Genomic analyses identify biological processes in ZKSCAN3-deficient colorectal cancer cells

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Abstract

Zinc finger with KRAB and SCAN domain 3 (ZKSCAN3) is associated with cell differentiation, cell proliferation and apoptosis, which has been reported as a critical driver of colorectal cancer. However, the mechanism and function of ZKSCAN3 in colorectal cancer is still unclear. Here, our objective is to identify the functional molecules and signaling by analyzing the RNA-seq data. The GSE172201 was created by the Illumina NovaSeq 6000 (Homo sapiens). The KEGG and GO analyses indicated the immune defense response to virus and transcription activity are major processes in the ZKSCAN3 KO colorectal cancer cells. Moreover, we determined ten key molecules including STAT1, MX1, DDX58, PPARG, EGFR, APP, BST2, DLG4, OASL, and IFIT2. Therefore, our study may provide the novel knowledge of ZKSCAN3 mediated colorectal cancer.

Introduction

Colorectal cancer is one the most common cancers in the world, which has the highest incidence in Europe and North America¹. The prognosis of colorectal cancer has increased during the past decades including Australia, US, Canada, and European countries¹⁻³. There is no simple factor that causes colorectal cancer⁴. The known risk factors include age, sex, family history, obesity and diabetes⁴. The molecules underlying progression of this cancer are essential since they involve in the prognosis and treatment⁵. The relationship between the molecules and mechanism has become the key to treat the hereditary forms of colorectal cancer⁶.

ZKSCAN3 is a kind of oncogene that is increased in colon cancer frequently⁷. ZKSCAN3 contains the zinc finger structure and is a member of the family of KRAB and SCAN domain proteins⁷. This protein family plays a critical role in biological processes including apoptosis⁸. It was reported that ZKSCAN3 is an activator for the progression of colon cancer⁹.

In this study, we determined the biological functions of ZKSCAN3 in colorectal cancer by using the RNA-seq data. We identified a number of DEGs and biological processes and constructed the protein-protein interaction (PPI) network. The DEGs and PPI network may shed light on the progression mechanism of colorectal cancer.

Methods

Data resources

Gene dataset GSE172201 was downloaded from the GEO database. The data was produced by the Illumina NovaSeq 6000 (Homo sapiens) (Department of Pathology, Kyung Hee University, 26 Kyungheedaero, Seoul, South Korea). The analyzed dataset includes 3 groups of WT control HCT116 colorectal cancer cell line and 3 groups of ZKSCAN3 KO HCT116-1 colorectal cancer cell line.

Data acquisition and processing

The data were organized and conducted by R package as previously described¹⁰⁻¹⁴. We used a classical t-test to identify DEGs with $P < 0.05$ and fold change ≥ 1.5 as being statistically significant.

The Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) KEGG and GO analyses were conducted by the R package (clusterProfiler) and Reactome. $P < 0.05$ were considered statistically significant.

Protein-protein interaction (PPI) networks

The Molecular Complex Detection (MCODE) was used to construct the PPI networks. The significant modules were produced from constructed PPI networks and String network. The pathway analyses were performed by using Reactome (<https://reactome.org/>), and $P < 0.05$ was considered significance.

Results

Identification of DEGs of ZKSCAN3-deficient colorectal cancer cell line

To study the effects of ZKSCAN3 in colorectal cancers, we analyzed the RNA-seq data from the ZKSCAN3 knockout (KO) colorectal cancer cell line. A total of 139 genes were identified with the threshold of $P < 0.05$. The top up- and down-regulated genes in the ZKSCAN3 KO colorectal cancer cell line were identified by the heatmap and volcano plot (Figure 1). The top ten DEGs were listed in Table 1.

Enrichment analysis of DEGs in the ZKSCAN3-deficient colorectal cancer cell line

To determine the mechanism of DEGs by the effects of ZKSCAN3-deficient in colorectal cancer cell line, we performed the KEGG and GO analyses (Figure 2). We identified the top ten KEGG items which include “Herpes simplex virus 1 infection”, “Human papillomavirus infection”, “Epstein–Barr virus infection”, “Alcoholism”, “Viral carcinogenesis”, “Axon guidance”, “Antigen processing and presentation”, “ECM–receptor interaction”, “Pancreatic cancer”, and “Proteasome”. We also identified the top ten biological processes including “response to virus”, “kidney development”, “defense response to virus”, “defense response to symbiont”, “embryonic skeletal system morphogenesis”, “negative regulation of viral process”, “negative regulation of viral genome replication”, “regulation of viral genome replication”, “response to interferon–beta”, and “response to interferon–alpha”. We identified the top ten cellular components of GO including “cell–cell junction”, “transport vesicle”, “cell–substrate junction”, “collagen–containing extracellular matrix”, “endocytic vesicle”, “exocytic vesicle”, “contractile fiber”, “adherens junction”, “basement membrane”, and “platelet alpha granule lumen”. We then identified the top ten biological processes of GO, which contains “DNA–binding transcription activator activity”, “DNA–binding transcription activator activity, RNA polymerase II–specific”, “integrin binding”, “MHC protein complex binding”, “extracellular matrix structural constituent conferring tensile strength”, “oxidoreductase activity, acting on the aldehyde or oxo group of donors”, “calmodulin–dependent protein kinase activity”, “MHC class II protein complex binding”, “ion channel inhibitor activity”, and “type I transforming growth factor beta receptor binding”.

Construction of PPI network in the ZKSCAN3-deficient colorectal cancer cell line

To understand the potential associations of DEGs, we constructed the PPI network by the Cytoscape software. The combined score > 0.2 was used as a cutoff to create the PPI network by linking the 108 nodes and 93 edges. The Table 2 illustrated the top ten genes with the highest degree scores. The top two cluster modules were showed in Figure 3. We further evaluated the DEG and PPI by Reactome map (Figure 4) and figured out the top ten significant biological processes including “Activation of anterior HOX genes in hindbrain development during early embryogenesis”, “Activation of HOX

genes during differentiation”, “Interferon alpha/beta signaling”, “RUNX2 regulates genes involved in cell migration”, “Interferon Signaling”, “Transcriptional regulation by RUNX2”, “Regulation of RUNX2 expression and activity”, “Unblocking of NMDA receptors, glutamate binding and activation”, “Ras activation upon Ca²⁺ influx through NMDA receptor”, and “Negative regulation of NMDA receptor-mediated neuronal transmission” (Supplemental Table S1).

Discussion

Though there are two pathways (gatekeeper and caretaker) related to the progression of colorectal cancer¹⁵, the exact mechanism is still not clear. Thus, the treatment of colorectal cancer focusing on specific molecules attracts the most attention.

We found the immune defense response to virus and transcription activity are the mainly impacted processes in ZKSCAN3-deficient colorectal cancer cells. Lili Deng et al found the virus of Guang9 strain harboring IL-24 (VG9-IL-24) can repress the progression of colorectal cancer tumor by enhancing oncolysis and apoptosis as well as inducing the antitumor immune effects¹⁶. Adrian Jarzyński et al found the HPV and BKV infections can lead to the neoplastic process¹⁷. Shuaishuai Teng et al identified that the transcription factors FOXA2 and HNF1A can bind to the gained enhancers and activate the gene transcription to further promote the liver metastasis¹⁸. Moreover, ZKSCAN3 is a critical transcriptional repressor, which is higher expression in invasive compared with noninvasive colorectal cancer¹⁹.

Based on the PPI network, we identified a variety of interaction molecules in ZKSCAN3-deficient colorectal cancer cells. Chao Liu et al found that STAT1 regulates the inhibition of FOXM1 to enhance the gemcitabine sensitivity in pancreatic cancer²⁰. Abrar I Aljohani et al found MX1 expression was related to the aggressiveness of cancer, including tumor size, grade, index scores, and high Ki67 expression, which is considered as an independent predictor of poor outcome in invasive breast cancer²¹. Yu-Chan Chang et al found the glucose transporter 4 promotes the oral cancer through the DDX58 signaling²². Andre Luiz Prezotto Villa et al found the expression of PPARG in colorectal cancer is related to the staging and clinical evolution²³. Circadian gene clocks and its downstream molecules are related to many cell functions including

metabolism, immune, proliferation, and differentiation²⁴⁻³³. PPARG is found to be a novel circadian transcription factor in adipogenesis and osteogenesis³⁴. EGFR is related to the pathogenesis and progression of various cancers such as lung cancer³⁵. GPCR and RGS proteins and downstream signaling pathways involve in the regulation of cell functions including proliferation, differentiation, migration, and secretion³⁶⁻⁴⁰. RGS proteins also play essential roles in a variety of diseases such as arthritis, osteoporosis, pain, and heart diseases⁴¹⁻⁴⁸. RGS16 was found to be co-immunoprecipitated with EGFR and phosphorylated on both tyrosine residues after EGF stimulation in cancer cells⁴⁹. APP was found to be increased in various cancer types, including lung and breast cancer⁵⁰. BST2 is expressed in cancer cells, which enhances the progression of tumor and metastasis⁵¹. Keisuke Handa et al found DLG4 is a tumor inhibitor in the development of HPV-associated cervical cancers⁵². OASL proteins can mediate the cellular survival and affect the progression of cancer⁵³. The downregulation of IFIT2 is related to the increased cell proliferation and metastasis in gastric cancer patients⁵⁴. In summary, our study identified the significant effects of ZKSCAN3 in colorectal cancer cells. The immune defense response to virus and transcription activity are the mainly impacted processes involved in the ZKSCAN3 mediated cancer cells. Therefore, this study may be beneficial to the treatment of colorectal cancer.

Author Contributions

Zhiwen Qian, Tingxiang Chang, Tingting Zhang, Jing Wang: Methodology. Hanming Gu: Conceptualization, Writing and Editing.

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Declarations of interest

There is no conflict of interest to declare.

Figure 1. Heatmap and volcano plot were created from the WT and ZKSCAN3-deficient colorectal cancer cells

(A) Heatmap of significant DEGs. Significant DEGs ($P < 0.01$) were used to produce the heatmap.

(B) Volcano plot for DEGs of the WT and ZKSCAN3-deficient colorectal cancer cells. The most significantly changed genes are highlighted by grey dots.

Figure 2. KEGG and GO analyses of DEGs between the WT and ZKSCAN3-deficient colorectal cancer cells

(A) KEGG analysis, (B) Biological processes, (C) Cellular components, (D) Molecular functions.

Figure 3. The PPI network analyses of DEGs between the WT and ZKSCAN3-deficient colorectal cancer cells

The cluster (A) and cluster (B) were constructed by MCODE.

Figure 4. Reactome map representation of the significant biological processes between the WT and ZKSCAN3-deficient colorectal cancer cells

Table 1

Entrez gene	Gene symbol	Fold-change	Regulation
Top 10 down-regulated DEGs			
26298	EHF	-7.739803829	Down
2904	GRIN2B	-7.181081368	Down
6678	SPARC	-5.871691208	Down
92745	SLC38A5	-5.409798061	Down
107984158	LOC107984158	-5.369470151	Down
7447	VSNL1	-5.31342666	Down
9358	ITGBL1	-5.105865851	Down
60489	APOBEC3G	-5.027707987	Down
10561	IFI44	-4.797661758	Down
6515	SLC2A3	-4.500514925	Down
Top 10 up-regulated DEGs			
1800	DPEP1	8.227595159	up
11199	ANXA10	6.660789481	up
7273	TTN	5.324255484	up
105372842	LOC105372842	4.993254219	up
283383	ADGRD1	4.035544471	up
54742	LY6K	3.783942219	up
945	CD33	3.738284193	up
547	KIF1A	3.730261687	up
26240	FAM50B	3.545457095	up
57822	GRHL3	3.477021065	up

Table 2. Top ten genes demonstrated by connectivity degree in the PPI network

Gene symbol	Gene title	Degree
STAT1	Signal Transducer And Activator Of Transcription 1	23
MX1	MX Dynamin Like Gtpase 1	17
DDX58	Dexd/H-Box Helicase 58	16
PPARG	Peroxisome Proliferator Activated Receptor Gamma	15
EGFR	Epidermal Growth Factor Receptor	15
APP	Amyloid Beta Precursor Protein	14
BST2	Bone Marrow Stromal Cell Antigen 2	14
DLG4	Discs Large MAGUK Scaffold Protein 4	14
OASL	2'-5'-Oligoadenylate Synthetase Like	13
IFIT2	Interferon Induced Protein With Tetratricopeptide Repeats 2	12

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