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 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 glucocerebroside enzyme), GBA2, (encoding non-lysosomal glucosylceramidase enzyme) GBA3 (encoding cytosolic beta-glucosylceramidase enzyme) GBA3 (encoding cytosolic beta-glucosylceramidase enzyme) SCARB2 and PSAP have the maximum genetic alteration which is observed in colon adenocarcinoma.
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 UNCAgilent450, 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 activator of glucocerebrosidase) IL1A, TNF , IL6, IL8, and 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 | P value | Fold | Death | Control |
|--------|---------|------|-------|---------|
| 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

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 | P value | Fold | Death/Control | Alive/Control |
|--------|---------|------|---------------|---------------|
| GBA    | 0.01678 | 7.73E-07 | 0.00524 | 1.06E-05 |
| GBA3   | 0.38846 | 7.12E-12 | 0.00016 | 2.86E-05 |
| SCARB2 | 4.05E-09 | 1.79E-21 | 2.62E-12 | 2.13E-24 |
| PSAP   | 0.00016 | 2.86E-05 | 0.00161 | 0.01904 |
| IL1A   | 2.62E-12 | 2.13E-24 | 0.38161 | 0.01904 |
| TNF    | 1.08E-27 | 7.09E-53 | 7.09E-53 | 7.48E-22 |
| IL8    | 2.60E-11 | 7.48E-22 | 2.60E-11 | 7.48E-22 |
| LDHA   | 4.26E-10 | 2.06E-40 | 4.26E-10 | 2.06E-40 |

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).

![Figure 1: Genomic alteration of the target genes in colon adenocarcinoma.](image)

**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 colonoadenocarcinoma. 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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