Investigating the pharmacological mechanisms of SheXiang XinTongNing against coronary heart disease based on network pharmacology

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Research

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Abstract

Background SheXiang XinTongNing, a commercially available Chinese patent medicine, has been widely used in the treatment of coronary heart disease. However, the mechanisms of SheXiang XinTongNing are still unclear. The aim of this study was to investigate the pharmacological mechanisms of SheXiang XinTongNing against coronary heart disease via network analysis.

Method The traditional Chinese medicine system pharmacology analysis platform was used to screen the potential active constituents of the six traditional Chinese medicines in SheXiang XinTongNing, and the potential targets were obtained from PharmMapper. The genome annotation database platform was used to screen the candidate targets related to coronary heart disease. Then the drug-components-targets network and protein interaction network were built by Cytoscape 3.6.0 software. Further, GO bio-functional enrichment analysis and KEGG pathway enrichment analysis were performed through annotation, visualization and integrated discovery database.

Results Results showed that the drugs-components-targets network contains 104 targets and 62 key components. The protein interaction network consisted of 107 nodes; key targets included Bcl2l1, IGF1, SRC, CASP3, et al. Functionally, the candidate targets were significantly associated with multiple pathways such as PI3K-Akt signaling pathway, MAPK signaling pathway, Ras signaling pathway, FoxO signaling pathway, Endocrine resistance. Given the above, the pharmacological activities of SheXiang XinTongNing may be predominantly related to several factors such as cell apoptosis, inflammation and angiogenesis.

Conclusion XTN can effectively attenuate the symptoms of coronary heart disease through diverse pathways. The research proves that network pharmacology can successfully reveal the mechanisms of traditional Chinese medicine in a holistic view. Our systematic analysis lays a foundation for further studying.

Background

Cardiovascular disease is a leading cause of death worldwide that caused 17.3 million deaths globally[1]. As one of the most important cardiovascular diseases, coronary heart disease(CHD) causes the most death and disability. It represents a substantial societal burden in developed countries and accounts for one-third of all deaths in the adult population[2, 3]. The mortality of CHD is supposed to increase in developing countries from approximately 9 million in 1990 to about 19 million by 2020[4]. Notably, a new study suggested that patients with cardiovascular disease are more likely to be infected with COVID-19[5]. Data from the National Health Commission showed that 17 percent of COVID-19 patients had the comorbidity of CHD[6]. High blood pressure, cholesterol levels, diabetes, obesity have been considered as major determining factors of CHD[7]. Women with onset of type 1 diabetes before age 10 have a 60-times increased risk of CHD[8]. In addition, life behaviors, such as alcohol intake and cigarette consumption[9, 10], environmental toxic metal contaminants[11] and the degree of ApoB are also related to the augment

of CHD data[12]. Apart from those, it is reported that HIV infection caused a substantially increased risk of CHD[13]. Currently, modification of lifestyles, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) and medication therapy such as nitrates, beta receptor-blockers, statins, antiplatelet drugs are the mainstream therapeutic methods for CHD. Nevertheless, there are many limitations in the treatment of CHD, such as side effects of drugs especially Western drugs, lack of comprehensive management, patients' resistance to changing lifestyles[14].

Traditional Chinese medicine (TCM), originated from China, which is characterized by its minor side effects and synergistic therapeutic efficacies, has been long used in clinical practice and plays indispensable roles in various diseases. In particular, it has broadened the ideas of therapeutic approaches and achieved crucial effects in CHD[15, 16]. According to the TCM theory, the pathogenesis of coronary heart disease may be phlegm turbidity, cold coagulation, qi stagnation and blood stasis[17]. At present, there are many TCM preparations and Chinese patent drugs for relieving chest congestion, activating Qi and promoting blood circulation for removing blood stasis, which show remarkable effects in CHD. Particularly, SheXiang XinTongNing(XTN), a commercially available Chinese patent medicine which has been widely used in clinical treatment of CHD. XTN is composed of 6 herbs, including Moschus (Shexiang, SX), Ligusticum chuanxiong (Chuanxiong, CX), Rhizoma Corydalis(Yanhusuo, YHS), Panax ginseng(Renshen, RS), Borneolum Syntheticum(Bingpian, BP) and Styrax(Suhexiang, SHX). Among them, SX is the principal drug and plays a role in resuscitation; CX mainly promotes blood circulation and activates qi; YHS principally regulates qi-flowing for relieving pain. The combination of CX and YHS are the assistant drugs, playing a prominent role in improving the two essentials (qi and blood) of human bodies to alleviate the diseases; BP is the adjuvant drug which exerts functions in activating brain and clearing away for resuscitation. In addition, it enhances the effects of principal and assistant drugs. The formulae conforms to the theory of TCM and the six kinds of herbs have a synergistic effect, so as to achieve a prominent efficacy in relieving CHD. However, it is precisely because of the multiple components and multiple targets of TCM that the mechanism of TCM is difficult to be clarified. Although XTN has been applied in clinic for a long time, the underlying mechanisms of XTN are still vague.

Network Pharmacology is a systematic method to study the mechanisms of drugs and diseases based on the network construction of drugs, constituents, genes, protein targets, and diseases[18]. It coincides well with the holistic ideas of 'network target, multicomponent therapeutics' of TCM and contributes greatly to the prediction of potential drugs and the screening of the components, targets as well as pathways of drugs[19]. In previous study, the network pharmacology has been used in elucidating the key components and mechanisms of TCM involved in their therapeutic effects, such as the mechanisms of Erxian Decoction against TNF- α induced osteoblast apoptosis[20], the mechanisms of Huayu-Qiangshen-Tongbi formula on rheumatoid arthritis[21], the anticancer mechanisms of Compound Kushen Injection against hepatocellular carcinoma[22].

In this study, a network pharmacology approach was adopted to illuminate the underlying mechanisms of XTN against CHD through following steps: (1) Screening the chemical components of the six herbs

contained in XTN; (2) Predicting the candidate targets of XTN related to CHD; (3) Illustrating a drug-components-targets network and a protein interaction(PPI) network; (4) Functional analysis of XTN for investigating the mechanisms of XTN acting on CHD.

As a consequence, our study could provide novel insights into the mechanisms of XTN treating CHD. More generally, offers support for further study. The flowchart of our study was shown in Fig. 1.

Methods

Active components screening

TCMSP(traditional Chinese medicine system pharmacology analysis platform) is a specialized computational platform for systematic pharmacology-based analysis, which contains the information of herbs. The identities of the chemical components in YHS, SX, CX, RS, BP, SHX were retrieved from TCMSP database (<http://tcmbspw.com/>)[23]. The oral availability (OB) and drug-likeness (DL) are considered as two key indicators in drug screen. The OB index represents the percentage of drugs reaching the circulation after oral administration, and the DL index is a qualitative parameter that estimate the similarity between a substance and an existing drug[24]. The OB threshold was set at 40% ($OB > 40\%$) and the threshold of DL was set at 0.18($DL \geq 0.18$), by which the active ingredients were selected. Since SX has not been detected in the database, and there are some compounds with high content or strong activity but low OB or DL in the above five herbs reported in the literature, thus, tetrahydropalmatine, tetrandrine, tetramethylolactone, ligustilide, ligustrazine, ginsenosides (Rb1, Rg1, Rg3, Rd, Re), muscone, cinnamaldehyde and Bienenl benzoate in XTN were also incorporate in the study. The 3D structures of each active component were retrieved from Pubchem (<https://pubchem.ncbi.nlm.nih.gov/>) [25]and saved in .sdf format.

Putative and Candidate targets of drugs

In addition, the putative targets hitting every components of XTN were obtained through PharmMapper (<http://www.lilab-ecust.cn/pharmmapper/>) database[26]. PharmMapper is one of the reverse molecular docking methods developed by reverse pharmacophore mapping based on ligand features, which uses active small molecules as probes to search for potential drug targets and thus predict the biological activity of small molecules. The program can quickly obtain drug target information by retrieving four databases, Target Bank, Drug Bank, Binding DB and PDTD[27]. Due to its advantages of fast operation speed and comprehensive target information, it has been extensively used in the research of TCM targets. Firstly, the .sdf format file of the active components of XTN was uploaded into PharmMapper, then we used the reverse pharmacophore matching method to get the virtual screening results. The active small molecules were used as probes to search for potential drug targets. When the docking score between molecules and targets, that is, the molecular-target matching degree (Fit Score) is greater than 4.5, it is considered that the target interacts with the chemical components in XTN, thus the putative target is screened out.

The PDB ID of targets was converted into the Gene name with UniProt database(<http://www.uniprot.org/>) [28]. Subsequently, the target genes related to coronary heart disease were collected with "coronary heart disease" as key words in genome annotation database platform(Genecards) (<https://www.genecards.org/>) [29]database, and the common targets were screened as the candidate targets of XTN.

Network construction

To investigate the relationship of XTN and CHD, the drug-components-targets network and protein interaction(PPI) network were constructed with Cytoscape 3.6.0 software(<https://cytoscape.org/>)[30]. In the drugs-components-targets graphical network, the drug, the active drug molecules and the candidate targets refer to the nodes of network; the edges, which connected the nodes refer to the interactions, and the number of edges in the network refers to the node values.

Further, in order to clarify the interaction between the potential target proteins of XTN, the PPI network model of the screened target proteins was constructed on STRING platform(<http://string-db.org/>)[31]. The protein type was set to "Homo sapiens" (human) for operation, the lowest interaction threshold was set to medium "medium confidence", and other parameters were kept at the default setting. Screen the top 30 core targets, then the PPI network model was imported into Cytoscape 3.6. 0 software, the Network Analysis function was used for analysis, and the size of the node was adjusted in accordance with the connection degrees (the greater the connection degree is, the closer the node is related to other nodes, and the more important it is in the network), and the PPI network diagram was established.

Pathway enrichment analysis and biological functional analysis

The annotation, visualization and integrated discovery database (DAVID) database(<https://david.ncifcrf.gov/>)[32] is a biological information database that integrates biological data and analytical tools together, which can be used for pathway analysis and biological function analysis. The KEGG signal pathway enrichment analysis and GO biological process enrichment of the candidate targets of XTN were carried out by DAVID database. The biological processes and pathways with $P < 0.01$ were selected and sorted in line with the number of enriched genes from large to small, then the top 20 biological processes and pathways were chosen for visualization analysis.

Results

Active compounds in XTN

Retrieved from TCMSP database, the components of the 6 herbs in XTN were collected. On the basis of threshold value of $OB > 40\%$ and $DL \geq 0.18$, 62 active compounds were selected as shown in Table 1.

Table 1
Active compounds of 6 herbs and their OB and DL

Compound	herb	Chemical	OB	DL
C01	YHS1	Cryptopin	78.74	0.72
C02	YHS2	Dihydrosanguinarine	59.31	0.86
C03	YHS3	(R)-Canadine	55.37	0.77
C04	YHS4	Hyndarin	73.94	0.64
C05	YHS5	Capaurine	62.91	0.69
C06	YHS6	Clarkeanidine	86.65	0.54
C07	YHS7	Corydaline	65.84	0.68
C08	YHS8	Corydalmine	52.5	0.59
C09	YHS9	Corynoline	46.06	0.85
C10	YHS10	methyl-2-(3,4,6,7-tetramethoxyphenanthren-1-yl)ethanamine	61.15	0.44
C11	YHS11	Dehydrocorybulbine	46.97	0.63
C12	YHS12	dehydrocorydaline	41.98	0.68
C13	YHS13	Dehydrocorydalmine	43.9	0.59
C14	YHS14	Fumaricine	43.95	0.72
C15	YHS15	isocorybulbine	40.18	0.66
C16	YHS16	leonticine	45.79	0.26
C17	YHS17	13-methylpalmatrubine	40.97	0.63
C18	YHS18	N-methyl-laurotetanine	41.62	0.56
C19	YHS19	Pseudoprotopine	53.75	0.83
C20	YHS20	saulatine	42.74	0.79
C21	YHS21	stylophine	48.25	0.85
C22	YHS22	tetrahydroprotopapaverine	57.28	0.33
C23	YHS23	2,3,9,10-tetramethoxy-13-methyl-5,6-dihydroisoquinolino[2,1-b]isoquinolin-8-one	76.77	0.73
C24	YHS24	Stigmasterol	43.83	0.76
C25	YHS25	palmatine	64.6	0.65

Compound	herb	Chemical	OB	DL
C26	YHS26	Fumarine	59.26	0.83
C27	YHS27	bicuculline	69.67	0.88
C28	YHS28	Bulbocapnine	47.54	0.69
C29	YHS29	quercetin	46.43	0.28
C30	YHS30	Isocorypalmine	35.77	0.59
C31	YHS31	columbamine	26.94	0.59
C32	CX1	Mandenol	42	0.19
C33	CX2	Myricanone	40.6	0.51
C34	CX3	Perlolyrine	65.95	0.27
C35	CX4	senkyunone	47.66	0.24
C36	CX5	wallichilide	42.31	0.71
C37	CX6	FA	68.96	0.71
C38	CX7	Senkyunolide A	26.56	0.07
C39	CX8	(Z)-Ligustilide	53.72	0.07
C40	CX9	tetramethylpyrazine	20.01	0.03
C41	RS1	Diop	43.59	0.39
C42	RS2	Inermin	65.83	0.54
C43	RS3	kaempferol	41.88	0.24
C44	RS4	Aposiopolamine	66.65	0.22
C45	RS5	Celabenzine	101.88	0.49
C46	RS6	Dianthramine	40.45	0.2
C47	RS7	arachidonate	45.57	0.2
C48	RS8	Frutinone A	65.9	0.34
C49	RS9	Girinimbin	61.22	0.31
C50	RS10	malkangunin	57.71	0.63
C51	RS11	suchilactone	57.52	0.56
C52	RS12	ginsenoside Rb1	—	—
C53	RS13	ginsenoside Rg1	—	—

Compound	herb	Chemical	OB	DL
C54	RS14	ginsenoside Rg3	---	---
C55	RS15	ginsenoside Rd	---	---
C56	RS16	ginsenoside Re	---	---
C57	SX1	Musccone	---	---
C58	BP1	asiatic acid	---	---
C59	BP2	bronyl acetate	41.38	0.71
C60	BP3	dipterocarpol	59.3	0.51
C61	SHX1	cinnamaldehyde	41.71	0.76
C62	SHX2	BENZYL BENZOATE	31.99	0.02

Candidate targets screening

As results, a total of 831 putative targets were screened from PharmMapper. Among them, there were 341 putative targets for YHS, 212 for CX, 182 for RS, 11 for SX, 71 for BP and 12 for SHX. Further, we obtained 104 candidate targets connected with CHD from Genecards platform, among which the top ten in terms of degree included TTR, PIPN1, AKR1C3, PDE4D, HSP90AA1, FKBP1A, MME, MAPK14, VDR and CA2.

Construction of drug-components-targets network

In addition, we generated drug-components-targets network on the basis of Cytoscape 3.6.0 software. As shown in Fig. 2, the network comprises of 171 nodes, the nodes in yellow are the six herbs in XTN, the nodes in blue are the chemical components of drugs and the nodes in red are the candidate targets.

Construction of PPI network

The STRING database was used to construct PPI network model. Then the model was introduced into Cytoscape 3.6. 0 software to produce PPI network diagram(Fig. 3). As shown in Fig. 4, the top 30 core proteins include ALB, IGF1, SRC, CASP3, EGFR, ESR1,HRAS, HSP90AA1, MAPK14, STAT1, Bcl2I1, NOS3, AR, IL2, NR3C1, PPARG, KDR, MAP2K1, ACE, PGR, ABL1, F2, CCNA2, GSK3B, CDK2, LCK, PTPN1, REN, CDKN1B and KNT. .

Functional analysis of candidate targets

As exhibited in Fig. 5, the candidate targets of XTN were involved in numerous biological functions, including steroid hormone receptor activity, nuclear receptor activity, transcription factor activity, director ligand regulated sequence-specific binding, steroid binding, monocarboxylic acid binding, nuclear receptor coactivator activity, protein tyrosine kinase activity, carboxylic acid binding, transmembrane receptor protein kinase activity, organic acid binding, fatty acid binding, transcription coactivator activity,

transmembrane receptor protein tyrosine kinase activity, hormone binding, endopeptidase activity, phosphatase binding, protein phosphatase binding, DNA-binding transcription activator activity, RNA polymerase- α -specific, SH2 domain binding and nuclear hormone receptor binding.

In addition, the KEGG pathway enrichment shed light on the pathways that the candidate targets involved in. As shown in Fig. 6, the treatment of XTN against CHD was closely associated with PI3K-Akt signaling pathway, MAPK signaling pathway, Ras signaling pathway, Rap1 signaling pathway, EGFR tyrosine kinase inhibitor resistance, FoxO signaling pathway, Th17 cell differentiation, Endocrine resistance, etc.

Discussion

TCM refers to a natural healthcare, holistic system based on over 2000 years of principles and practice which takes all aspects of patients' life into account rather than just apparent symptoms[33,34]. As the saying goes, "treatment aiming at its pathogenesis" and "treating both manifestation and root cause of disease". TCM prescriptions are usually made up of several herbs to play a synergistic role. At the same time, this also makes it difficult to interpret the mechanism of TCM, hindering its widespread clinic application in the world[35]. Network pharmacology connects the main, supplementary and auxiliary therapeutic components of traditional Chinese medicine prescriptions with the main, supplementary and auxiliary targets in the disease network[36]. In the present study, the network pharmacology approach offers an effective channel for uncovering the mechanisms of XTN including its active components and CHD-related targets. Firstly, we focused on the 62 candidate targets. Secondly, drug-components-targets network were constructed. Thirdly, the PPI network was constructed. Subsequently, we analyzed the mechanism of XTN by mapping the candidate targets onto the pathway enrichment.

XTN is a classic TCM formula composing of 6 herbs with considerable effects on CHD. After OB and DL filtering, 62 bioactive compounds were obtained from TCMSP databases that is commonly adopted[37]. The pharmacological activities of these components in CHD have been reported previously. For example, Dehydrocorydalin, an active component of YHS, is known for its anti-platelet, anti-inflammatory and anti-myocardial hypoxia activities[38]; Hyndarin is a natural alkaloid isolated from YHS, which has been proved to exert various cardiovascular effects, namely anti-apoptosis, anti-oxidant, cardioprotection and improving cerebral ischemia-reperfusion injuries[39–41]. In addition, Muscone is the active compound of SX, several studies have shown that it has anti-cerebral ischemia and anti-myocardial ischemia activities. Accordingly, this indicates that multiple components of XTN function through multiple targets.

There are 104 overlapping targets genes between XTN and CHD. Besides, we obtained the top 10 genes from the drug-components-targets network according to the degree value, which may be the key genes in the treatment of CHD. Moreover, we get the core proteins of interests, Casp3 and Bcl2l1 from PPI network. Casp3 is closely related to apoptosis and plays critical role in apoptotic pathway[42]. One of the earliest changes of apoptosis is characterized by the emergence of a series of proteases - Caspases. Activated caspases cleaves many intracellular enzymes and causes morphological changes of apoptotic cells; the

core of this process is exactly the activation of Casp-3[43]. Bcl2l1 is an anti-apoptotic protein, which is a downstream protein in the PI3K-Akt pathway. Based on the results of biological functional analysis, there are a variety of pathways like PI3K-Akt signaling pathway, MAPK signaling pathway, FoxO signaling pathway[44], Ras signaling pathway[45] and Endocrine resistance[46], are robustly correlated with the pathogenesis of CHD. Interestingly, the PI3K-AKT signaling pathway has been reported to participate in the signal transduction that related to various cell activities such as proliferation, differentiation and apoptosis[47]. It balances the pro-apoptotic (Bax, Bad, Bcl-xs) and anti-apoptotic (Bcl-2, Bcl-xl) in Bcl-2 family via activation of caspases and the Bcl-2 family, thereby tightly regulates cell apoptosis as shown in Fig. 7[48]. Meanwhile, as the members of Bcl-2 family, Bcl-2 and Bcl-xl are also significant anti-oxidant proteins that play a vital role in scavenging free radicals and reducing the production of superoxides[49]. Zhu et al. demonstrated that the up-regulation of Bcl2 expression in PI3K-Akt pathway can effectively protect the injury caused by ischemia and hypoxia[50]. Apart from this, the MAPK pathway, which is relevant with the occurrence of various pathological processes, mediates a variety of cell functions, such as proliferation, differentiation, transformation and apoptosis through phosphorylation of cytoskeletal proteins and nuclear transcription factor [51]. A study has shown that the activation of MAPK pathway may stimulate the release of some inflammatory mediators, specifically MMP9 and IL-6, which leads to the process of atherosclerosis[52]. Additionally, Yuan et al. [53]believed that the up-regulation of MAPK pathways could promote angiogenesis. In general, the effect of XTN against CHD may achieve by regulating the expression of apoptosis factors, inflammatory mediators and via multiple pathways such as PI3K-Akt pathway and MAPK pathway.

It seems that the network pharmacology approach is suitable for deciphering the mechanisms of CHD. The utilization of systematic pharmacology may broaden our ideas in CHD medication therapy. However, there are still some limitations in our study. On the one hand, our research is on the basis of virtual screen and prediction that is lack of experimental support. On the other hand, the process of OB and DL screening is more likely to cause data missing of some constituents with lower OB or DL value but stronger activities. In response to these problems, In future research, further experiment validation will be conducted to verify the pathways and mechanism of XTN by in vitro and in vivo experiments.

Conclusion

In summary, the mechanism of XTN treating for CHD was analyzed systematically based on network pharmacology in this study. It offers new insights into exploring of the mechanisms underlying effects of XTN on CHD. We collected the active compounds and candidate targets of XTN, established a drug-component-targets network and a PPI network and obtained the pathways relating to CHD. The active components and targets of XTN are distributed in different pathways which can play a synergistic role in the prevention and treatment of CHD. Target proteins combining with pathway enrichment analyses indicated that XTN exerted its anti-CHD effect by regulating multiple pathways, including FoxO signaling pathway, Ras signaling pathway, Endocrine resistance, PI3K-Akt mediated cell apoptosis pathway, MAPK mediated anti-inflammatory and angiogenesis pathways and so forth. This study presents a fast,

economical and comprehensive method for the studies of XTN from a holistic view, which lays a foundation for further study and clinic utility.

Abbreviations

XTN: SheXiang XinTongNing; CHD: coronary heart disease; PCI: percutaneous coronary intervention; CABG :coronary artery bypass grafting; TCM: Traditional Chinese medicine; SX :Moschus (Shexiang); CX :Ligusticum chuanxiong (Chuanxiong); YHS: Rhizoma Corydalis(Yanhusuo); RS :Panax ginseng(Renshen); BP :Borneolum Syntheticum(Bingpian); SHX: Styrax(Suhexiang);TCMSP: traditional Chinese medicine system pharmacology analysis platform; OB :oral availability; DL:drug-likeness ; DAVID: annotation, visualization and integrated discovery database

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Z-QM and JL conceived and designed the study. GL and JL collected the data. J-XL and X-YL performed the data analysis, L-YJ and G-YC wrote the manuscript. All authors are responsible for reviewing data. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

The datasets generated and/or analysed during the current study are available in the TCMSP, <http://tcmspw.com/>

Pubchem <https://pubchem.ncbi.nlm.nih.gov/>

PharmMapper <http://www.lilab-ecust.cn/pharmmapper/>

UniProt <http://www.uniprot.org/>

Genecards <https://www.genecards.org/>

Cytoscape 3.6.0 <https://cytoscape.org/>

STRING <http://string-db.org/>

DAVID <https://david.ncifcrf.gov/>

Ethics approval and consent to participate

Not applicable.

Consent for publication

The manuscript is approved by all authors for publication.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

The flowchart of the network pharmacology-based strategy for unraveling the mechanisms of XTN against CHD.

Figure 2
drug-components-targets network of 6 herbs in XTN predicted to have 104 candidate targets, the blue nodes represents chemical components and the red are candidate targets.

Figure 3

PPI network of XTN against CHD.

Figure 4

PPI network core proteins

Figure 5

Top 20 of biological process enrichment. Results showed that the candidate targets involved in a variety of biological processes, such as steroid hormone receptor activity, nuclear receptor activity, transcription factor activity, director ligand regulated sequence-specific binding

Figure 6

Top 20 of pathway enrichment. Molecular signaling pathways of XTN were highlighted, such as PI3K-Akt signaling pathway, MAPK signaling pathway, Ras signaling pathway, Rap1 signaling pathway

Figure 7

Illustration of the biological process PI3K-Akt pathway caused by candidate targets.