

Analysis of Gaucher Disease Responsible Genes in Colorectal Adenocarcinoma

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Abstract

Gaucher disease is a hereditary genetic abnormality which defects the pathway of sphingolipid catabolism. The mutation of GBA gene which encodes lysosomal β -glucosidase enzyme is the main characteristics of the disease also is observed in different cancer types. To find the relation between the disease and colon adenocarcinoma, the responsible gene expression of Gaucher disease was analyzed. The gene expression of colon adenocarcinoma was compared between death and alive patients and analyzed statistically to profile the differences between Gaucher disease genes expression changes. GBA, GBA2, GBA3, SCARB2 and PSAP have the maximum genetic alteration which is observed in colon adenocarcinoma.

Keywords: Gaucher disease; Colon adenocarcinoma; Glucosphingolipid; Genetic mutations; Macrophages; Immune dysregulation

Introduction

Gaucher disease (GD) is an autosomal recessive inborn error in the pathway of sphingolipid catabolism. Biochemically, this disease is characterized by a deficiency of lysosomal β -glucosidase (glucocerebrosidase, GCase) enzyme due to the mutation of GBA gene [1]. The natural substrate of this lysosomal enzyme is glucocerebroside (also called glucosylceramide) mainly present on the cytoplasmic face of cellular membranes and on the cell surface. Lysosomal β -glucosidases play a key role in recycling of this substrate by degradation of glucosphingolipid from membranes of apoptotic white blood cells and senescent red blood cells. Genetic mutations of GBA gene affect the enzyme's catalytic activity, stability and result in the storage of hydrophobic glucocerebroside in the lysosomes of macrophage cells. The consequent accumulation of glucocerebroside in macrophages throughout the body leads to enlargement of the spleen and liver, skeletal disease and immune dysregulation [2]. The mutation of PSAP gene that encodes activator protein saposin C (enhances the activity of GCase) may cause gaucher disease rarely [3,4]. Gaucher disease can be classified into three types depending on the presence or absence of neurological features; Type I GD1 - adult or visceral form is characterized by the lack of central nervous system (CNS) involvement and accounts for almost 95% of GD; Type II GD2 - infantile progressive neuropathic form with a life expectancy of <2 years; Type III (GD3) - juvenile, subacute neuropathic form [5]. Pathologically, patients with the adult non-neuropathic form of the disease have deposition of glucocerebroside in lysosomes of reticuloendothelial cells, particularly in the spleen, bone marrow and liver and frequently there is hepatosplenomegaly, anemia, and thrombocytopenia. It has been suggested that these tissue abnormalities in some Gaucher patients may trigger macrophage activation and could result in the enhanced inflammatory agents secretion and had increased levels of

pro-inflammatory (i.e., TNF α , IL-6, IL-8, and IL-1b) and anti-inflammatory cytokines (i.e., CD14) in serum and/ or tissues [6-13]. TNF α production has been suggested as a response to glucosylceramide accumulation in Gaucher disease patients (a macrophage activation marker [2]). It has been reported that the immune dysregulation, aberrant macrophage activation and inflammatory imbalances increase the incidence of malignant disorders in patients Gaucher disease Type 1 (GD1) [2,6,7]. In 1982, Lee reported that 19 of the 35 deaths that occurred due to malignant disease among 239 patients with type1 Gaucher disease; 3 of the patients had a diagnosis of multiple myeloma [6]. In 2005, Rosenbloom et.al reported cancer incidence among 2742 with patients Gaucher disease, using International Gaucher Registry they found that 10 of patients had multiple myeloma were diagnosed after the age 50 years [2].

How the insufficiency of GCase activity and the subsequent metabolic disturbances related to glucosylceramide and other sphingolipids could lead to such inflammatory imbalances remains unclear. Inflammation is thought to play a critical role in the advancement of cancer, particularly colorectal cancer [8]. As indicated by the reports, the processing of meat, by adding preservatives such as salt or sodium nitrite to prevent the growth of germs or smoking the meat to preserve or enhance color and flavor, may add compounds that might increase the potential of these foods to cause cancer. Studies have linked high intake of red meat, and particularly of processed meats with an increased risk of colorectal cancer [9]. In order to determine the relation of inflammatory imbalances and cancer development in patient with Gaucher disease and healthy people. We studied 10 genes. Inflammatory agents could be common factor for increasing the risk of cancer in both Gaucher patients and normal colorectal cancer patients. To better understand how the inflammatory imbalances lead to cancer in gaucher patient and normal human, we selected 10 genes which are GBA (encoding lysosomal glucocerebrosidase enzyme), GBA2, (encoding non-lysosomal glucosylceramidase enzyme) GBA3 (encoding cytosolic beta-

glucosidase enzyme), SCARB2 (encodes lysosomal integral membrane protein type 2 (LIMP-2) responsible for the transport of GCase to the lysosome), PSAP (The PSAP gene (encoding saposin C which is an activator of glucocerebrosidase) IL1A, TNF, IL6, IL8, and LDHA.

Materials and Methods

Materials

Gene expression genomic data was the main type of material for the research. In addition to that, clinical data also has been used to find the patients (n=18 dead), (n=163 alive). The all data, gene expression and clinical data, have been downloaded from TCGA as UNCAgent450, Agilent Expression 244K microarrays, COAD cancer type. In addition to that, control gene expression data have been used to compare the differences of the gene expression.

Methods

First of all the clinical data have been separated into dead and alive patients. The gene expression of the dead and alive patients also has been designed for them to measure the target genes, which could be effective in colon cancer, GBA, GBA2, GBA3, SCARB2, PSAP, IL1A, TNF, IL6, IL8, LDHA. The main idea of the method is to compare the target genes between dead and alive patients. t-test has been applied to the gene expression values to find the statistically significant P-value between dead and alive dataset [14-15].

Results

The target genes were all applied to statistical calculation to find significant changes. The genes were separated into two groups, colon cancer dead and colon cancer alive patients. The first analysis is the comparison between the cancer and control value. The target genes are generally high expressed in dead colon cancer patients, except GBA and LDHA low expressed ones -1.71 and -3.36 respectively. Then, the genes firstly were compared with control gene expression in healthy cell to see the differences between the cancer and control. P value of the GBA, GBA3, SCARB2, PSAP, IL1A, TNF, IL6 and LDHA were statistically significant (Table 1).

	Cancer Death	Control	Fold	P value
GBA	-0.22	0.13	-1.71	0.05
GBA2	-0.4	-0.65	0.61	0.061
GBA3	3.25	0.52	6.21	0.051
SCARB2	0.44	1.37	0.32	0.01
PSAP	0.15	0.65	0.23	0.015
IL1A	0.21	3.19	0.06	0.016
TNF	1.34	1.4	0.96	0.045
IL6	0.68	5.66	0.12	0.029
IL8	0.25	4.19	0.06	0.108
LDHA	-1.45	0.43	-3.36	0.05

P value of the gray ones is statistically significant genes

Table 1: The target gene colon cancer (Dead) gene expression.

Almost the similar result has been got from the target genes cancer-alive expression. While GBA and LDHA have low expressed the others show higher expressed profile. In addition to that, p value of SCARB2, PSAP, IL1A, TNF, IL6 and LDHA genes were statistically significant (Table 2).

	Cancer Alive	Control	Fold	P Value
GBA	-0.28	0.13	-2.12	0.063
GBA2	-0.36	-0.65	0.54	0.07
GBA3	3.09	0.52	5.9	0.065
SCARB2	0.58	1.37	0.42	0.016
PSAP	0.29	0.65	0.45	0.022
IL1A	0.41	3.19	0.13	0.023
TNF	1.62	1.4	1.16	0.057
IL6	0.33	5.66	0.06	0.036
IL8	0.38	4.19	0.09	0.112
LDHA	-1.34	0.43	-3.11	0.059

P value of the gray ones is statistically significant genes

Table 2: The target gene colon cancer (Alive) gene expression.

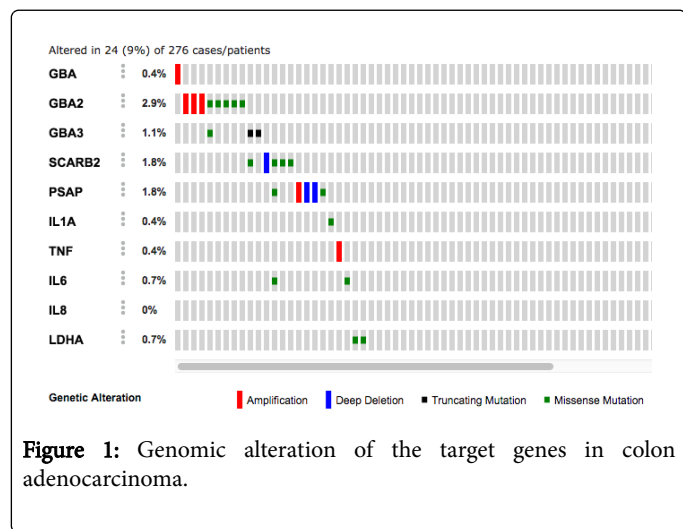
The target genes were statistically analyzed by comparison dead-control and alive-control separately. Then, the t-test results show that both groups have statistically significant p value (Table 3).

	P value	
	Death/Control	Alive/Control
GBA	0.01678	7.73E-07
GBA2	0.00524	1.06E-05
GBA3	0.38846	7.12E-12
SCARB2	4.05E-09	1.79E-21
PSAP	0.00016	2.86E-05
IL1A	2.62E-12	2.13E-24
TNF	0.38161	0.01904
IL6	1.08E-27	7.09E-53
IL8	2.60E-11	7.48E-22
LDHA	4.26E-10	2.06E-40

Table 3: The P value comparison between death and alive cancer patients.

The Gaucher disease responsible genes genetic alteration is also tested by a genomic web tool (<http://www.cbioportal.org/>)

data_sets.jsp). According to the analysis, GBA2 has the maximum genetic alteration %2.9. The missense mutation mostly is observed in GBA2, SCARB2, IL6 and LDHA. While amplification and deletion are also observed in GBA, GBA2, PSAP, GBA3 shows the highest truncating mutation (Figure 1).



Discussion and Conclusion

Colon cancer is one of the rising cancer types especially among the urban citizens. Food additives which are used for most of the industrialized food products could be harmful for changing epigenetics of human genome. Gaucher disease is a kind of some enzyme disabilities because of somatic mutation. It is already known that the disease is related to some other cancer types. Therefore, we decide to analyze the gene expression and genomic alteration of the genes which are responsible for Gaucher disease in colon adenocarcinoma. As a result of the analysis, the genes expression profile shows that they are genetically dynamic ones. In the future, the disease could be used as a signal to diagnose the cancer types.

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