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Parathyroid Hormone-Like Hormone *(PTHLH)* Feedback Mitosis to Downstream DNA Replication Coupling Postreplication Repair-Induced Cell Proliferation Network in No-Tumor Hepatitis/Cirrhotic Tissues (HBV or HCV Infection) by Systems-Theoretical Analysis

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Abstract

Based on analysis of biological processes in the same low expression Parathyroid Hormone-Like Hormone (*PTHLH*) activated feedback mitosis and downstream DNA replication-mediated cell proliferation Gene Ontology (GO) network of no-tumor Hepatitis/Cirrhotic Tissues (HBV or HCV infection) compared with the corresponding high expression (fold change ≥2) activated (Gene Ontology) GO network of human Hepatocellular Carcinoma (HCC), we proposed *PTHLH* activated network that upstream consisted of cell division, cell proliferation, mitosis, mitotic checkpoint, nucleosome assembly, spindle organization and biogenesis; Downstream network cell cycle, cell cycle arrest, centrosome cycle, chromosome segregation, DNA replication, DNA replication checkpoint, G1/S transition of mitotic cell cycle, mitotic chromosome condensation, mitotic G2 checkpoint, mitotic spindle checkpoint, positive regulation of cell proliferation, regulation of cell proliferation, traversing start control point of mitotic cell cycle, positive regulation of DNA repair, postreplication repair, DNA damage response, response to DNA damage stimulus, cell division, cell proliferation, mitosis, mitotic checkpoint, nucleosome assembly, spindle organization and biogenesis, as a result of feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation in no-tumor hepatitis/cirrhotic tissues. Our hypothesis was verified by the different *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network of no-tumor hepatitis/cirrhotic tissues compared with the corresponding inhibited GO network of HCC, or the same compared with the corresponding inhibited GO network of no-tumor hepatitis/cirrhotic tissues. We constructed *PTHLH* feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation network that upstream BUB1B activated *PTHLH*, and downstream *PTHLH*-activated *BUB1B, CCNA2, CDC6, BRCA1* in no-tumor hepatitis/cirrhotic tissues from (*Gene Expression Omnibus)* GEO data set using gene regulatory network inference method and our programming.

Keywords: Computation; *PTHLH* feedback; GO network of HCC

Introduction

Parathyroid Hormone-Like Hormone (*PTHLH*) is one of our identified significant low expression genes in no-tumor Hepatitis/Cirrhotic Tissues (HBV or HCV infection) compared with high expression (fold change ≥2) human Hepatocellular Carcinoma (HCC) from (*Gene Expression Omnibus)* GEO data set GSE10140-10141(http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE10140, http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE10141) [1].

Study of Parathyroid Hormone-Like Hormone (*PTHLH*) is presented in several papers as follows: Parathyroid hormone-like hormone (*PTHLH*) inhibits decidualization of human uterine fibroblast cells by an autocrine/paracrine mechanism [2]; Porcine *PTHLH* gene and its relationship with sow teat number [3]; *PTHLH* is downregulated by a *cis*-regulatory site in translocation t(8;12)(q13;p11.2) and leads to Brachydactyly Type E [4]; *PTHLH* expression in human gastric mucosa enterochromaffin-like cells [5]; *PTHLH* deletion and point mutations cause brachydactyly type E [6]; Near the *PTHLH* gene, genome-wide significance and replication of the chromosome 12p11.22 locus for peripartum cardiomyopathy [7]; Duplication of 12p11.23 to 12p11.22 including *PTHLH* is related to symmetrical enchondromatosis [8]; Parathyroid Hormone-Like Activity in a Renal Carcinoma Producing Hypercalcemia [9]; A parathyroid hormone-like substance is contained in renal adenocarcinoma [10]. Yet the low expression *PTHLH* feedback mitosis and downstream DNA replication-mediated cell proliferation mechanism and network in no-tumor hepatitis/cirrhotic tissues is not clear and remains to be elucidated.

In this study, biological processes and occurrence numbers of the same *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network in no-tumor hepatitis/cirrhotic tissues were identified and computed compared with the corresponding activated GO network of HCC, the different compared with the corresponding inhibited GO network of HCC, and the same compared with the corresponding inhibited GO network of no-tumor hepatitis/cirrhotic tissues from total *PTHLH* activated GO network of no-tumor hepatitis/cirrhotic tissues by using knowledge and our programming. We extracted and computed the same *PTHLH* feedback mitosis and downstream DNA replication-mediated cell proliferation molecular network and numbers in *PTHLH* activated network of no-tumor hepatitis/cirrhotic tissues compared with *PTHLH* activated network of HCC. We identified simultaneous occurrence of biological processes between the same *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network of no-tumor hepatitis/cirrhotic tissues compared with the corresponding activated GO network of HCC,

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and the different compared with the corresponding inhibited GO network of HCC, or the same compared with the corresponding inhibited GO network of no-tumor hepatitis/cirrhotic tissues for putting forwards hypothesis of feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation. We further identified the same *PTHLH* up- and/or down-stream molecular network including different molecules but same GO term corresponding to feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation in *PTHLH* activated network of no-tumor hepatitis/cirrhotic tissues compared with *PTHLH* activated network of HCC.

Materials and Methods

Microarrays 6,144 genes were used for analyzing *PTHLH* feedback mitosis and downstream DNA replication-mediated cell proliferation mechanism and constructing molecular network of no-tumor hepatitis/cirrhotic tissues based on (*Gene Expression Omnibus)* GEO data set GSE10140-10141 (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE10140, http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE10141). The raw microarray data was preprocessed by log base 2.

225 significant low expression molecules in no-tumor hepatitis/cirrhotic tissues compared with human Hepatocellular Carcinoma (HCC) were identified using Significant Analysis of Microarrays (SAM) (http://www-stat.stanford.edu/~tibs/SAM/) [11]. We selected two classes paired and minimum fold change ≥2 under the false-discovery rate was 0%.

PTHLH feedback mitosis and downstream DNA replication-mediated cell proliferation mechanism of no-tumor hepatitis/cirrhotic tissues was analyzed by using Molecule Annotation System, MAS (CapitalBio Corporation, Beijing, China; http://bioinfo.capitalbio.com/mas3/). The primary databases of MAS integrated various well-known biological resources, such as Gene Ontology (http://www.geneontology.org/), KEGG (http://www.genome.jp/kegg/), BioCarta (http://www.biocarta.com/), GenMapp (http://www.genmapp.org/), HPRD (http://www.hprd.org/), MINT (http://mint.bio.uniroma2.it/mint/Welcome.do), BIND (http://www.blueprint.org/), Intact (http://www.ebi.ac.uk/intact/), UniGene (http://www.ncbi.nlm.nih.gov/unigene), OMIM (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim) and disease ((http://bioinfo.capitalbio.com/mas3/).

Biological processes and occurrence of the same *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network in no-tumor hepatitis/cirrhotic tissues were identified and compared with the corresponding activated GO network of HCC, the different biological process of *PTHLH* activated compared with the corresponding inhibited GO network of HCC, and the same biological process of *PTHLH* activated compared with the corresponding inhibited GO network of no-tumor hepatitis/cirrhotic tissues from total *PTHLH* activated GO network of no-tumor hepatitis/cirrhotic tissues by using knowledge and our programming.

We extracted and computed the same *PTHLH* feedback mitosis and downstream DNA replication-mediated cell proliferation molecular network and numbers in *PTHLH* activated network of no-tumor hepatitis/cirrhotic tissues compared with *PTHLH* activated network of HCC.

We identified simultaneous occurrence of biological processes between the same *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network of no-tumor hepatitis/cirrhotic tissues compared with the corresponding activated GO network of HCC, and the different compared with the corresponding inhibited GO network of HCC, or the same of *PTHLH* activated compared with the corresponding inhibited GO network of no-tumor hepatitis/cirrhotic tissues for putting forwards hypothesis of feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation.

At last, we identified the molecular relationship of feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation from *PTHLH* up- and/or down-stream activated molecular network of no-tumor hepatitis/cirrhotic tissues by GRNInfer [12] and our articles [13-26], and illustrated by GVedit tool.

Results

We extracted the same biological processes of *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network in no-tumor hepatitis/cirrhotic tissues compared with the corresponding activated GO network of human Hepatocellular Carcinoma (HCC) including cell cycle, cell cycle arrest, cell division, cell proliferation, centrosome cycle, chromosome segregation, cytokinesis after mitosis, DNA replication, DNA replication checkpoint, establishment of mitotic spindle localization, G1/S transition of mitotic cell cycle, mitosis, mitotic checkpoint, mitotic chromosome condensation, mitotic G2 checkpoint, mitotic spindle checkpoint, mitotic spindle organization and biogenesis, nucleosome assembly, positive regulation of cell proliferation, positive regulation of mitosis, regulation of cell proliferation, regulation of cyclin-dependent protein kinase activity, spindle organization and biogenesis, traversing start control point of mitotic cell cycle, double-strand break repair via homologous recombination, positive regulation of DNA repair, postreplication repair, DNA damage response, response to DNA damage stimulus;

The different biological processes of *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network in no-tumor hepatitis/cirrhotic tissues compared with the corresponding inhibited GO network of HCC contained centrosome cycle, centrosome separation, DNA replication checkpoint, keratinocyte proliferation, mitotic checkpoint, mitotic G2 checkpoint, mitotic spindle checkpoint, positive regulation of endothelial cell proliferation, regulation of cell proliferation, regulation of mitosis, spindle organization and biogenesis, sprouting angiogenesis, traversing start control point of mitotic cell cycle, positive regulation of DNA repair, postreplication repair, DNA damage response.

The same biological processes of *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network in no-tumor hepatitis/cirrhotic tissues compared with the corresponding inhibited GO network of no-tumor hepatitis/cirrhotic tissues included cell cycle, cell cycle arrest, cell division, cell proliferation, chromosome segregation, DNA replication, G1/S transition of mitotic cell cycle, keratinocyte proliferation, mitosis, mitotic chromosome condensation, mitotic spindle checkpoint, nucleosome assembly, positive regulation of cell proliferation, positive regulation of endothelial cell proliferation, sprouting angiogenesis, response to DNA damage stimulus, as shown in Table 1.

We extracted, added and deleted the repeating molecules of the same *PTHLH* activated up- and/or down-stream network in *PTHLH* activated molecular network of no-tumor hepatitis/cirrhotic tissues compared with *PTHLH* activated molecular network of HCC by our programming. We extracted the same *PTHLH* up- and/or down-stream biological processes corresponding to molecules in *PTHLH*

activated network of no-tumor hepatitis/cirrhotic tissues compared with *PTHLH* activated network of HCC by our programming for constructing *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation molecular network, respectively. We extracted and computed the same *PTHLH* feedback mitosis and downstream DNA replication-mediated cell proliferation molecular network and numbers in *PTHLH* activated network of no-tumor hepatitis/cirrhotic tissues compared with *PTHLH* activated network of HCC by our programming. Our result showed that upstream BUB1B activated *PTHLH*, and downstream *PTHLH*-activated *BUB1B, CCNA2, CDC6, BRCA1, NUSAP1* in no-tumor hepatitis/cirrhotic tissues, as shown in Table 2.

Discussion

Our aim is to study novel low expression *PTHLH* feedback mitosis and downstream DNA replication-mediated cell proliferation mechanism and molecular network in no-tumor hepatitis/cirrhotic tissues. In this study, biological processes and occurrence numbers of the same *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network in no-tumor hepatitis/cirrhotic tissues were identified and computed compared with the corresponding activated GO network of HCC, the different compared with the corresponding inhibited GO network of HCC, and the same compared with the corresponding inhibited GO network of no-tumor hepatitis/cirrhotic tissues from total *PTHLH* activated GO network of no-tumor hepatitis/cirrhotic tissues by using knowledge and our programming (Table 1).

We extracted the same up- and/or down-stream *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network in no-tumor hepatitis/cirrhotic tissues compared with the corresponding activated GO network of HCC, the different compared with the corresponding inhibited GO network of HCC, and the same compared with the corresponding inhibited GO network of no-tumor hepatitis/cirrhotic tissues, respectively.

The same biological processes of *PTHLH* activated feedback

The Same Biological Processes of *PTHLH* Activated Feedback Mitosis and Downstream DNA Replication-Mediated Cell Proliferation Network of No-tumor Hepatitis/cirrhotic Tissues Compared with Activated Network of HCC			
Terms	Numbers	Terms	Numbers
cell cycle	7	mitotic spindle checkpoint	1
cell cycle arrest	2	mitotic spindle organization and biogenesis	2
cell division	6	nucleosome assembly	3
cell proliferation	3	positive regulation of cell proliferation	2
centrosome cycle	1	positive regulation of mitosis	1
chromosome segregation	1	regulation of cell proliferation	1
cytokinesis after mitosis	1	regulation of cyclin-dependent protein kinase activity	3
DNA replication	2	spindle organization and biogenesis	2
DNA replication checkpoint	1	traversing start control point of mitotic cell cycle	1
establishment of mitotic spindle localization	1	double-strand break repair via homologous recombination	1
G1/S transition of mitotic cell cycle	2	positive regulation of DNA repair	1
mitosis	4	postreplication repair	1
mitotic checkpoint	2	DNA damage response	2
mitotic chromosome condensation	1	response to DNA damage stimulus	1
mitotic G2 checkpoint	1		
The Different Biological Processes of *PTHLH* Activated Feedback Mitosis and Downstream DNA Replication-Mediated Cell Proliferation Network of No-tumor Hepatitis/cirrhotic Tissues Compared with Inhibited Network of HCC			
Terms	Numbers	Terms	Numbers
centrosome cycle	1	regulation of cell proliferation	1
centrosome separation	1	regulation of mitosis	1
DNA replication checkpoint	1	spindle organization and biogenesis	2
keratinocyte proliferation	1	sprouting angiogenesis	1
mitotic checkpoint	2	traversing start control point of mitotic cell cycle	1
mitotic G2 checkpoint	1	positive regulation of DNA repair	1
mitotic spindle checkpoint	1	postreplication repair	1
positive regulation of endothelial cell proliferation	1	DNA damage response	2
The Same Biological Processes of *PTHLH* Activated Feedback Mitosis and Downstream DNA Replication-Mediated Cell Proliferation Network of No-tumor Hepatitis/cirrhotic Tissues Compared with Inhibited Network of No-tumor Hepatitis/cirrhotic Tissues			
Terms	Numbers	Terms	Numbers
cell cycle	7	mitosis	4
cell cycle arrest	2	mitotic chromosome condensation	1
cell division	6	mitotic spindle checkpoint	1
cell proliferation	3	nucleosome assembly	3
chromosome segregation	1	positive regulation of cell proliferation	2
DNA replication	2	positive regulation of endothelial cell proliferation	1
G1/S transition of mitotic cell cycle	2	sprouting angiogenesis	1
keratinocyte proliferation	1	response to DNA damage stimulus	1

Table 1: Biological processes occurrence numbers of the same *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network in no-tumor hepatitis/cirrhotic tissues compared with the corresponding activated GO network of HCC, the different compared with the corresponding inhibited GO network of HCC, and the same compared with the corresponding inhibited GO network of no-tumor hepatitis/cirrhotic tissues from total *PTHLH* activated GO network of no-tumor hepatitis/cirrhotic tissues by programming.

mitosis and downstream DNA replication-mediated cell proliferation GO network in no-tumor hepatitis/cirrhotic tissues that upstream consisted of cell division, cell proliferation, mitosis, mitotic checkpoint, nucleosome assembly, spindle organization and biogenesis; Downstream cell cycle, cell cycle arrest, cell division, cell proliferation, centrosome cycle, chromosome segregation, cytokinesis after mitosis, DNA replication, DNA replication checkpoint, establishment of mitotic spindle localization, G1/S transition of mitotic cell cycle, mitosis, mitotic checkpoint, mitotic chromosome condensation, mitotic G2 checkpoint, mitotic spindle checkpoint, mitotic spindle organization and biogenesis, nucleosome assembly, positive regulation of cell proliferation, positive regulation of mitosis, regulation of cell proliferation, regulation of cyclin-dependent protein kinase activity, spindle organization and biogenesis, traversing start control point of mitotic cell cycle, double-strand break repair via homologous recombination, positive regulation of DNA repair, postreplication repair, DNA damage response, response to DNA damage stimulus compared with the corresponding activated network of HCC.

The different biological processes of *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network in no-tumor hepatitis/cirrhotic tissues that upstream included keratinocyte proliferation, mitotic checkpoint, positive regulation of endothelial cell proliferation, spindle organization and biogenesis, sprouting angiogenesis; Downstream centrosome cycle, centrosome separation, DNA replication checkpoint, mitotic checkpoint, mitotic G2 checkpoint, mitotic spindle checkpoint, regulation of cell proliferation, regulation of mitosis, spindle organization and biogenesis, traversing start control point of mitotic cell cycle, positive regulation of DNA repair, postreplication repair, DNA damage response compared with the corresponding inhibited network of HCC.

The same biological processes of *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network in no-tumor hepatitis/cirrhotic tissues that upstream consisted of cell division, cell proliferation, keratinocyte proliferation, mitosis, nucleosome assembly, positive regulation of endothelial cell proliferation, sprouting angiogenesis; Downstream cell cycle, cell cycle arrest, cell division, cell proliferation, chromosome segregation, DNA replication, G1/S transition of mitotic cell cycle, mitosis, mitotic chromosome condensation, mitotic spindle checkpoint, nucleosome assembly, positive regulation of cell proliferation, response to DNA damage stimulus compared with the corresponding inhibited network of no-tumor hepatitis/cirrhotic tissues.

We identified simultaneous occurrence of biological processes between the same *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network of no-tumor hepatitis/cirrhotic tissues compared with the corresponding activated GO network of HCC, and the different compared with the corresponding inhibited GO network of HCC, or the same compared with the corresponding inhibited GO network of no-tumor hepatitis/cirrhotic tissues. Our result showed *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation network that upstream consist of cell division, cell proliferation, mitosis, mitotic checkpoint, nucleosome assembly, spindle organization and biogenesis; Downstream cell cycle, cell cycle arrest, centrosome cycle, chromosome segregation, DNA replication, DNA replication checkpoint, G1/S transition of mitotic cell cycle, mitotic chromosome condensation, mitotic G2 checkpoint, mitotic spindle checkpoint, positive regulation of cell proliferation, regulation of cell proliferation, traversing start control point of mitotic cell cycle, positive regulation of DNA repair, postreplication repair, DNA damage response, response to DNA damage stimulus, cell division, cell proliferation, mitosis, mitotic checkpoint, nucleosome assembly, spindle organization and biogenesis in no-tumor hepatitis/cirrhotic tissues.up- and/or down-stream. The relationships of mitosis and double-strand break repair are presented in some papers. Such as, Homologous recombination in meiosis and mitosis requires arabidopsis RAD51C gene [27]; From meiosis to mitosis double-strand break repair, recombination and synaptonemal complex is switched by yeast [28]. The relationships of mitosis or double-strand break repair with cell proliferation are presented in some papers. Such as, Daughter cell proliferation despite normal completion of mitosis is blocked by prolonged prometaphase [29]; the timely transit of cells by mitosis and tumor cell proliferation are controlled by phosphorylation of p62 by cdk1 [30]; How mitosis is hijacked to denucleate and modulate cell proliferation and differentiation is revealed by perturbing the ubiquitin pathway *in vivo* [31]; DNA double-strand break repair genes role in cell proliferation under low dose-rate irradiation conditions [32]; The logic of the Mitosis, Membrane, Magnesium(MMM) model for the regulation of animal cell proliferation [33]; Cell proliferation during mitosis and meiotic division II requires caenorhabditis elegans Elongin BC complex [34]; Cancer cell proliferation at mitosis are inhibited by antimitotic antifungal compound benomyl , by binding to a novel site in tubulin [35]; Blockage of endothelial cell proliferation related to a mitosis arrest inhibits tumor growth *in vivo* [36]; mitosis counts and immunoreactivity for proliferating cell nuclear antigen (PCNA) determines proliferation in malignant mesothelioma [37]; Failure of tripeptide colon mitosis inhibitor to inhibit the cell proliferation of dimethylhydrazine-induced colonic cancers in rats [38]; An endogenous colon mitosis inhibitor reduces the increased cell proliferation in colonic epithelium induced by dietary cholic acid and treatment with 1,2-dimethylhydrazine [39]; An endogenous colon mitosis inhibitor inhibit the increased colonic cell proliferation induced by cholic acid [40]. Therefore, we proposed *PTHLH* feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation in no-tumor hepatitis/cirrhotic tissues.

We extracted and computed the same *PTHLH* feedback mitosis and downstream DNA replication-mediated cell proliferation molecular network and numbers in *PTHLH* activated network of no-tumor hepatitis/cirrhotic tissues compared with *PTHLH* activated network of HCC (Table 2). We extracted the same *PTHLH* up- and/or down-stream molecular network including different molecules but same GO term corresponding to feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation in *PTHLH* activated GO network of no-tumor hepatitis/cirrhotic tissues compared with *PTHLH* activated network of HCC. Our result showed that *PTHLH* feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation network that upstream BUB1B activated *PTHLH*, and downstream *PTHLH*-activated *BUB1B, CCNA2, CDC6, BRCA1* in no-tumor hepatitis/cirrhotic tissues, as shown in Figure 1 and Figure 2.

The Same *PTHLH* Up- and Down-Stream Molecular Network and Numbers Corresponding to Feedback Mitosis and Downstream DNA Replication-Mediated Cell Proliferation in *PTHLH* Activated Network of No-Tumor Hepatitis/Cirrhotic Tissues Compared with *PTHLH* Activated Network of HCC	
Upstream	Numbers
BUB1B	1
Downstream	Numbers
BUB1B, CCNA2, CDC6, NUSAP1, BRCA1	5

Table 2: The same *PTHLH* feedback mitosis and downstream DNA replication-mediated cell proliferation molecular network and numbers in *PTHLH* activated network of no-tumor hepatitis/cirrhotic tissues compared with *PTHLH* activated network of HCC by our programming.

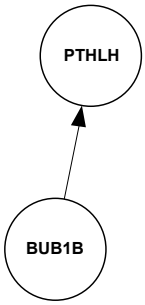

Figure 1: *PTHLH* upstream activated feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation network in no-tumor hepatitis/cirrhotic tissues by GRNInfer and our programming.

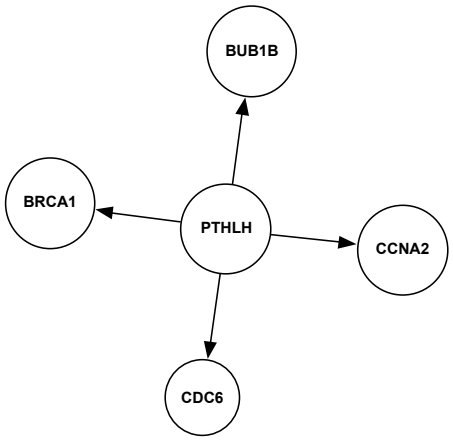

Figure 2: *PTHLH* downstream activated feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation network in no-tumor hepatitis/cirrhotic tissues by GRNInfer and our programming.

In summary, based on analysis of biological processes in the same low expression *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferationGO network of no-tumor hepatitis/cirrhotic tissues compared with the corresponding high expression (fold change ≥2) activated GO network of human Hepatocellular Carcinoma (HCC), we proposed *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation network that upstream consist of cell division, cell proliferation, mitosis, mitotic checkpoint, nucleosome assembly, spindle organization and biogenesis; Downstream cell cycle, cell cycle arrest, centrosome cycle, chromosome segregation, DNA replication, DNA replication checkpoint, G1/S transition of mitotic cell cycle, mitotic chromosome condensation, mitotic G2 checkpoint, mitotic spindle checkpoint, positive regulation of cell proliferation, regulation of cell proliferation, traversing start control point of mitotic cell cycle, positive regulation of DNA repair, postreplication repair, DNA damage response, response to DNA damage stimulus, cell division, cell proliferation, mitosis, mitotic checkpoint, nucleosome assembly, spindle organization and biogenesis, as a result of *PTHLH* feedback mitosis to downstream DNA replication coupling postreplication repair-induced cell proliferation in no-tumor hepatitis/cirrhotic tissues. Our hypothesis was verified by the different *PTHLH* activated feedback mitosis and downstream DNA replication-mediated cell proliferation GO network of no-tumor hepatitis/cirrhotic tissues compared with the corresponding inhibited GO network of HCC, or the same compared with the corresponding inhibited GO network of no-tumor hepatitis/cirrhotic tissues.

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