2	NOTCH1	18	13	31
3	HIF1A	24	5	29
4	EGFR	13	13	26
5	STAT1	18	7	25
6	AKT1	13	10	23
7	SRC	13	8	21
8	NF- κ B ^a	18	1	19
9	ETS1	14	4	18
10	EZH2	13	5	18

^aA family of proteins.

target [67]. Upregulation of UCA1 activated Wnt signaling and increased cisplatin resistance [68]. In lung cancer, it was reported that upregulation of SCGN [69], BIRC6 [70], EZH2 [71], ABCB1 [72], BCL2 [73], HSPA5/HSP90B1 [74] and TP53/LCMT2 [75] as well as downregulation of HOXA1 [76] were associated with chemoresistance. Numerous studies have reported the interplay between genes and signaling pathways in response to chemoresistance: in breast cancer, (IL17A [77]/BMP6 [78] and ERK), (ABCG2 [79]/BCL2 [80] and PI3K/Akt/NF- κ B) and (BIRC5 and PI3K/Akt2 pathway) [81]; in colon cancer, (SDC1 and EGFR) [82], (POSTN and PI3K/Akt/surviving) [83] and (BCL2 and

Table 3. Ranking of genes based on our proposed gene ranking algorithm from directly connected networks constructed by the MetaCore platform when the gene list shown in Table 1 was used

When all genes shown in Table 1 were used		
Ranking	Gene	Score
1	EGF	1128.1
2	SP1	1066.0
3	TP53	1043.0
4	VEGFA	1023.6
5	MYC	1000.5
6	ESR1	998.7
7	EGFR	998.7
8	EP300	994.9
9	IGF1	992.3
10	APAF1	986.4
Ovarian cancer		
1	TP53	332.4
2	EGFR	319.4
3	APAF1	314.8
4	STAT3	312.6
5	CYCS	312.2
6	BCL2L1	303.8
7	ERBB2	303.7
8	CASP9	301.4
9	XIAP	301.2
10	PTEN	300.9
Breast cancer		
1	TP53	276.9
2	EP300	268.6
3	ESR1	264.8
4	STAT3	263.0
5	JUN	260.5
6	SRC	258.0
7	HIF1A	255.6
8	MAPK1	248.3
9	CTNNB1	245.9
10	BRCA1	244.2
Pancreatic cancer		
1	TP53	247.8
2	EGFR	236.5
3	HIF1A	232.9
4	CBL	231.6
5	BAD	230.5
6	BCL2L1	227.6
7	STAT1	226.7
8	BCL2	223.7
9	AKT1	223.4
10	SRC	223.3

The score indicates the importance of genes in the network. As the score increases, the importance of the gene increases as well.

β 6-integrin-ERK/MAP kinase pathway) [84]; in ovarian cancer, (XIAP and PI3K/Akt) [85], (MSMB and Lin28b/Let-7) [86] and (SFRP5 and Wnt signaling pathway) [87]; in pancreatic cancer, (IGF1R and PI3K/Akt/NF- κ B) [88], (CASP8/CASP9/BCL2 and ERK) [89], (NRP1 and MAPK) [90] and (BNIP3 and PI3K/Akt pathway) [91]; in prostate cancer, (ABCC1 and NOTCH1) [92], (DAB2IP and Egr-1/Clusterin) [93] and (TLR4 and PI3K/Akt pathway) [94]; and in stomach cancer, (PROM1 and PI3K/Akt/p70S6K) [95], (CD44 and Hedgehog) [96], (TP53/MYC and PI3K/Akt and MAPK/ERK) [97] and (ABCB1 and p38-MAPK pathway) [1], where (gene and pathway).

Table 4. Significant biological processes and their corresponding genes

Ovarian cancer			
No.	Processes/genes	FDR	N
1	Development_blood vessel morphogenesis KLK7,CASP3,NF-kB,EGFR,NOTCH1,STAT3,JAG1,EDNRA,MAPK3,ERBB2,NOTCH1,KDR,STAT1,MAPK1; MAPK3,MAPK1,MAPK14,NOTCH1;NOTCH2,AKT2;AKT1,NOTCH1,MAPK8,CXCR4,VEGFB	1.08E-13	22
2	Signal transduction_NOTCH signaling NF-kB,EGFR,NOTCH1,STAT3,MAPK8,JAG1,MAPK14,MAPK3,WNT5A,ERBB2,NOTCH1,CD44,PTEN,MAPK1; MAPK3,CDKN1B,MAPK1,MAPK14,AKT2;AKT1,NOTCH1,AKT2,TP73,TP53,CFLAR,MAPK8	1.34E-13	24
3	Development_hemopoiesis, erythropoietin pathway NF-kB,STAT3,KIT,MAPK8,MAPK14,MAPK3,BCL2,KRAS,AKT1,STAT1,MAPK1;MAPK3,CDKN1B,MAPK1,MAPK14,BCL2L1,XIAP,AKT2;AKT1,MAPK8	2.51E-10	18
4	Development_EMT_regulation of epithelial-to-mesenchymal transition SNAI2,EGFR,NOTCH1,STAT3,MAPK8,JAG1,MAPK14,EDNRA,PTGS2,BCL2,NOTCH1,STAT1,PTEN,MAPK1; MAPK3,SNAI1,CDKN1B,MAPK14,AKT2;AKT1,PTK2,WNT5A,MAPK8,GSC	6.94E-10	22
5	Inflammation_amphoterin signaling NF-kB,MAPK8,MAPK14,MAPK3,TLR4,AKT1,MAPK1;MAPK3,MYD88,MAPK1,IL6,MAPK14,AKT2;AKT1,AKT2,MAPK8	1.18E-09	14
Breast cancer			
1	Signal transduction_NOTCH signaling PIK3CA,NF-kB,SMAD3,NOTCH1,STAT3,MAPK3,PDGFRB;PDGFRA,ERBB2,JUN,NOTCH1,CD44,TGFB1,PTEN, EP300,EIF4E,MAPK1;MAPK3,PDGFRA,SRC,MAPK1,PDGFRB,TGFB1,AKT2;AKT1,NOTCH1,TP53,PIK3CA,HIF1A,CTNNB1	1.64E-18	27
2	Development_EMT_regulation of epithelial-to-mesenchymal transition PIK3CA,KRT8,ESR1,SMAD3,NOTCH1,STAT3,JUN,PDGFRB;PDGFRA,PTGS2,BCL2,JUN,NOTCH1,TGFB1, PTEN,MAPK1;MAPK3,SNAI1,PDGFRA,SRC,PDGFRB,TGFB1,AKT2;AKT1,FGF1,TNF,HIF1A,CTNNB1	5.34E-15	25
3	Cell cycle_G1-S growth factor regulation PIK3CA,NF-kB,SMAD3,STAT3,JUN,MAPK3,ERBB2,JUN,JUN,AKT1,TGFB1,MAPK1;MAPK3,PRKCE,PDGFRA, SRC,MAPK1,PRKCE,TGFB1,AKT2;AKT1,FGF1,IGF1,PIK3CA	1.55E-14	22
4	Inflammation_IL-2 signaling PIK3CA,NF-kB,ESR1,STAT3,JUN,MAPK3,BCL2,JUN,PTEN,MAPK1;MAPK3,MAPK1,PRKCE,BCL2L1,ESR1,AKT2;AKT1,PIK3CA	2.01E-13	16
5	Inflammation_IL-6 signaling PIK3CA,CASP3,NF-kB,STAT3,JUN,MAPK3,BCL2,JUN,AKT1,YWHAE,MAPK1;MAPK3,MAPK1,AKT2;AKT1,YWHAZ,PIK3CA,YWHAZ,YWHAE;SFN	1.88E-12	16
Pancreatic cancer			
1	Signal transduction_NOTCH signaling SRC,NF-kB,TP63,EGFR,HES1,NOTCH1,MAPK8,NEU1,NOTCH2,AKT2;AKT1,NOTCH1,WNT5A,SKP2,BTRC, BTRC,ERBB2,DLL4,NOTCH1,TP53,CD44,CCND1,MAPK8,NOTCH2,HIF1A	3.23E-16	23
2	Development_EMT_regulation of epithelial-to-mesenchymal transition IL1B,SRC,EGFR,NOTCH1,MUC1,MAPK8,ETS1,AKT2;AKT1,PTGS2,BCL2,DLL4,NOTCH1,PTK2,S100A4,CBL, WNT5A,STAT1,MAPK8,MET,MAP3K7,HIF1A,SNAI1,ILK,KRT18	7.48E-15	24
3	Development_blood vessel morphogenesis IL1B,SRC,NF-kB,EGFR,NOTCH1,NRP1,NOTCH1;NOTCH2,AKT2;AKT1,F2R,NOTCH1,ERBB2,DLL4,L1CAM, NOTCH1,STAT1,MAPK8,ABCG2,MET,HIF1A,CXCR4	8.64E-13	20
4	Apoptosis_anti-apoptosis mediated by external signals via PI3K/AKT IL1B,BAD,SRC,NF-kB,IL6,EGFR,BCL2L1,AKT2;AKT1,APAF1,BCL2,ERBB2,BIRC5,TP53,IGF1R,PTK2,CASP9,CBL,MET,ILK	9.79E-11	19
5	Development_hedgehog signaling SRC,BMI1,SHH,TP63,HES1,GLI1,NOTCH1,SIRT1,NOTCH1,WNT5A,SKP2;BTRC,BTRC,SHH,NOTCH1,TP53,AKT1,CCND1,MDK,SNAI1	4.16E-10	19

FDR indicates the significance of biological processes identified.

FDR: false discovery rate.

Discussion

We conducted a literature search to find peer-reviewed published studies on chemoresistance with the aim of identifying chemoresistance-related genes, networks showing gene interactions and pathways. To our best knowledge, this is the largest literature review that surveyed papers published on chemoresistance for several cancers.

Unsurprisingly, in our literature review, the PI3K/Akt pathway was commonly found as one of the important pathways associated with chemoresistance in several cancers. The PI3K/Akt pathway is involved in cell growth, proliferation and survival [98, 99]. Alterations to the PI3K/Akt pathway are common in human cancers [100]. The activation of the PI3K/Akt pathway contributes to resistance to specific therapeutic agents [101]. Inhibition of this pathway can induce suppression of cell

proliferation and in some circumstances promote cell death in cancer cells [102]. PI3K/Akt pathway inhibitors have been shown to lead to successful chemotherapy by reversing the repression of apoptosis and resistance to therapeutic agents [103, 104]. Hence, the PI3K/Akt pathway has become an attractive target for drug development.

To identify protein-protein interaction networks that can be constructed using a list of genes found via literature review, we used the MetaCore integrated software suite. This analysis resulted in highly condensed networks, implying that there are strong biological interactions among these genes, especially hub genes that interact with many genes. The results support a general assumption that genes with similar functions are often clustered and linked to each other in biological networks. In particular, it is noted that p53 (TP53) has the most interactions

with other proteins in several cancers. It has been reported that mutant TP53 is associated with chemoresistance in different cancers. Kandioler-Eckersberger et al. found that fluorouracil, epirubicin and cyclophosphamide (FEC) therapy is dependent on normal p53, whereas paclitaxel responds to p53-deficient breast cancer patients [105]. Fiorini et al. found that mutant p53 stimulates chemoresistance to gemcitabine in pancreatic adenocarcinoma cells, observing a significant expression of CDK1 and CCNB1 genes in mutant p53 cell lines, while a significant decrease for these genes in wild-type p53 cell lines [106]. Bush and Li reviewed the relationship between p53 and multi-drug transporters with respect to cancer chemoresistance and concluded that the relationship is conditional, depending on cellular environment, therapeutic agents and the nature of the p53 mutation [107]. To investigate the biological importance of genes, we applied our gene ranking algorithm to protein-protein interaction networks identified using the MetaCore platform. It was found that TP53 was first ranked in ovarian, breast and pancreatic cancers. Consequently, it is obvious that TP53 plays an important role in chemoresistance as a 'beacon' gene that helps identify critical gene cascades, although it has not been used as a clinical marker for chemoresistance [108].

In conclusion, these networks identified emphasize the multifactorial dependence of overall treatment response on many genes that are often mutated in individual tumors. For future work, we hypothesize that these network results could help guide the design of multigene predictive signatures with the increased probability of chemotherapy success.

Key Points

- Chemoresistance is a major obstacle to successful therapy in human cancer and is associated with many genes and multiple complex biological mechanisms.
- We surveyed chemoresistance-related genes and biological pathways through a comprehensive literature review.
- We analyze genes found through literature review, and then use a curated database to identify significant pathways and protein-protein interaction networks.

Supplementary Data

Supplementary data are available online at <http://bib.oxfordjournals.org/>.

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References

- Guo X, Ma N, Wang J, et al. Increased p38-MAPK is responsible for chemotherapy resistance in human gastric cancer cells. *BMC Cancer* 2008;**8**:375.
- Rivera E, Gomez H. Chemotherapy resistance in metastatic breast cancer: the evolving role of ixabepilone. *Breast Cancer Res* 2010;**12**(Suppl 2):S2.
- Yang JY, Chang CJ, Xia W, et al. Activation of FOXO3a is sufficient to reverse mitogen-activated protein/extracellular signal-regulated kinase kinase inhibitor chemoresistance in human cancer. *Cancer Res* 2010;**70**:4709–18.
- Antoon JW, White MD, Slaughter EM, et al. Targeting NFκB mediated breast cancer chemoresistance through selective inhibition of sphingosine kinase-2. *Cancer Biol Ther* 2011;**11**:678–89.
- An Y, Ongkeko WM. ABCG2: the key to chemoresistance in cancer stem cells?. *Expert Opin Drug Metab Toxicol* 2009;**5**:1529–42.
- Gasco M, Crook T. p53 family members and chemoresistance in cancer: what we know and what we need to know. *Drug Resist Update* 2003;**6**:323–8.
- Lv L, Li Y, Deng H, et al. MiR-193a-3p promotes the multi-chemoresistance of bladder cancer by targeting the HOXC9 gene. *Cancer Lett* 2015;**357**:105–13.
- Wen X, Zhang HD, Zhao L, et al. Ginsenoside Rh2 differentially mediates microRNA expression to prevent chemoresistance of breast cancer. *Asian Pac J Cancer Prev* 2015;**16**:1105–9.
- Chuthapisith S, Layfield R, Kerr ID, et al. Proteomic profiling of MCF-7 breast cancer cells with chemoresistance to different types of anti-cancer drugs. *Int J Oncol* 2007;**30**:1545–51.
- Abdullah LN, Chow EK. Mechanisms of chemoresistance in cancer stem cells. *Clin Transl Med* 2013;**2**:3.
- Colak S, Zimmerlin CD, Fessler E, et al. Decreased mitochondrial priming determines chemoresistance of colon cancer stem cells. *Cell Death Differ* 2014;**21**:1170–7.
- Coley HM. Mechanisms and strategies to overcome chemotherapy resistance in metastatic breast cancer. *Cancer Treat Rev* 2008;**34**:378–90.
- Chao SY, Chiang JH, Huang AM, et al. An integrative approach to identifying cancer chemoresistance-associated pathways. *BMC Med Genomics* 2011;**4**:23.
- Lønning PE. Genes causing inherited cancer as beacons to identify the mechanisms of chemoresistance. *Trends Mol Med* 2004;**10**:113–18.
- Deng H, Lv L, Li Y, et al. The miR-193a-3p regulated PSEN1 gene suppresses the multi-chemoresistance of bladder cancer. *Biochim Biophys Acta* 2015;**1852**:520–8.
- Pan B, Yi J, Song H. MicroRNA-mediated autophagic signaling networks and cancer chemoresistance. *Cancer Biother Radiopharm* 2013;**28**:573–8.
- MetaCore™. <http://thomsonreuters.com/metacore/>
- Zhang XL, Jia Q, Lv L, et al. Tumorspheres derived from HCC cells are enriched with cancer stem cell-like cells and present high chemoresistance dependent on the Akt pathway. *Anticancer Agents Med Chem* 2015;**15**:755–63.
- Asuthkar S, Stepanova V, Lebedeva T, et al. Multifunctional roles of urokinase plasminogen activator (uPA) in cancer stemness and chemoresistance of pancreatic cancer. *Mol Biol Cell* 2013;**24**:2620–32.
- Paldino E, Tesori V, Casalbone P, et al. Tumor initiating cells and chemoresistance: which is the best strategy to target colon cancer stem cells?. *Biomed Res Int* 2014;**2014**:859871.
- Siddique HR, Saleem M. Role of BMI1, a stem cell factor, in cancer recurrence and chemoresistance: preclinical and clinical evidences. *Stem Cells* 2012;**30**:372–8.
- Dontu G, Liu S, Wicha MS. Stem cells in mammary development and carcinogenesis: implications for prevention and treatment. *Stem Cell Rev* 2005;**1**:207–13.
- Li S, Yue D, Chen X, et al. Epigenetic regulation of CD271, a potential cancer stem cell marker associated with chemoresistance and metastatic capacity. *Oncol Rep* 2015;**33**:425–32.
- Kang MJ, Kim HP, Lee KS, et al. Proteomic analysis reveals that CD147/EMMPRIN confers chemoresistance in cancer stem cell-like cells. *Proteomics* 2013;**13**:1714–25.

25. Crea F, Danesi R, Farrar WL. Cancer stem cell epigenetics and chemoresistance. *Epigenomics* 2009;1:63–79.
26. Vidal SJ, Rodriguez-Bravo V, Galsky M, et al. Targeting cancer stem cells to suppress acquired chemotherapy resistance. *Oncogene* 2014;33:4451–63.
27. Misawa A, Katayama R, Koike S, et al. AP-1-Dependent miR-21 expression contributes to chemoresistance in cancer stem cell-like SP cells. *Oncol Res* 2010;19:23–33.
28. Okamoto N, Yasukawa M, Nguyen C, et al. Maintenance of tumor initiating cells of defined genetic composition by nucleostemin. *Proc Natl Acad Sci USA* 2011;108:20388–93.
29. Suzuki S, Okada M, Shibuya K, et al. JNK suppression of chemotherapeutic agents-induced ROS confers chemoresistance on pancreatic cancer stem cells. *Oncotarget* 2015;6:458–470.
30. Chuthapisith S, Eremin J, El-Sheemey M, et al. Breast cancer chemoresistance: emerging importance of cancer stem cells. *Surg Oncol* 2010;19:27–32.
31. Larue L, Bellacosa A. Epithelial-mesenchymal transition in development and cancer: role of phosphatidylinositol 3' kinase/AKT pathways. *Oncogene* 2005;24:7443–54.
32. Meng F, Speyer CL, Zhang B, et al. PDGFR α and β play critical roles in mediating Foxq1-driven breast cancer stemness and chemoresistance. *Cancer Res* 2015;75:584–93.
33. Li J, Liu H, Yu J, et al. Chemoresistance to doxorubicin induces epithelial-mesenchymal transition via upregulation of transforming growth factor β signaling in HCT116 colon cancer cells. *Mol Med Rep* 2015;12:192–8.
34. Hara J, Miyata H, Yamasaki M, et al. Mesenchymal phenotype after chemotherapy is associated with chemoresistance and poor clinical outcome in esophageal cancer. *Oncol Rep* 2014;31:589–96.
35. Hoshino H, Miyoshi N, Nagai K, et al. Epithelial-mesenchymal transition with expression of SNAI1-induced chemoresistance in colorectal cancer. *Biochem Biophys Res Commun* 2009;390:1061–5.
36. Kurrey NK, Jalgaonkar SP, Joglekar AV, et al. Snail and slug mediate radioresistance and chemoresistance by antagonizing p53-mediated apoptosis and acquiring a stem-like phenotype in ovarian cancer cells. *Stem Cells* 2009;27:2059–68.
37. Cheng ZX, Wang DW, Liu T, et al. Effects of the HIF-1 α and NF- κ B loop on epithelial-mesenchymal transition and chemoresistance induced by hypoxia in pancreatic cancer cells. *Oncol Rep* 2014;31:1891–8.
38. White EJ, Martin V, Liu JL, et al. Autophagy regulation in cancer development and therapy. *Am J Cancer Res* 2011;1:362–72.
39. Altman BJ, Rathmell JC. Metabolic stress in autophagy and cell death pathways. *Cold Spring Harb Perspect Biol* 2012;4:a008763.
40. Zhuang W, Qin Z, Liang Z. The role of autophagy in sensitizing malignant glioma cells to radiation therapy. *Acta Biochim Biophys Sin (Shanghai)* 2009;41:341–51.
41. Sui X, Chen R, Wang Z, et al. Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment. *Cell Death Dis* 2013;4:e838.
42. Ge J, Chen Z, Huang J, et al. Upregulation of autophagy-related gene-5 (ATG-5) is associated with chemoresistance in human gastric cancer. *PLoS One* 2014;9:e110293.
43. Wu S, Wang X, Chen J, et al. Autophagy of cancer stem cells is involved with chemoresistance of colon cancer cells. *Biochem Biophys Res Commun* 2013;434:898–903.
44. Dean M, Fojo T, Bates S. Tumour stem cells and drug resistance. *Nat Rev Cancer* 2005;5:275–84.
45. Chen K, Huang YH, Chen JL. Understanding and targeting cancer stem cells: therapeutic implications and challenges. *Acta Pharmacol Sin* 2013;34:732–40.
46. Yakirevich E, Sabo E, Naroditsky I, et al. Multidrug resistance-related phenotype and apoptosis-related protein expression in ovarian serous carcinomas. *Gynecol Oncol* 2006;100:152–9.
47. Kamazawa S, Kigawa J, Kanamori Y, et al. Multidrug resistance gene-1 is a useful predictor of Paclitaxel-based chemotherapy for patients with ovarian cancer. *Gynecol Oncol* 2002;86:171–6.
48. Duan Z, Brakora KA, Seiden MV. Inhibition of ABCB1 (MDR1) and ABCB4 (MDR3) expression by small interfering RNA and reversal of paclitaxel resistance in human ovarian cancer cells. *Mol Cancer Ther* 2004;3:833–8.
49. Fojo AT, Ueda K, Slamon DJ, et al. Expression of a multidrug-resistance gene in human tumors and tissues. *Proc Natl Acad Sci USA* 1987;84:265–9.
50. Ricciardelli C, Ween MP, Lokman NA, et al. Chemotherapy-induced hyaluronan production: a novel chemoresistance mechanism in ovarian cancer. *BMC Cancer* 2013;13:476.
51. Kuo MT. Roles of multidrug resistance genes in breast cancer chemoresistance. *Adv Exp Med Biol* 2007;608:23–30.
52. Patil Y, Sadhukha T, Ma L, et al. Nanoparticle-mediated simultaneous and targeted delivery of paclitaxel and tariquidar overcomes tumor drug resistance. *J Control Release* 2009;136:21–9.
53. Ritchie TK, Kwon H, Atkins WM. Conformational analysis of human ATP-binding cassette transporter ABCB1 in lipid nanodiscs and inhibition by the antibodies MRK16 and UIC2. *J Biol Chem* 2011;286:39489–96.
54. Sims-Mourtada J, Izzo JG, Ajani J, et al. Sonic Hedgehog promotes multiple drug resistance by regulation of drug transport. *Oncogene* 2007;26:5674–9.
55. Dubitzky W. Understanding the computational methodologies of systems biology. *Brief Bioinform* 2006;7:315–17.
56. Kriete A, Lechner M, Clearfield D, et al. Computational systems biology of aging. *Wiley Interdiscip Rev Syst Biol Med* 2011;3:414–28.
57. Schadt EE, Linderman MD, Sorenson J, et al. Computational solutions to large-scale data management and analysis. *Nat Rev Genet* 2010;11:647–57.
58. Gomez-Cabrero D, Abugessaisa I, Maier D, et al. Data integration in the era of omics: current and future challenges. *BMC Syst Biol* 2014;8(Suppl 2):I1.
59. Wilkinson DJ. Bayesian methods in bioinformatics and computational systems biology. *Brief Bioinform* 2007;8:109–16.
60. Materi W, Wishart DS. Computational systems biology in cancer: modeling methods and applications. *Gene Regul Syst Bio* 2007;1:91–110.
61. Oh JH, Wong HP, Wang X, et al. A bioinformatics filtering strategy for identifying radiation response biomarker candidates. *PLoS One* 2012;7:e38870.
62. Ozbayraktar FB, Ulgen KO. Drug target identification in sphingolipid metabolism by computational systems biology tools: metabolic control analysis and metabolic pathway analysis. *J Biomed Inform* 2010;43:537–49.
63. Lecca P. An integrative network inference approach to predict mechanisms of cancer chemoresistance. *Integr Biol (Camb)* 2013;5:458–73.
64. Lynn KS, Lu CH, Yang HY, et al. Construction of gene clusters resembling genetic causal mechanisms for common complex disease with an application to young-onset hypertension. *BMC Genomics* 2013;14:497.

65. Royer L, Reimann M, Andreopoulos B, et al. Unraveling protein networks with power graph analysis. *PLoS Comput Biol* 2008;**4**:e1000108.
66. Lv L, Deng H, Li Y, et al. The DNA methylation-regulated miR-193a-3p dictates the multi-chemoresistance of bladder cancer via repression of SRSF2/PLAU/HIC2 expression. *Cell Death Dis* 2014;**5**:e1402.
67. Fu L, Liu N, Han Y, et al. ADAM10 regulates proliferation, invasion, and chemoresistance of bladder cancer cells. *Tumour Biol* 2014;**35**:9263–8.
68. Fan Y, Shen B, Tan M, et al. Long non-coding RNA UCA1 increases chemoresistance of bladder cancer cells by regulating Wnt signaling. *FEBS J* 2014;**281**:1750–8.
69. Bai Y, Sun Y, Peng J, et al. Overexpression of secretagogen inhibits cell apoptosis and induces chemoresistance in small cell lung cancer under the regulation of miR-494. *Oncotarget* 2014;**5**:7760–75.
70. Dong X, Lin D, Low C, et al. Elevated expression of BIRC6 protein in non-small-cell lung cancers is associated with cancer recurrence and chemoresistance. *J Thorac Oncol* 2013;**8**:161–70.
71. Xu C, Hao K, Hu H, et al. Expression of the enhancer of zeste homolog 2 in biopsy specimen predicts chemoresistance and survival in advanced non-small cell lung cancer receiving first-line platinum-based chemotherapy. *Lung Cancer* 2014;**86**:268–73.
72. Han L, Wang YF, Zhang Y, et al. Increased expression and function of P-glycoprotein in peripheral blood CD56+ cells is associated with the chemoresistance of non-small-cell lung cancer. *Cancer Chemother Pharmacol* 2012;**70**:365–72.
73. Sartorius UA, Krammer PH. Upregulation of Bcl-2 is involved in the mediation of chemotherapy resistance in human small cell lung cancer cell lines. *Int J Cancer* 2002;**97**:584–92.
74. Zhang L, Wang S, Wangtao, et al. Upregulation of GRP78 and GRP94 and its function in chemotherapy resistance to VP-16 in human lung cancer cell line SK-MES-1. *Cancer Invest* 2009;**27**:453–8.
75. Shih CM, Chen K, Wang YC, et al. Elevated p53 and p21waf1 mRNA expression in blood lymphocytes from lung cancer patients with chemoresistance. *Cancer Detect Prev* 2007;**31**:366–70.
76. Xiao F, Bai Y, Chen Z, et al. Downregulation of HOXA1 gene affects small cell lung cancer cell survival and chemoresistance under the regulation of miR-100. *Eur J Cancer* 2014;**50**:1541–54.
77. Cochaud S, Giustiniani J, Thomas C, et al. IL-17A is produced by breast cancer TILs and promotes chemoresistance and proliferation through ERK1/2. *Sci Rep* 2013;**3**:3456.
78. Lian WJ, Liu G, Liu YJ, et al. Downregulation of BMP6 enhances cell proliferation and chemoresistance via activation of the ERK signaling pathway in breast cancer. *Oncol Rep* 2013;**30**:193–200.
79. Zhang W, Ding W, Chen Y, et al. Up-regulation of breast cancer resistance protein plays a role in HER2-mediated chemoresistance through PI3K/Akt and nuclear factor-kappa B signaling pathways in MCF7 breast cancer cells. *Acta Biochim Biophys Sin (Shanghai)* 2011;**43**:647–53.
80. Simstein R, Burow M, Parker A, et al. Apoptosis, chemoresistance, and breast cancer: insights from the MCF-7 cell model system. *Exp Biol Med (Maywood)* 2003;**228**:995–1003.
81. Xing H, Weng D, Chen G, et al. Activation of fibronectin/PI-3K/Akt2 leads to chemoresistance to docetaxel by regulating survivin protein expression in ovarian and breast cancer cells. *Cancer Lett* 2008;**261**:108–19.
82. Wang X, Zuo D, Chen Y, et al. Shed Syndecan-1 is involved in chemotherapy resistance via the EGFR pathway in colorectal cancer. *Br J Cancer* 2014;**111**:1965–76.
83. Xiao ZM, Wang XY, Wang AM. Periostin induces chemoresistance in colon cancer cells through activation of the PI3K/Akt/survivin pathway. *Biotechnol Appl Biochem* 2015;**62**:401–6.
84. Liu S, Wang J, Niu W, et al. The β 6-integrin-ERK/MAP kinase pathway contributes to chemo resistance in colon cancer. *Cancer Lett* 2013;**328**:325–34.
85. Cheng JQ, Jiang X, Fraser M, et al. Role of X-linked inhibitor of apoptosis protein in chemoresistance in ovarian cancer: possible involvement of the phosphoinositide-3 kinase/Akt pathway. *Drug Resist Updat* 2002;**5**:131–46.
86. Yan BX, Ma JX, Zhang J, et al. PSP94 contributes to chemoresistance and its peptide derivative PCK3145 represses tumor growth in ovarian cancer. *Oncogene* 2014;**33**:5288–94.
87. Su HY, Lai HC, Lin YW, et al. Epigenetic silencing of SFRP5 is related to malignant phenotype and chemoresistance of ovarian cancer through Wnt signaling pathway. *Int J Cancer* 2010;**127**:555–67.
88. Tian X, Hao K, Qin C, et al. Insulin-like growth factor 1 receptor promotes the growth and chemoresistance of pancreatic cancer. *Dig Dis Sci* 2013;**58**:2705–12.
89. Zhao Y, Shen S, Guo J, et al. Mitogen-activated protein kinases and chemoresistance in pancreatic cancer cells. *J Surg Res* 2006;**136**:325–35.
90. Wey JS, Gray MJ, Fan F, et al. Overexpression of neuropilin-1 promotes constitutive MAPK signalling and chemoresistance in pancreatic cancer cells. *Br J Cancer* 2005;**93**:233–41.
91. Akada M, Crnogorac-Jurcevic T, Lattimore S, et al. Intrinsic chemoresistance to gemcitabine is associated with decreased expression of BNIP3 in pancreatic cancer. *Clin Cancer Res* 2005;**11**:3094–101.
92. Liu C, Li Z, Bi L, et al. NOTCH1 signaling promotes chemoresistance via regulating ABCC1 expression in prostate cancer stem cells. *Mol Cell Biochem* 2014;**393**:265–70.
93. Wu K, Xie D, Zou Y, et al. The mechanism of DAB2IP in chemoresistance of prostate cancer cells. *Clin Cancer Res* 2013;**19**:4740–9.
94. Zhang Y, Wang Y, Yuan J, et al. Toll-like receptor 4 ligation confers chemoresistance to docetaxel on PC-3 human prostate cancer cells. *Cell Biol Toxicol* 2012;**28**:269–77.
95. Zhu Y, Yu J, Wang S, et al. Overexpression of CD133 enhances chemoresistance to 5-fluorouracil by activating the PI3K/Akt/p70S6K pathway in gastric cancer cells. *Oncol Rep* 2014;**32**:2437–44.
96. Yoon C, Park DJ, Schmidt B, et al. CD44 expression denotes a subpopulation of gastric cancer cells in which Hedgehog signaling promotes chemotherapy resistance. *Clin Cancer Res* 2014;**20**:3974–88.
97. Liu SQ, Yu JP, Yu HG, et al. Activation of Akt and ERK signaling pathways induced by etoposide confer chemoresistance in gastric cancer cells. *Dig Liver Dis* 2006;**38**:310–18.
98. Hua K, Feng W, Cao Q, et al. Estrogen and progesterone regulate metastasis through the PI3K/AKT pathway in human ovarian cancer. *Int J Oncol* 2008;**33**:959–67.
99. Zhao Y, Li Y, Ma H, et al. Modification of sialylation mediates the invasive properties and chemosensitivity of human hepatocellular carcinoma. *Mol Cell Proteomics* 2014;**13**:520–36.
100. Osaki M, Oshimura M, Ito H. PI3K-Akt pathway: its functions and alterations in human cancer. *Apoptosis* 2004;**9**:667–76.
101. Martini M, De Santis MC, Braccini L, et al. PI3K/AKT signaling pathway and cancer: an updated review. *Ann Med* 2014;**46**:372–83.

102. Courtney KD, Corcoran RB, Engelman JA. The PI3K pathway as drug target in human cancer. *J Clin Oncol* 2010;**28**:1075–83.
103. Fresno Vara JA, Casado E, de Castro J, et al. PI3K/Akt signalling pathway and cancer. *Cancer Treat Rev* 2004;**30**:193–204.
104. Hennessy BT, Smith DL, Ram PT, et al. Exploiting the PI3K/AKT pathway for cancer drug discovery. *Nat Rev Drug Discov* 2005;**4**:988–1004.
105. Kandioler-Eckersberger D, Ludwig C, Rudas M, et al. TP53 mutation and p53 overexpression for prediction of response to neoadjuvant treatment in breast cancer patients. *Clin Cancer Res* 2000;**6**:50–6.
106. Fiorini C, Cordini M, Padroni C, et al. Mutant p53 stimulates chemoresistance of pancreatic adenocarcinoma cells to gemcitabine. *Biochim Biophys Acta* 2015;**1853**:89–100.
107. Bush JA, Li G. Cancer chemoresistance: the relationship between p53 and multidrug transporters. *Int J Cancer* 2002;**98**:323–30.
108. Knappskog S, Lønning PE. P53 and its molecular basis to chemoresistance in breast cancer. *Expert Opin Ther Targets* 2012;**16**(Suppl 1):S23–30.