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Cytosolic Iron-Sulfur Protein Assembly 1 (*CIAO1*) Downstream Activation of Phospholipase A2 and Hormone-Mediated Signaling-Induced Cell Death Network in Human Hepatocellular Carcinoma (HCC) by Systems-Theoretical Analysis

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Abstract

We constructed the significant high expression (fold change ≥ 2) cytosolic iron-sulfur protein assembly 1 (*CIAO1)* downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death network in human Hepato Cellular Carcinoma (HCC), compared with low expression no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) in GEO data set, by using integration of gene regulatory activated and inhibited network inference method. Our result showed that *CIAO1* downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death upstream network had no result, and downstream *CIAO1*-activated *PLA2G1B, NUP62* in HCC. By integrative analysis of biological processes simultaneous occurrence between the different *CIAO1* activated downstream cell death gene ontology (GO) network of HCC compared with *CIAO1* activated downstream cell death GO network of no-tumor hepatitis/cirrhotic tissues, and the same compared *CIAO1* inhibited downstream cell death GO network of no-tumor hepatitis/cirrhotic tissues, or the different compared *CIAO1* inhibited downstream cell death GO network of HCC, we proposed and verified that *CIAO1* activated upstream network had no result; Downstream network consisted of activation of phospholipase A2, cell death, protein kinase cascade, regulation of signal transduction, hormone-mediated signaling, negative regulation of epidermal growth factor receptor signaling pathway, negative regulation of MAPK (Mitogen Activated Protein Kinase) activity, negative regulation of Ras protein signal transduction in HCC, as a result of downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death in HCC.

Keywords: Cytosolic iron-sulfur protein assembly 1 (*CIAO1)*; Human hepatocellular carcinoma (HCC); Downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death network; Systems-theoretical analysis

Introduction

Cytosolic iron-sulfur protein assembly 1 (*CIAO1*) is our identified significant high expression (fold change ≥ 2) gene in human hepatocellular carcinoma (HCC) compared with low expression no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) from GEO (Gene Expression Omnibus) 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].

We interpreted *PLA2G1B* and *NUP62* by using gene ontology (GO). *PLA2G1B* cellular component, molecular function and biological process are relevant to extracellular region, extracellular space; receptor binding, calcium ion binding, hydrolase activity, bile acid binding, cell surface binding, calcium-dependent phospholipase A2 activity; activation of MAPK activity, neutrophil mediated immunity, fatty acid biosynthesis, phospholipid metabolism, actin filament organization, signal transduction, protein kinase cascade, glucose transport, leukotriene biosynthesis, neutrophil chemotaxis, organismal lipid catabolism, positive regulation of DNA replication, phosphatidylcholine metabolism, positive regulation of fibroblast proliferation, arachidonic acid secretion, positive regulation of protein secretion, positive regulation of immune response, activation of NF-kappaB transcription factor, positive regulation of calcium ion transport into cytosol, positive regulation of specific transcription from RNA polymerase II promoter, activation of phospholipase A2, interleukin-8 production, cellular response to insulin stimulus (GO database). *NUP62* cellular component, molecular function and biological process are relevant to nucleus, nuclear pore, nucleolus, cytoplasm, centrosome, nucleocytoplasmic shuttling complex, nuclear membrane; chromatin binding, protein serine/threonine kinase activity, nucleocytoplasmic transporter activity, protein binding, structural constituent of nuclear pore, receptor signaling complex scaffold activity, transcription regulator activity, SH2 domain binding, ubiquitin binding, thyroid hormone receptor binding, PTB (Phosphotyrosine-binding) domain binding; cell surface receptor linked signal transduction, cell aging, cell death, negative regulation of cell proliferation, hormone-mediated signaling, regulation of signal transduction, protein transport, negative regulation of epidermal growth factor receptor signaling pathway, negative regulation of apoptosis, positive regulation of I-kappaB kinase/NF-kappaB cascade, negative regulation of MAPK activity, positive regulation of epidermal growth factor receptor signaling pathway, positive regulation of transcription, negative regulation of Ras protein signal transduction, mRNA transport, intracellular protein transmembrane transport (GO database).

Study of cytosolic iron-sulfur protein assembly 1 (*CIAO1)* is presented in several papers as follows: Mouse knock-out of IOP1 protein reveals its indispensable role in mammalian cytosolic iron-sulfur protein biogenesis [2]; Tah18 transfers electrons to Dre2 in cytosolic iron-sulfur protein biogenesis [3]; A role for IOP1 in mammalian

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cytosolic iron-sulfur protein biogenesis [4]; The essential cytosolic iron-sulfur protein Nbp35 acts without Cfd1 partner in the green lineage [5]; Role of human mitochondrial Nfs1 in cytosolic iron-sulfur protein biogenesis and iron regulation [6]; Activation of the iron regulon by the yeast Aft1/Aft2 transcription factors relys on mitochondrial but not cytosolic iron-sulfur protein biogenesis [7]; Gene structure and mutation causing X-linked sideroblastic anemia with ataxia with cytosolic iron-sulfur protein maturation disruption [8]. Downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death is presented in some papers. Such as, Cytoplasmic phospholipase A2 levels correlate with apoptosis in human colon tumorigenesis [9]; Potentiation by vitamin D analogs of TNFalpha and ceramide-induced apoptosis in MCF-7 cells is related to activation of cytosolic phospholipase A2 [10]; 1,25-Dihydroxyvitamin D3 protects human leukemic cells from tumor necrosis factor-induced apoptosis through inactivation of cytosolic phospholipase A2 [11]; Phospholipase A2-activating protein (PLAA) enhances cisplatin-induced apoptosis in HeLa cells [12]; Alpha-Tocopheryl succinate contributes to apoptosis in erbB2-expressing breast cancer cell via NF-kappaB pathway [13]; Gene network signaling in hormone responsiveness modifies autophagy and apoptosis in breast cancer cells [14]; Rho/ROCK/actin signaling regulates membrane androgen receptor induced apoptosis in prostate cancer cells [15]; Gonadotropin-releasing hormone type II contributes to apoptosis of human endometrial cancer cells by activating GADD45alpha [16]. Yet the distinct high expression *CIAO1* downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death network in HCC remains to be elucidated. Here we constructed the high expression *CIAO1* activated downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death network in HCC from GEO data set by gene regulatory network inference method based on linear programming and decomposition procedure.

In this study, we constructed *CIAO1* upstream and downstream activated and inhibited downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death network in no-tumor hepatitis/cirrhotic tissues and HCC. The biological process and data analysis of the low- and high- expression *CIAO1* downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death network was done in no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) and HCC by gene ontology (GO) database. By comparison with the same and different upstream and downstream GO and numbers of *CIAO1* activated and inhibited downstream cell death network between no-tumor hepatitis/cirrhotic tissues and HCC, we put forward hypothesis of *CIAO1* activated downstream cell death network of downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death in HCC.

Materials and Methods

Microarrays 6,144 genes were used for analyzing *CIAO1* downstream cell death mechanism and constructing molecular network of HCC from our total network of 225 significant high expression (fold change ≥ 2) molecules in HCC compared with no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) based on 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.

Significant expressed genes for studying *CIAO1* downstream cell death mechanism and molecular network were identified using significant analysis of microarrays (SAM) (http://www-stat.stanford.edu/~tibs/SAM/) [17]. We selected two classes unpaired and minimum fold change ≥ 2 and chose the significant highly expressed value genes of HCC compared with that of no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) under the false-discovery rate was 0%.

CIAO1 downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death network was constructed based on GRNInfer and GVedit tools (http://www.graphviz.org/About.php). GRNInfer is a novel mathematic method called GNR (Gene Network Reconstruction tool) based on linear programming and a decomposition procedure for inferring gene network [18]. We established *CIAO1* activated network of HCC based on the fold change ≥ 2 distinguished genes and selected parameters as lambda 0.0 because we used one data set. Lambda was a positive parameter which balanced the matching and sparsity terms in the objective function. Using different thresholds, we could predict various networks with the different edge density. The threshold parameters make the edge whose strength of link is smaller than threshold not shown in the network graph. The smaller this parameter, the more edges in the network graph. We selected threshold as 1.0e-7.

CIAO1 downstream cell death mechanism of HCC was analyzed using Molecule Annotation System, MAS (CapitalBio Corporation, Beijing, China; http://bioinfo.capitalbio.com/mas3/). MAS is a Web-based software toolkit for a whole data mining and function annotation solution to extract and analyze biological molecules relationships from public databases. 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 (www.ncbi.nlm.nih.gov/UniGen), OMIM (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim) and disease ((http://bioinfo.capitalbio.com/mas3/). MAS offers various query entries and graphics. The algorithm is P, Q value in GO and pathway of module was presented in reference [19].

Results

We analyzed *CIAO1* downstream cell death mechanism and constructed molecular network of HCC from our total network of 225 significant high expression molecules (fold change ≥ 2) from 6,144 genes of HCC compared with no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) by GRNInfer, respectively.

We extracted the biological process of GO terms and did numbers data analysis of the different biological processes of *CIAO1* activated downstream cell death network in HCC compared with activated network of no-tumor hepatitis/cirrhotic tissues, the same biological processes of *CIAO1* activated downstream cell death network in HCC compared with inhibited network of no-tumor hepatitis/cirrhotic tissues, as shown in Table 1. GO terms and numbers data was analyzed the different biological processes of *CIAO1* activated compared with inhibited downstream cell death network in HCC, as shown in Table 2.

CIAO1 activated downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death network was constructed in HCC. Our result showed that upstream had no result, and the downstream *CIAO1*-activated *PLA2G1B, NUP62* in HCC, as shown in Figure 1 and Figure 2.

Discussion

Our aim is to study novel high expression *CIAO1* downstream

The Different Biological Processes of *CIAO1* Activated Downstream Cell Death Network of HCC Compared with Activated Network of No-tumor Hepatitis/ cirrhotic Tissues	
Terms	**Numbers**
protein kinase cascade	**1**
activation of phospholipase A2	**1**
regulation of signal transduction	**1**
cell death	**1**
hormone-mediated signaling	**1**
negative regulation of epidermal growth factor receptor signaling pathway	**1**
negative regulation of MAPK activity	**1**
negative regulation of Ras protein signal transduction	**1**
fatty acid biosynthesis	**1**
organismal lipid catabolism	**1**
phosphatidylcholine metabolism	**1**
phospholipid metabolism	**1**
The Same Biological Processes of *CIAO1* Activated Downstream Cell Death Network of HCC Compared with Inhibited Network of No-tumor Hepatitis/ cirrhotic Tissues	
Terms	**Numbers**
None	**0**

Table 1: GO Terms and numbers data analysis of the different biological processes of *CIAO1* activated downstream cell death network of HCC compared with activated network of no-tumor hepatitis/cirrhotic tissues, the same biological processes of *CIAO1* activated downstream cell death network of HCC compared with inhibited network of no-tumor hepatitis/cirrhotic tissues.

The Different Biological Processes of *CIAO1*Activated Downstream Cell Death Network of HCC Compared with Inhibited Network of HCC	
Terms	**Numbers**
negative regulation of epidermal growth factor receptor signaling pathway	**1**
negative regulation of MAPK activity	**1**
negative regulation of Ras protein signal transduction	**1**
protein kinase cascade	**1**
regulation of signal transduction	**1**
activation of phospholipase A2	**1**
cell death	**1**
hormone-mediated signaling	**1**
fatty acid biosynthesis	**1**
organismal lipid catabolism	**1**
phosphatidylcholine metabolism	**1**
phospholipid metabolism	**1**

Table 2: GO Terms and numbers data analysis of the different biological processes of *CIAO1* activated downstream cell death network of HCC compared with inhibited network of HCC.

cell death mechanism and molecular network in HCC. We have already constructed and analyzed some novel molecular network from different databases presented in our articles [19-32]. In this study, we constructed *CIAO1* upstream and downstream activated and inhibited downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death network in no-tumor hepatitis/cirrhotic tissues and HCC. The biological process and data analysis of the low- and high expression *CIAO1* downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death network was done in no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) and HCC by GO database. By comparison with the same and different upstream and downstream GO and numbers of *CIAO1* activated and inhibited downstream cell death network between no-tumor hepatitis/ cirrhotic tissues and HCC, we put forwards hypothesis of *CIAO1* activated downstream cell death network of downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death in HCC.

We extracted the biological process of GO terms and did numbers data analysis of the different biological processes of *CIAO1* activated downstream cell death network in HCC compared with activated network of no-tumor hepatitis/cirrhotic tissues, the same biological processes of *CIAO1* activated downstream cell death network in HCC compared with inhibited network of no-tumor hepatitis/cirrhotic tissues (Table 1 and Table 2). We constructed the high expression (fold change ≥ 2) *CIAO1* activated downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death network in human hepatocellular carcinoma (HCC) compared with low expression no-tumor hepatitis/cirrhotic tissues (HBV or HCV infection) in GEO data set using integration of gene regulatory network inference method. Our result showed that *CIAO1* downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death upstream network had no result, and downstream *CIAO1*-activated *PLA2G1B, NUP62* (Figure 1 and Figure 2) in HCC.

By further comparison with the same biological processes of and different gene ontology (GO) of *CIAO1* activated and inhibited downstream cell death network between no-tumor hepatitis/cirrhotic tissues and HCC, we found that the different biological processes of *CIAO1* activated upstream network had no result; Downstream network consisted of protein kinase cascade, activation of phospholipase A2, regulation of signal transduction, cell death, hormone-mediated signaling, negative regulation of epidermal growth factor receptor signaling pathway, negative regulation of MAPK activity, negative regulation of Ras protein signal transduction in HCC compared with activated network of no-tumor hepatitis/cirrhotic tissues.

Figure 1: *CIAO1* upstream activated phospholipase A2 and hormone-mediated signaling-induced cell death network in HCC by GRNInfer and our programming.

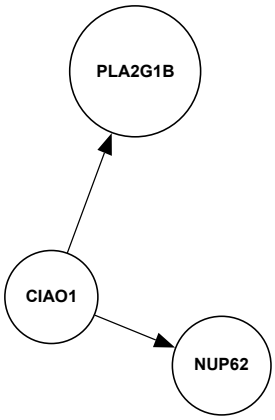

Figure 2: *CIAO1* downstream activated phospholipase A2 and hormone-mediated signaling-induced cell death network in HCC by GRNInfer and our programming.

The same biological processes of *CIAO1* activated upstream network had no result; downstream network had no result in HCC compared with inhibited network of no-tumor hepatitis/cirrhotic tissues.

The different biological processes of *CIAO1* activated network had no result; Downstream network included negative regulation of epidermal growth factor receptor signaling pathway, negative regulation of MAPK activity, negative regulation of Ras protein signal transduction, protein kinase cascade, regulation of signal transduction, activation of phospholipase A2, cell death, hormone-mediated signaling compared with inhibited network of HCC.

By integrative analysis of biological processes simultaneous occurrence between the different *CIAO1* activated downstream cell death gene ontology (GO) network of HCC compared with *CIAO1* activated downstream cell death GO network of no-tumor hepatitis/cirrhotic tissues, and the same compared *CIAO1* inhibited downstream cell death GO network of no-tumor hepatitis/cirrhotic tissues, or the different compared *CIAO1* inhibited downstream cell death GO network of HCC, we proposed and verified that *CIAO1* activated upstream network had no result; Downstream network included activation of phospholipase A2, cell death, protein kinase cascade, regulation of signal transduction, hormone-mediated signaling, negative regulation of epidermal growth factor receptor signaling pathway, negative regulation of MAPK activity, negative regulation of Ras protein signal transduction in HCC, as a result of downstream activation of phospholipase A2 and hormone-mediated signaling-induced cell death in HCC.

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