

The molecular mechanisms associated with PIN7, a protein-protein interaction network of seven pleiotropic proteins

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3 4 **Abstract:**

5 The protein-protein interaction network of seven pleiotropic proteins (PIN7) contains proteins with
6 multiple functions in the aging and age-related diseases (TPPII, CDK2, MYBBP1A, p53, SIRT6,
7 SIRT7, and BSG). At the present work, the pathway enrichment, the gene function prediction and
8 the protein node prioritization analysis were applied for the examination of main molecular
9 mechanisms driving PIN7 and the extended network. Seven proteins of PIN7 were used as an input
10 for the analysis by GeneMania, a Cytoscape application, which constructs the protein interaction
11 network. The software also extends it using the interactions retrieved from databases of
12 experimental and predicted protein-protein and genetic interactions. The analysis identified the
13 p53 signaling pathway as the most dominant mediator of PIN7. The extended PIN7 was also
14 analyzed by Cytohubba application, which showed that the top-ranked protein nodes belong to the
15 group of histone acetyltransferases and histone deacetylases. These enzymes are involved in the
16 reverse epigenetic regulation mechanisms linked to the regulation of PTK2, NFκB, and p53
17 signaling interaction subnetworks of the extended PIN7. The analysis emphasized the role of PTK2
18 signaling, which functions upstream of the p53 signaling pathway and its interaction network
19 includes all members of the sirtuin family. Further, the analysis suggested the involvement of
20 molecular mechanisms related to metastatic cancer (prostate cancer, small cell lung cancer),
21 hemostasis, the regulation of the thyroid hormones and the cell cycle G1/S checkpoint. The

additional data-mining analysis showed that the small protein interaction network MYBBP1A-p53-TPPII-SIRT6-CD147 controls Warburg effect and MYBBP1A-p53-TPPII-SIRT7-BSG influences mTOR signaling and autophagy. Further investigations of the detail mechanisms of these interaction networks would be beneficial for the development of novel treatments for aging and age-related diseases.

Keywords: TPPII, p53, CDK2, MYBBP1A, SIRT7, SIRT6, CD147

Abbreviations: PTK2 – Protein tyrosine kinase 2; PIN7 – protein interaction network of seven pleiotropic proteins

Introduction:

The molecular mechanisms occurring in the living organisms are based on the complexity of diverse types of interactions. The solving of the complex biological networks is one of the most challenging tasks occurring during the interpretation of the multiple factors affecting the outcome of the targeting of the metabolic and signaling pathways. The interaction networks constructed based on the databases with genomic and proteomic data can assist in the identification of the controlling network nodes suitable for the pharmacological interventions. Likewise, they could be applied for the gene function predictions if the experimental data are missing.

According to the basic model of the network medicine the targeting of the disease pathologies through just the single node seems not feasible (Nolan, 2007). The idea to study the interaction networks is supported by the theory, that the proteins interacting directly via protein-protein interactions are very probably participating on the identical cellular and molecular functions. If

they represent disease genes, the mutations in their genes lead to similar disease phenotypes (Oti, 2006). The most promising drug targeting strategies are based on the partial inhibition of several nodes within the interaction network instead of the complete inhibition of the single node (Csermely et al., 2005), which is pharmaceutically very challenging.

PIN7 is a protein-protein interaction network created by seven proteins (TPPII, MYBBP1A, p53, CDK2, SIRT6, SIRT7, and CD147) connected via multiple physical interactions, which interestingly share their functions in tumorigenesis, neurodegeneration, and aging (Nahálková, 2016). The animal and cellular models with downregulated or knockout TPPII, p53, SIRT6, SIRT7 and MYBBP1A expression levels demonstrate similar age-related phenotype features, which suggests mutual molecular mechanisms driving the functions of the interacting proteins. They exhibit a shortened lifespan, premature aging, and altered lipid metabolism (Nahálková, 2016). The current study shows the protein function prediction analysis and the identification of the essential protein nodes driving the typical functions of PIN7 nodes and its extended network. The results are discussed in light of the potential use of the central protein nodes for the discovery of new regulatory ways of the pharmaceutical interventions.

Materials and methods:

The bioinformatic analysis was accomplished using Cytoscape (3.6.1) software (Cline et al., 2007) equipped with GeneMania (3.4.1) (Warde-Farley et al., 2010), ClusterOne (1.0) (Nepusz et al., 2012), Cytohubba (0.1) (Schneider and Laskowski, 1974), and Agilent Literature Search 3.1.1 (Cline et al., 2007) applications. The GeneMania (3.4.1) database search was performed using PIN7 (TPPII, MYBBP1A, CDK2, p53, SIRT6, SIRT7, CD147) as a query against *H. sapiens*

database and including all types of the interaction networks. The analysis was set up for a finding of the top 20 related genes and at the most 20 attributes via GO Molecular function weighting. Figure S1 shows the legend determining the types of the nodes and their interactions.

The resulting network was further analyzed by ClusterOne application for the identification of the most significant interaction groups, which was set up as following: Basic parameters: Minimum size - 3; Minimum density - auto; Edge weights - normalized max weight; Advanced parameters: Node penalty - 2; Haircut threshold - 0; Merging method - multi-pass; Similarity - Simpson coefficient; Overlap threshold - 0.8; Seeding method - from every node.

The central protein nodes and pathways of the extended PIN7 network were identified by the Cytohubba application using the topological method Maximum click centrality (MCC), which provides according to the developers the highest precision in the prediction of the essential nodes (Schneider and Laskowski, 1974). The analysis settings were further adjusted for the selection of the first-stage nodes and the display of the shortest path.

Results and discussion:

PIN7 nodes are involved in the molecular mechanisms of tumorigenesis, age-related diseases as well as healthy aging. Therefore, the pharmacological modulators of PIN7 and the extended network could provide alternative solutions for anti-tumor, anti-aging and neuroprotection therapies. They play multiple functions within the cell cycle, apoptosis, the cytoskeleton remodeling and the regulation of the primary metabolism of the tumor cells including aerobic glycolysis and lipid metabolism (Nahálková, 2016). The aging-related molecular function is supported by the similar phenotypes of TPPII, p53, SIRT6, SIRT7, and MYBBP1A knockout mice

and cell models, which suggest that PIN7 takes part in the mechanisms regulating the cellular senescence, aging and the length of lifespan (Nahálková, 2016). Likewise, the expression of the node CD147 (BSG, EMMPRIN) correlates with aging since this glycoprotein is differentially upregulated in the skin of the older adults (Li et al., 2011) and the hearts of the aging mouse and rat models (Huet et al., 2015). CD147 is a marker of age-dependent platelet activation. However, the monocyte expression correlates with coronary artery disease without the significant impact of the age (Pennings et al., 2010).

The molecular mechanisms driving PIN7 are deduced based on the functions of the most studied protein nodes since the interactions between PIN7 nodes are not fully characterized. At the present study, the bioinformatic analysis was applied for the prediction of the new molecular mechanisms driving PIN7 and the extended interaction network. For this purpose, the consolidated pathway enrichment analysis and the gene function prediction analysis (GeneMania) was implemented in combination with the cluster analysis (ClusterOne) and the protein node prioritization (CytosHubba). The results will provide the base for further experimental studies by redirecting them towards potentially useful and applicable pharmaceutical targets.

Gene function prediction and protein node prioritization

The consolidated pathway model predictions integrated with GeneMania analysis are based on the applications of the combined database annotations with protein-protein interactions, genomic data and mRNA expression data (Bader et al., 2004). GeneMania analysis of PIN7 using GO Molecular function weighting revealed several consolidated pathways related to metastatic cancer (prostate cancer, small cell lung cancer), the regulation of the thyroid hormones and the cell cycle G1/S

checkpoint as a result of the gene-set enrichment (Fig. 1). The resulting PIN7 extended by GeneMania was further analyzed by the application ClusterOne, which identify the most significant overlapping protein complexes and assemble the most functionally related interacting proteins and signaling pathways into the groups.

Figure 2 shows three resulting overlapping protein complexes with the high scores (quality > 0.5). The most significant cluster 1 emphasizes the interactions of p53 and CDK2, which appear as central nodes of PIN7 with the functional connections to 8/10 consolidated signaling pathways highlighted by the GeneMania analysis. Further, the cluster 1 excludes PTK2 signaling and hemostasis ranked with the lower priority and involved in cluster 2. BSG included in cluster 2 is based on the results of the analysis involved in the hemostasis and indirectly in PTK2 signaling. CD147 contributes to the interactions of platelets with monocytes, which supports this finding (Schulz et al., 2011). Further, the gene silencing of CD147 has a down-regulating effect on PTK2 expression in hepatocellular cell carcinoma through the ERK1/2 pathway, which makes CD147 the attractive target for the pathway inhibition in the cancer cells (Xu et al., 2007). The third significant cluster grouped the whole sirtuin family with the PTK2 signaling, which validated the results of the analysis by GeneMania application and it will be the subject of further discussions.

PTK2 (FAK) signaling subnetwork (priority nodes CREBBP, EP300, KAT2B, CDKN1A, TP53, RELA, NFKB1, HDAC1, SIRT1, SIRT6, SIRT7)

The protein-tyrosine kinase (PTK2) (Focal Adhesion Kinase; FAK) signaling pathway obtained high scores by GeneMania, ClusterOne and Cytohubba analysis (Fig. 1, Fig. 2, Fig. 3). The PTK2 interaction cluster constructed by GeneMania application included all the top rank protein nodes

of the extended PIN7 highlighted by the Cytohubba analysis (Fig. 1C) and three PIN7 nodes (p53, SIRT6, SIRT7). The statistical analysis of the second-order sirtuin interaction network constructed from the data retrieved from the human genomic aging resource dataset supports the presented results as well. PTK2 and PTK2B are among the proteins connecting the sirtuins to the mechanisms of aging (Sharma et al., 2013).

PTK2 is considered a target for cancer therapy for about the last 20 years. The targeted decreasing of PTK2 expression is highly desirable for breast cancer treatments since the tumor cells contain high expression levels of the enzyme. PTK2 functionally supports all stages of the mammary tumorigenesis from the initiation up to the metastasis through the promotion of the cancer cell proliferation, migration, and senescence resistance. RAS and PI3K signaling are PTK2 dependent and the silencing of the kinase can make the RAS initiated mammary tumor cells senescent and non-invasive (Pylayeva et al., 2009). N-terminus of PTK2 also physically interacts with the N-terminal transactivation domain of p53 and inhibits its transcription, which makes PTK2 (Golubovskaya et al., 2005) a central upstream protein node for the regulation of p53. Further, p53 binds to PTK2 promoter and represses its transcription during the tumorigenesis (Golubovskaya et al., 2008). It creates the regulatory feedback loop between the two signaling pathways, which provides an attractive option for pharmacological interventions.

SIRT1 and SIRT3 actively regulate PTK2 gene expression; however, the detail mechanisms of the functionality are not known. PTK2 is a substrate of SIRT1, which was demonstrated by observations completed using myeloid-specific SIRT1 knockout mice. The animals have specifically upregulated PTK2 both at mRNA and protein levels. Conversely, the upregulation of SIRT1 in HEK293 cells caused downregulation of PTK2 and its acetylation (Ka et al., 2015).

Moreover, the sirtuins are linked to the NF- κ B signaling pathway, which further controls PTK2 signaling (Fig. 3). SIRT1 decreases NF- κ B1 signaling through the deacetylation of NF- κ B1 (Lee et al., 2009) and NF- κ B1 positively regulates PTK2 expression by direct binding to the PTK2 promoter and the activation of its transcriptional activity (Golubovskaya et al., 2004). Previously, it was suggested that the oncogenic function of SIRT3 is beside other crucial signaling pathways, mediated through PTK2 (Chen et al., 2014). SIRT3 binds near to the transcription start site of PTK2 gene, which is followed by the deacetylation of H4K16 at PTK2 promoter (Iwahara et al., 2012). Then, the overexpression of the nuclear SIRT3 represses the stress-induced activation of PTK2, and the stress-induced degradation of the nuclear SIRT3 activates the PTK2 transcriptional activity (Iwahara et al., 2012).

The modulators of the sirtuins and other protein nodes of PTK2 signaling subnetwork (Fig. 3) provide alternative options for the targeting of the PTK2 expression. Because of the regulatory function of the PTK2 signaling pathway, it represents the pharmaceutical drug target for the modulation of the p53 pathway.

Hemostasis (priority nodes CREBBP, EP300, TP53, HDAC1)

Hemostasis as a physiological process of the stopping of the blood flow on the site of the injury has obtained high score among the pathways significantly driving the functions of PIN7, which nodes are highly connected to the molecular mechanisms of aging (Fig. 4). The mutation of the genes belonging to the pathways with the roles in the blood coagulation and wound healing is significantly linked to the longevity in the primates, and they accumulate pleiotropic effects (Muntane et al., 2018). It is in agreement with the antagonistic pleiotropy theory of aging

(Williams, 2006) and with the aging-related functions of several protein nodes of PIN7 (Nahálková, 2016).

BARD1 signaling (priority node p53)

The interaction network of BRCA1 associated ring domain 1 (BARD1) contains one priority node p53 and two PIN7 nodes (p53 and CDK2). BARD1 is a protein essential for the tumor suppressor function of BRCA1. It physically interacts with the N-terminal region of BRCA1 and its mutations are the subjects of the oncogenic transformations in breast cancer (Wu et al., 1996).

TSH signaling

The constructed Thyroid Stimulating Hormone (TSH) interaction network (Fig. 5) does not contain any priority nodes; however, it involves two PIN7 proteins (BSG, CDK2). TSH affects BSG expression through the complex generated with monocarboxylate transporters (MCT), which are required for the efflux of the lactic acid produced by the TSH stimulated glycolysis. The presence of the hormone further upregulates the complex of MCT/BSG, which is necessary for the expression of BSG and its translocation to the cytoplasmic membrane (Fanelli et al., 2003).

G1/S pathway (priority nodes CDKN1A, HDAC1, TP53) and RB signaling

The interaction network controlling G1/S checkpoint emphasizes the role of three priority nodes CDKN1A, HDAC1, TP53, while CDK2 is also a part of the network as PIN7 node. Since retinoblastoma protein (RB) has a significant regulatory function on G1/S checkpoint and it is included in the network, both interaction networks were merged (Fig. 6). The role of p53, CDK2,

ATM, ATR and RB signaling in the regulation of G1/S checkpoint of the cell cycle was already previously well summarized elsewhere (Bartek and Lukas, 2001). The expression of TP53 causes cell cycle arrest by the transcriptional activation of CDKN1A (Yu et al., 2003) and both priority nodes plays a role in the induction of G1/S checkpoint as a response to DNA damage after irradiation (Badie et al., 2008). Additional priority node HDAC1 and other histone deacetylases belonging to the HDAC class I and II have an importance for the treatment of chemotherapy-resistant and metastatic cancers. Non-specific HDAC inhibitors can arrest the cancer cells in G1/S checkpoint, which corresponds to the decreased phosphorylation of CDK2 and causes the apoptosis of the sarcoma cells (Kaltenegger et al., 2017). Finally, another protein regulatory node of the interaction network is RB, since its low phosphorylation can arrest the mammalian cells in the late G1 (Berndt et al., 2004).

Histone acetyltransferases/deacetylases and their target proteins (priority nodes CREBBP, p300, KAT2B, p53, CDKN1A, HDAC1, SIRT1)

The prioritization of the proteins and pathways within the extended PIN7 performed by CytosHubba application (Fig. 1C) emphasized the role of the proteins involved in the transcriptional regulation of the histone and non-histone substrates through acetylation/deacetylation of ϵ -amino group of the lysine (Yang and Seto, 2007). The highest significance nodes CREBBP, EP300, and KAT2, represent the histone acetyltransferases (HATs), which acetylate their substrates by transferring the acetyl group to the lysine through acetyl-CoA. Top rank protein nodes HDAC1 and SIRT1 are the histone deacetylases (HDACs), which are significantly linked especially to PTK2 signaling subnetwork (Fig. 3), p53 and NF- κ B signaling pathways. The enzymatic complex CREBBP/p300 (CBP/p300) can acetylate all four histones, and it occurs in the complex with KAT2B (PCAF).

The recruitment of CREBBP bromodomain to the binding site AcK382 of p53 is required for the transcriptional activation of other top rank protein node cyclin-dependent kinase inhibitor p21 (CDKN1A), and it leads to G1 cell cycle arrest as a part of DNA damage response (Mujtaba et al., 2004).

The regulation of the Warburg effect (PIN7 nodes CD147, TPPII, SIRT6, MYBBP1A, p53)

Several protein nodes of PIN7 engage in a role in the metabolism of the cancer cells by altering glucose metabolism. CD147 regulates the Warburg effect by increasing the aerobic glycolysis of the cancer cells through the inhibition of p53 signaling (Huang et al., 2014). The downregulation of CD147 decreases the malignant potential in pancreatic cancer cells probably through the effect on the functionality of the lactate transporters MCT1 and MCT4 when the cells are dependent on the Warburg effect (Schneiderhan et al., 2009). Among other protein nodes, TPPII regulates the major glycolytic enzymes necessary for the metabolism of cancer cells (Lu et al., 2014), specifically pyruvate kinase M2 (PKM2) and hexokinase 2 (HK2) (Christofk et al., 2008). The isoform PKM2 is considered as a critical player in the promotion of the tumorigenesis by supporting the metabolic switch towards aerobic glycolysis occurring in Warburg effect. Likewise, the decreased expression of SIRT6 in tumors accelerates glycolysis, tumor growth and suppresses the oxidative phosphorylation by elevating the HIF-1 α transcription (Sebastián et al., 2012). All three protein nodes with the controlling effect on the glycolysis (CD147, TPPII, and SIRT6) interact with MYBBP1A (Nahálková and Tomkinson, 2014); (Huttlín et al., 2017); (Polyakova et al., 2012), the regulatory protein of p53 transcription (Ono et al., 2014). MYBBP1A enhances the p53 transcription by direct interaction with C-terminal lysine, which augments its tetramerization and facilitates its acetylation through p53-p300 interaction (Kuroda et al., 2011) (Ono et al., 2014).

The central protein node p53 both negatively regulates glycolysis and positively controls the oxidative phosphorylation (Madan et al., 2011), and it directly interacts with other protein nodes of PIN7. Together with p53, these protein nodes create small interaction network with direct protein-protein interactions, which might represent the subject for multitarget control of the Warburg effect.

NF- κ B signaling

NF- κ B1 and RelA are two members of the NF- κ B group of the structurally conserved proteins, which were included on the list of the priority protein nodes driving the extended PIN7 (Fig. 1C). The involvement of the NF- κ B signaling pathway in PIN7 function is not surprising, since the proteins TPPII, MYBBP1A, and SIRT6 affect the function of NF- κ B (Nahálková, 2016). The hyperactivity of NF- κ B signaling was previously associated to the premature and healthy aging (Kawahara et al., 2009), which could also mediate the aging-related functionality of several PIN7 proteins (Owen et al., 2007); (Polyakova et al., 2012); (Kawahara et al., 2009); (Nahálková, 2016). The inhibition of apoptosis, the stimulation of the cell proliferation and the increasing of the immune and inflammatory responses by NF- κ B signaling is potentially interesting for the development of Alzheimer's disease, cancer, and diabetes treatments (Serasanambati and Chilakapati, 2016). Its direct regulation is, however, rather difficult due to the potentially multiple side effects. NF- κ B complex consists of several regulatory proteins, it has a high number of molecular targets, and it is involved in too many human pathologies. Its pleiotrophic functionality in human diseases would require the multitargeting of the interaction network such as PIN7.

Literature mining and Agilent Literature Search 3.1.1

Regulation of mTOR and autophagy by PIN7 nodes TPPII, SIRT7, p53, and CD147

Another molecular mechanism potentially mediating the age-related effects of PIN7 is mTOR signaling and autophagy (Nahálková, 2016). This theory is supported by several experimental pieces of evidence of the physical interactions between PIN7 and mTOR and by the basic concept of the network medicine, that the proteins interacting directly via protein-protein interactions are very probably participating on the identical cellular and molecular functions (Oti, 2006).

The most crucial consolidated pathway linked to the function of the extended PIN7 is p53 signaling pathway (Fig. 1), which controls mTOR signaling. In medullary thyroid cancer, the function of the tumor suppressor p53 inhibits the tumorigenesis by reducing mTOR signaling and reverse, the mTOR pathway is activated by the loss of p53 function mutations (Datan et al., 2016). Direct targeting of p53 is under intensive scientific investigation for the last 40 years, however with little clinical outcome for the patients. Therefore, the alternative targets downstream of p53 such as mTOR signaling pathway represent encouraging option for the cancer treatment (Datan et al., 2016).

Further literature mining and the use of Agilent Literature Search 3.1.1 application identified additional interactions between central protein nodes of PIN7 and mTOR (Fig. 7). The enzymatic activity of TPPII has a significant influence on mTOR signaling (Lu et al., 2014) and SIRT7 directly physically interacts with mTOR (Tsai et al., 2014). The SIRT7 downregulation also activates autophagy in rat cardiac fibroblasts through the direct effect on the mTOR pathway (Araki et al., 2015).

Further, the interaction of another PIN7 node CD147 with mTOR was identified by the combination of the affinity purification and MS identification. The downregulation of CD147 decreased the expression of AKT and mTOR, which suggests that the regulation probably occurs through the PI3K/AKT/mTOR pathway. CD147 also has an activation effect on autophagy in PC3 cells (Fang et al., 2015). MYBBP1A is linked to PIN7 through protein-protein interactions with CD147, TPPII, p53 and SIRT7, which were demonstrated experimentally (Huttlin et al., 2015) (Tsai et al., 2012) (Jiang et al., 2017) (Kuroda et al., 2011) (Nahálková and Tomkinson, 2014). Three linking nodes SIRT7, TPPII, and CD147 have functional relationships on mTOR signaling, which might suggest a functional connection between MYBBP1A and mTOR as well. It seems PI3K/AKT/mTOR signaling pathway has importance in patients with low MYBBP1A levels due to the degradation caused by DNA damage (George et al., 2015).

In the most cases, the mTOR activity inhibits autophagy (Liang et al., 1999) (Qu et al., 2003) (Zappavigna et al., 2013), which is involved in the longevity effects. Interestingly, the inhibition of the second the most significant node EP300 (p300) by salicylate stimulates autophagy and activates the calorie-restriction effect, which has an impact on longevity (Pietrocola et al., 2018). However, the autophagy also represents a significant antitumor mechanism, despite there are exceptions with the promotion effect (Zappavigna et al., 2013). The autophagy activators and inhibitors are highly desirable for cancer therapies due to the double role of autophagy in cancer (Journal, 2015).

The elucidation of the molecular mechanisms connecting the interaction network MYBBP1A-p53-TPPII-SIRT7-BSG to mTOR signaling and autophagy would be beneficial for the development of the treatments of cancer, aging, and age-related diseases. Further exploration of new mTOR

inhibitors and autophagy modulators would be beneficial for the achieving of the anti-cancer and neuroprotective treatments and for the active life extension.

Conclusions

The pleiotropic character of the fairly small interaction network PIN7 is rather interesting since its protein nodes are suitable multiple targets for the pharmaceutical interventions. Here, the bioinformatic analysis exposed several key signaling pathways and the essential nodes driving the PIN7 network extended by GeneMania application. The most dominant is the p53 signaling pathway, and the significantly scored protein nodes HATs and HDACs interaction networks, which represent the reverse epigenetic regulation mechanisms regulating PTK2, NFκB, and p53 signaling. The analysis emphasized the role of PTK2 signaling with mutual regulatory of the p53 signaling pathway, which has the potential for further experimental discoveries. The elucidation of the regulation of Warburg effect by small interaction network MYBBP1A-p53-TPPII-SIRT6-CD147 and the clarification of the regulatory effect of MYBBP1A-p53-TPPII-SIRT7-BSG on mTOR signaling and autophagy would be beneficial for the development of novel treatment for cancer, aging, and age-related diseases.

Conflicts of interest

There is no conflict to declare

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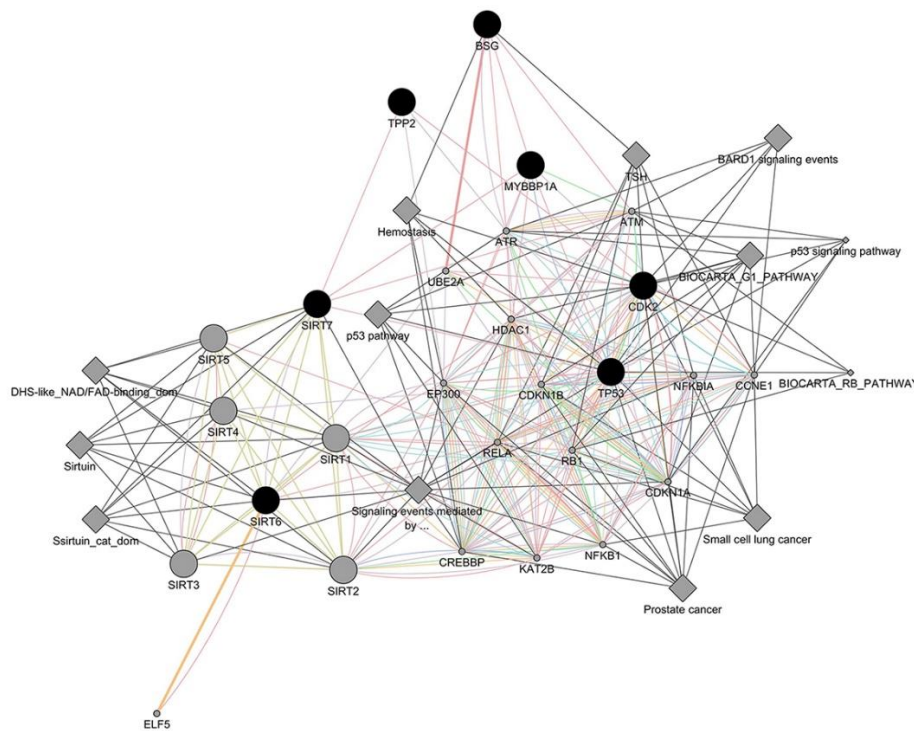
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A.



B.

Consolidated Pathway	Score	Database description
Prostate cancer	32.75	KEGG hsa05215 Prostate cancer
p53 pathway	4.97	PATHWAY INTERACTION DATABASE NCI-NATURE CURATED DATA P53 PATHWAY p53 pathway
Hemostasis	3.98	REACTOME REACT_60444 Hemostasis
BARD1 signaling events	3.20	PATHWAY INTERACTION DATABASE NCI-NATURE CURATED DATA BARD1 SIGNALING EVENTS
TSH	3.17	NETPATH TSH TSH
BIOCARTE_G1_PATHWAY	3.02	MSIGDB_C2 BIOCARTE_G1_PATHWAY BIOCARTE_G1_PATHWAY
Signaling events mediated by focal adhesion kinase	2.35	PATHWAY INTERACTION DATABASE NCI-NATURE CURATED DATA SIGNALING EVENTS MEDIATED BY FOCAL ADHESION KINASE
Small cell lung cancer	2.16	KEGG hsa05222 Small cell lung cancer
BIOCARTE_RB_PATHWAY	0.83	MSIGDB_C2 BIOCARTE_RB_PATHWAY BIOCARTE_RB_PATHWAY
p53 signaling pathway	0.04	KEGG hsa04115 p53 signaling pathway

C.

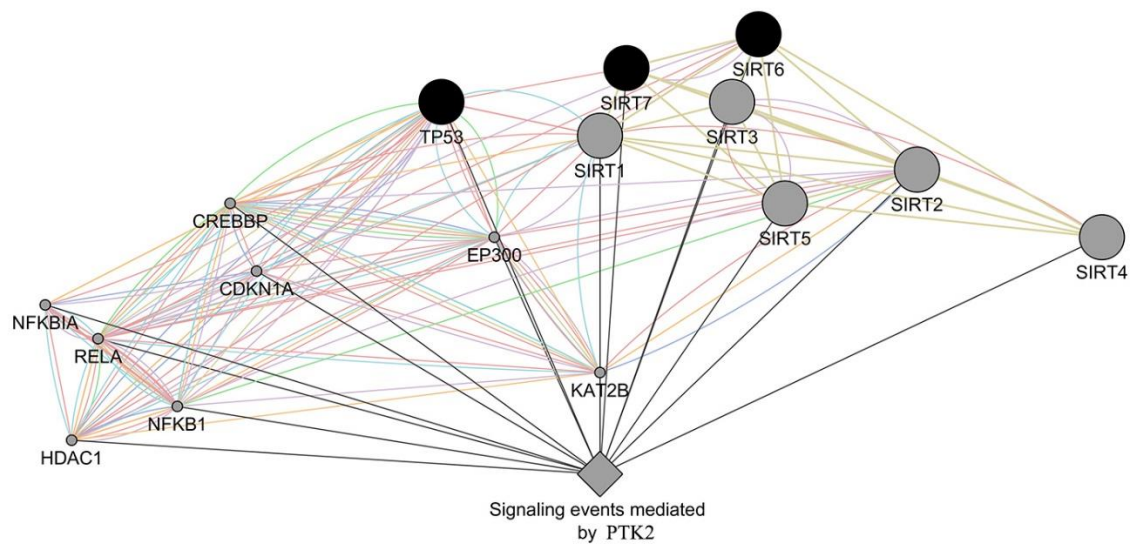
Rank	Protein node/signaling pathway	Score
1	CREBBP	61056.0
2	EP300	60510.0
3	KAT2B	58326.0
4	Signaling events mediated by PTK2	57030.0
5	CDKN1A	56292.0
6	TP53	55794.0
7	RELA	53048.0
8	NFKB1	52830.0
9	HDAC1	51432.0
10	SIRT1	27008.0

1

2 Figure 1 GeneMania analysis of PIN7 using GO Molecular function weighting (A.) identified
3 several consolidated pathways driving the effect of the extended interaction network (B.). The
4 protein node prioritization of the extended PIN7 was further performed by Cytohubba (0.1)
5 application using the topological method Maximum click centrality (MCC), the selection of the
6 first-stage nodes and the display of the shortest path as the analysis settings.



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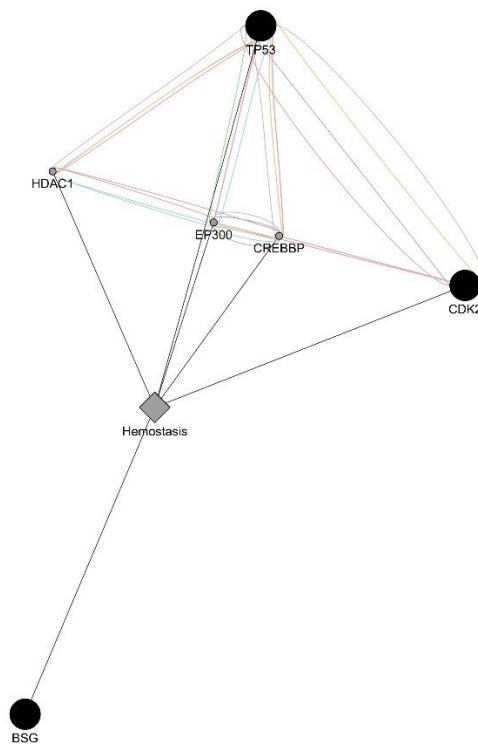
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3 Figure 3 The interaction network of PTK2 signaling pathway obtained by GeneMania analysis of
4 the extended PIN7.

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3 Figure 4 The interaction network of the hemostasis pathway obtained by GeneMania analysis of
4 the extended PIN7.

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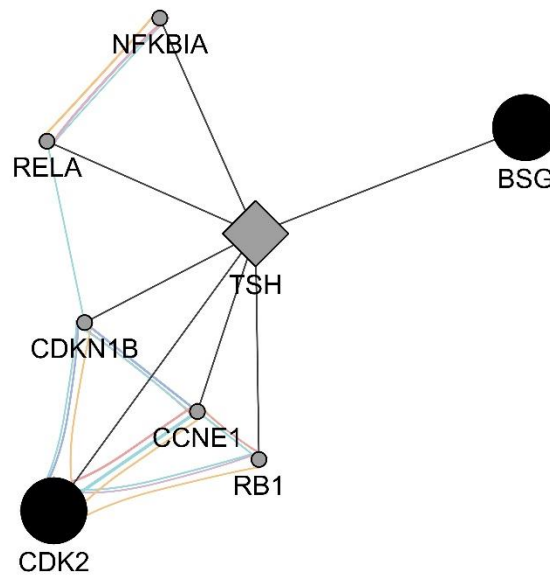


Figure 5 The interaction network of TSH signaling pathway obtained by GeneMania analysis of the extended PIN7.

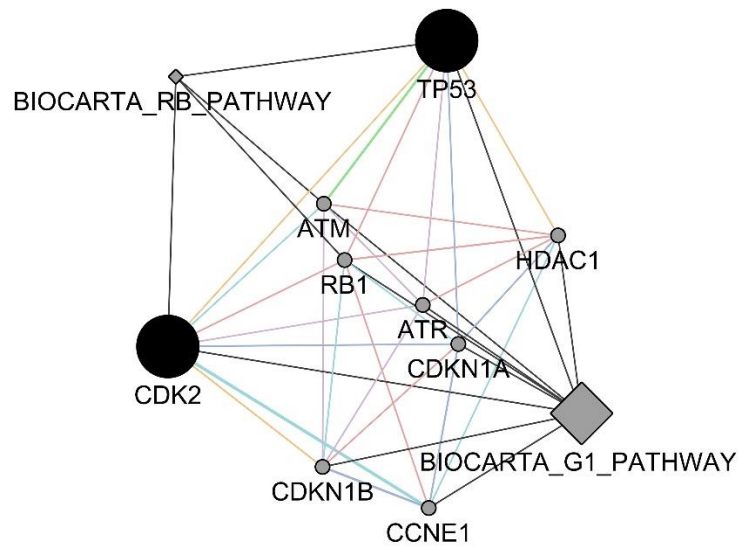
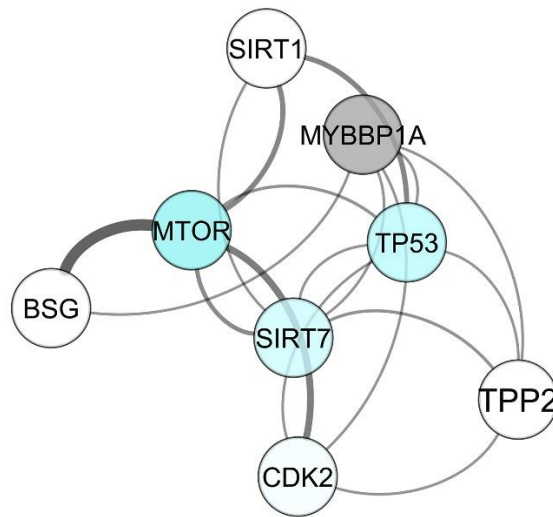


Figure 6 The interaction network of the G1/S pathway merged with RB signaling, which was obtained by GeneMania analysis of the extended PIN7.




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3 Figure 7 The interaction network of PIN7 and mTOR constructed based on the data mining and
 4 Agilent Literature Search 3.1.1. The analysis was performed using the Cytoscape 3.6.1 software
 5 with NetworkAnalyzer 3.3.2 layout. Edge and node mapping is shown in Fig. 2S.

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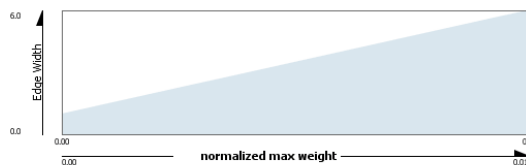
Node Shape Mapping

Node Shape	node type
	attribute








Node Fill Color Mapping

Node Fill Color	node type
	attribute
	query
	result

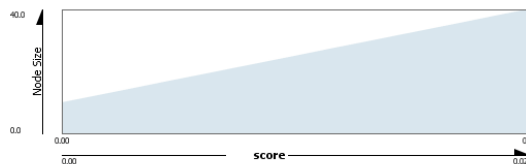
Edge Width Mapping



Edge Stroke Color (Unselected) Mapping

Edge Stroke Color (Unselected)	data type
	Co-expression
	Co-localization
	Genetic Interactions
	Pathway
	Physical Interactions
	Predicted
	Shared protein domains

Node Size Mapping



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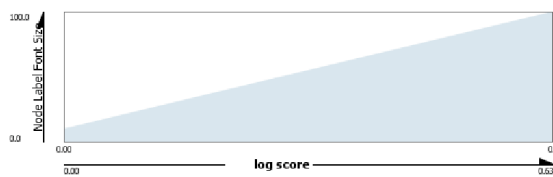
3 Figure 1S The node and edge mapping of the protein interaction networks created by GeneMania

4 analysis.

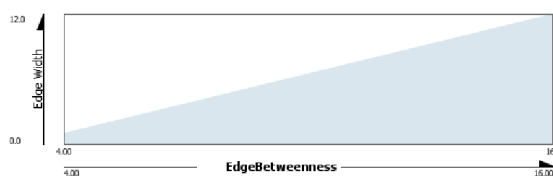
Edge Stroke Color (Unselected) Mapping



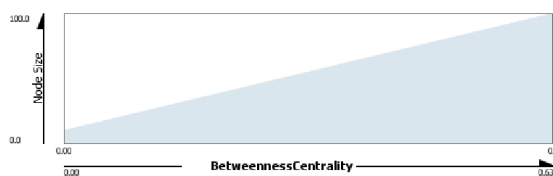
Node Label Font Size Mapping



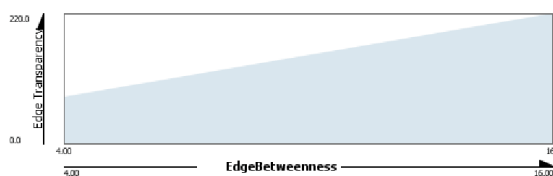
Edge Width Mapping



Node Size Mapping



Edge Transparency Mapping



Node Fill Color Mapping



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3 Figure 2S The node and edge mapping of the interaction network of PIN7 and mTOR.