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Prognostic Roles of Mitochondrial Transcription Termination Factor 1 and Mitochondrial Transcription Elongation Factor in Colon Adenocarcinoma

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Abstract: ***Mitochondrial transcription elongation factor (TEFM) and mitochondrial transcription termination factor MTERF1 modulate and regulate mitochondrial gene transcription and metabolism in most of the cells present in the body. Earlier studies have indicated that MTERF1 and TEFM play a pivotal role in pathogenesis of different types of cancer. However, the mRNA expression and prognostic roles of MTERF1 and TEFM in colon cancer patients remains unknown. The current objective was to investigate the alteration in mRNA expression level using FPKM data available in TCGA database, and evaluation of prognostic roles of MTERF1 and TEFM in patients with colon cancer using the Human Protein Atlas Database. The mRNA expression levels of TEFM were significantly increased in colon cancer patients as compared with normal colon tissue samples. the mRNA levels of MTERF1 was significantly decreased in colon cancer tissue compared to the normal adjacent tissues. High mRNA expression levels of TEFM and low mRNA expression levels were strongly associated with an improved overall survival rate (OS) in patients with colon adenocarcinoma. These results indicate the prognostic values of MTERF1 and TEFM expression levels in colon cancer. The findings from the present study may be useful for understanding the basic molecular mechanism of colon adenocarcinoma for making effective and efficient therapeutic treatments.***

Keywords: Overall Survival rate (OS), MTERF1, TEFM

1. Introduction

In accordance with the data presented by the International Agency of Research on cancer, headed by The World Health Organisation, in 2021(1), Colon cancer is observed to be the third most fatal and fourth most prevalent type of cancer (2, 3). There has been a steady rise in both the incidences and mortality of patients with this type of cancer, particularly in western countries due to various reasons such as life style, obesity, consumption of red meat etc (4), and this is the reason why there is an urgent need for prognostic biomarkers for predicting overall survival of patients affected by this type of cancer.

1.1 Background and Context

Mitochondria are recognized as the energy transducing organelles of eukaryotic cells in which the fuel to drive metabolism in cells are transformed into ATP by the process of electron transport chains and oxidative phosphorylation systems (5, 6). The major functions of mitochondrial proteins involve nitrogen metabolism, fatty acid and pyruvate oxidation (7). Mitochondria are also called as semi autonomous organelles as they have their own genetic material that is circular double stranded DNA present in the mitochondrial matrix which makes them unique from the other cell organelles (8). The mammalian mitochondrial genome is 16569 base pairs long and the strands of the DNA duplex can be differentiated by the difference in the G+T base composition that leads to varied buoyant densities of each strand namely heavy and light in denaturing caesium chloride gradients (9). Most of the genetic information is present and encoded on the H-strand (Heavy) as it contains genes for 2 rRNAs, 14 tRNAs, and 12 polypeptides. The light strand contains genes for 8 tRNAs and a single polypeptide (10, 11, 12).

Mitochondrial transcription starts in the major non-coding region containing the LSP (light strand promoter) and the HSP (heavy strand promoter) and is regulated by mitochondrial transcription factors such as TFAM (Mitochondrial Transcription factor A), POLRMT (mitochondrial DNA-directed RNA polymerase), MTERFs (Mitochondrial Transcription termination factors), TEFM (Mitochondrial transcription elongation factor), TFB1M & TFB2M (Transcription factors 1 & 2) (13, 14, 15, 16, 17).

MTERF (Mitochondrial Transcription termination factors) serve a pivotal role expression of the mitochondrial gene (15). It is a family of termination factors consisting of 4 members MTERF 1,2,3,4 (16, 17). The structure of MTERFs consists of repetitions of 30 amino acid molecules (17). Earlier studies have shown that MTERFs play a role in anchoring Mitochondrial DNA replication and exert crucial functions in termination and initiation of mitochondrial transcription (18). MTERF1 is the authoritative mitochondrial transcription termination factor. It is able to regulate the mitochondrial gene expression by preventing Light strand transcription interface within mtDNA (18).

TEFM (Mitochondrial Transcription Elongation Factor) is known to be one of the most crucial molecules for regulation mitochondrial replication-transcription switch. It controls both the Elongation and RNA processing of the mitochondrial transcription. TEFM contains two tandemly repeated helix-hairpin-helix motif and a single Rnase-H fold. TEFM enhances the processivity of mitochondrial transcription elongation by binding to mtRNAP, mtDNA and the nascent RNA and thus stabilizes the mtRNAP transcription elonga-

tion complex (19, 20, 21, 22). However to the best of our knowledge, there are no reports made on the prognostic roles of MTERF1 and TEFM in patients having Colon cancer, In addition role of both these genes remains a mystery in COAD, therefore, the present study aimed to investigate the expression and prognostic values of MTERF1 and TEFM in COAD.

1.2 Scopes and objectives

Mitochondrial genome transcription and its link with cancer has always remain elusive, recent studies have shown that mitochondrial transcription factors and their expression levels show a positive correlation with the alteration in their copy number during non small cell lung adenocarcinoma (23).

Major objective of this study was to find out whether the mitochondrial transcription factors MTERRF1 and TEFM had a positive correlation with respect to their mRNA levels and OS rate of patients affected with colon adenocarcinoma using bioinformatics data tools.

1.3 Achievements

The results of the present study showed that mRNA expression levels of MTERF1 and TEFM are highly altered in colon cancer patient samples and it has a strong correlation with the improved overall survival rate of the patients. The results of the current study can be used to carry out early prognosis and can be used to develop different therapeutics that target the particular mitochondrial transcription factors and hence can help in increasing the survival probability of the patients.

1.4 Overview

In this study, a bioinformatics approach was used for studying the change in expression levels of MTERF1 and TEFM and their link with the overall survival rate. Heatmaps showing differential expression in normal and colon cancer affected samples are presented, Box-plots showing quantified difference between the expression levels of the above stated genes are presented and lastly the overall survival probability is estimated using survival plots.

2. Review of Literature

Colon cancer is considered to one of the most dangerous and third most common type of cancer when it comes to study of oncology (24). By gender COAD is considered to be the second most prevalent type of cancer in women (9.2 %) and third for men (10%) (25).The main cause of colon adenocarcinoma are mutations in specific genes just like other type cancers, these mutations usually appear in oncogenes, tumor suppressor genes and the genes which are directly or indirectly related to DNA repair mechanisms (26). The most common gene that is mutated during colon adenocarcinoma is APC genes (Adenomatous Polyposis Coli). It is still a mystery as to whether genomic instability inititates adenocarcinomas or these arise during the process of mutation itself (27). The major pathways that are involved in this type of cancer are WNT signalling pathways, Ras/Map kinase pathways and CIN pathways (24, 28).

The overall survival rates during different stages of Colon adenocarcinnomas are 91% (localized carcinoma), 72% (regional carcinoma), 14% (metastatic carcinoma) (29).

Some of the most common prognostic factors used in prognosis of COAD are overall Survival rates, ALP values (Alkaline phosphate), CEA levels (Carcino-embryonic antigens), CA-A19 (sialyl lewis a) (24, 30, 31, 32). Research for probable mitochondrial biomarkers is still at a naive stage in the field of oncology.

Mitochondrial are those cellular components of the cell that are majorly involved in biogenesis of energy that is required by each and every cell in the body for carrying out various metabolical and catabolical activities (33). The mitochondrial genome is constantly under a threat for mutation due to the presence of reactive oxygen species which is made by the mitochondria itself during oxidative phosporylation. The cancer cells are studied extensively and it is a known fact that cancer cells require high levels of both energy and proliferation, this infers that mitochondria in some sense plays a key role in cancer progression as well as induction (34,35). Some of the most common mutations (point) are m8893T>G occurs in MT-ATPase 6 gene, m3460G>A occurs in MT-ND1 gene (36). Mitochondrial genome regulation is a key component in cancer advancement as these regulators maintain the ultimate balance for expression levels of the mitochondrial proteins that ultimately carry out mitochondrial functions such as oxidative phosporylation (37). Some of the major regulators of mitochondrial genome transcription are POLRMT, TEFM, MTERF1, TFB2M (38, 39). These regulators are found to have an abnormal scientific behaviour in different types of cancer.

Mitochondrial transcription termination factor 3 is known to a negative regulator of the mitochondrial transcription. It is found to have an over expression in various types of cancer such as liver cancer, lung cancer, pancreatic cancer, breast cancer and brain cancer (40). Using different patient data sets the expression of MTERF 3 was found to have a strong relation with the patient's survival rate (41), In multiple types of disease MTERFs and TEFM which are mitochondrial transcription regulators, they show a key role in prognosis.

Previous studies have revealed that abnormalities in MTERF1 binding may result in mitochondria related diseases which includes Kearn-sayre syndrome (42), studies of post transcriptional modification patterns of mtDNA, a disease called as MELAS (mitochondrial encephalopathy lactic acidosis) was revealed due to mutation in the mtDNA binding site for MTERF1 (43). Other neurological disorders such as Parkinson's disease diabetes, Alzheimer's disease and cancer are associated with mitochondrial dysfunction resulting from change in mitochondrial gene expression. In lung cancer, MTERFs expression levels have shown positive correlation with prognosis of OS in NSCLC patients (44).

For TEFM, According to previous studies it was found that TEFM levels in cell have a positive association with differ-

ent types of cancer such as Hepatocarcinoma, in this type of cancer, TEFM has shown positive association with the progression and prognosis in the cancer affected patients (43).

3. Aims and objectives

The aim of the present study was to find out the correlation between the mRNA expression levels of MTEF1 and TEFM with the improved OS rate in colon cancer affected patients using bioinformatics tools and analysis.

Objectives were to:-

1) Visualize the change in mRNA levels of MTERF1 AND TEFM,
2) Quantify the change in mRNA levels
3) To find the survival curves for patients suffering from colon cancer when the expression levels of MTERF1 and TEFM are high and low.
4) The final objective was to find whether MTERF1 and TEFM can be used as early biomarker for prognosis of COAD patients.

4. Materials and methods

4.1 Expression level variation of MTERF1 and TEFM in COAD patients

The present study analyzed the change in expression of mRNA levels of the transcription factors MTEF1 and TEFM with colon cancer affected patients from R studio Using TCGA database (https://www.cancer.net/cancer-types/colorectal-cancer/statistics) a total of 50 normal colon tissue sample data and 300 colon cancer (178 early stage samples and 122 late stage) affected tissue sample data were downloaded that contained the FPKM and TPM values (Fragments per Kilo base of transcript per million Map reads) of the mRNA that gave the expression values of all the genes expressed in the tissue. The data was filtered and scaled to obtain the expression data for 19 proteins out of which 13 proteins were proteins that the mitochondrial genome codes and 5 mitochondrial transcription factors (TFAM, TFB2M, MTEF1, TEFM, POLRMT). This analysis was done as a visualization analysis for expression level changes of MTEF1 and TEFM.

4.2 Quantification of change in expression levels of TEFM and MTEF1 in COAD patients

After the visualization analysis, a quantification analysis was done using the same patient data used in visualization analysis and the software used was again R studio. The patients mRNA expression data was used to obtain boxplots to compare and quantify the change in expression of MTERF1 and TEFM in colon cancer affected patients.

4.3 Association between MTERF1 and TEFM expression levels and clinic-pathological characteristics of COAD patients

The present study was used The Human Protein Atlas database (https://www.proteinatlas.org) to evaluate the prognostic values of MTERF1 and TEFM in patients with COAD. According to median level expression of all patients with COAD included in the analysis, patients were divided into two groups: High expression group and low expression group. P-value < 0.05 was considered to be an indicative of statistically significant difference.

5. Tests and Results

5.1 Varied expression of MTERF1 and TEFM in COAD

The results that were observed after generating the heat-map (Fig 1) of all the 19 proteins showed that in normal colon tissue sample the expression of TEFM is low whereas in COAD samples the expression was comparatively high, It was also observed that the expression levels of MTERF1 was less in normal colon tissue sample but it was high in colon cancer affected patients.

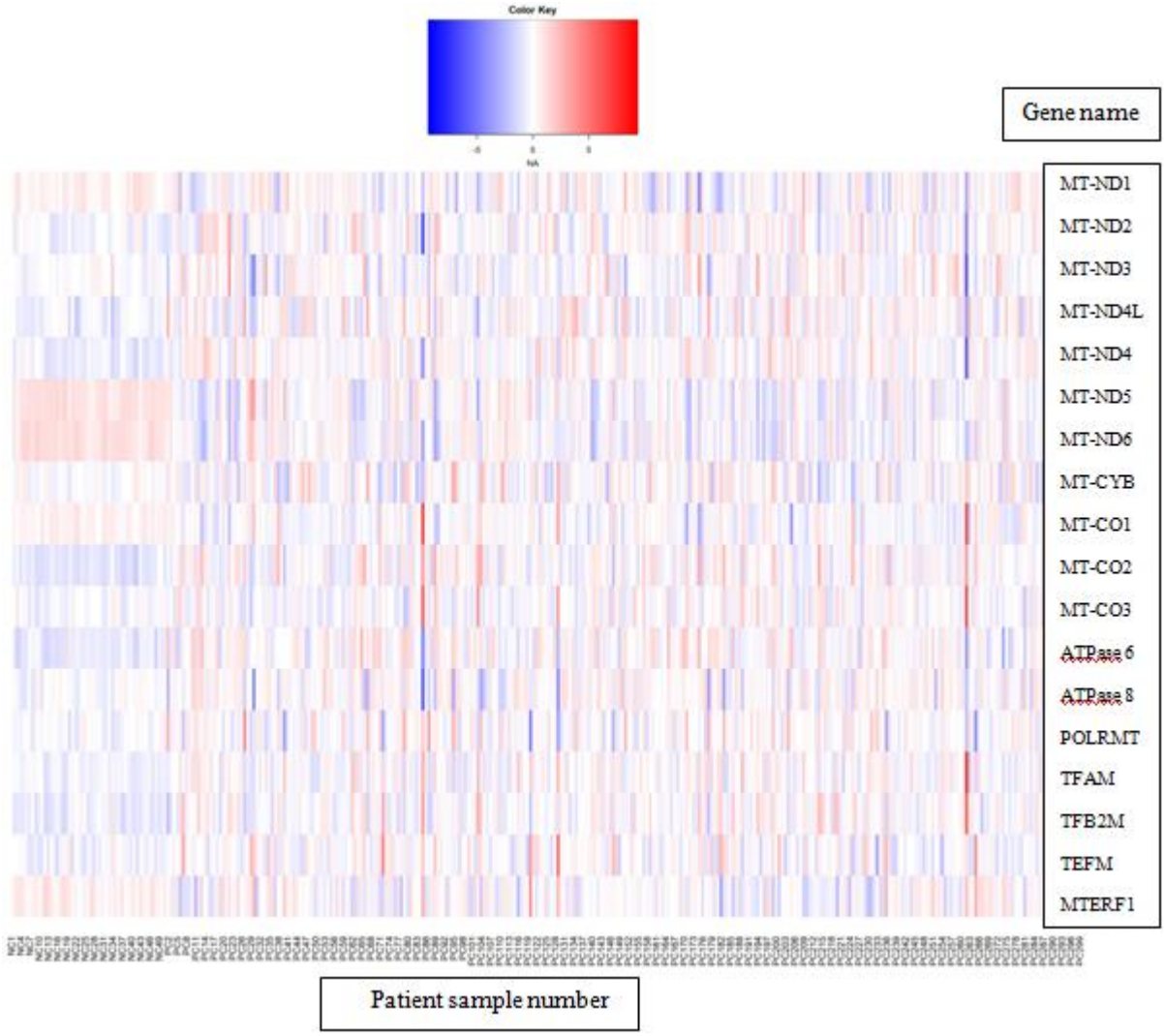

Figure 1 Alteration in expression Levels of different Mitochondrial Proteins and Transcription factors. The alteration of expression levels of different mitochondrial proteins were visualized using R studio. Expression levels vary from low to high and can be visualized as blue to red.

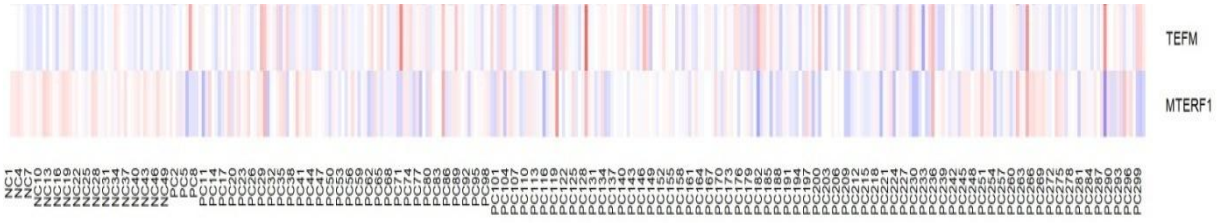

Figure 2 shows the zoomed view of Variations in expression levels of TERM and MTERF1 in Colon cancer affected samples n= 300 (For colon cancer tissue sample) n= 50 (For normal tissue sample).

5.2 Significant Changes in expression levels of MTERF1 and TEFM in COAD during quantification.

The results obtain after the following analysis were the P-values for MTERF1 and TEFM which were 3.76e-11 and 1.98e-05 respectively, shown in fig.3and fig.4

The P-values gives a bio-statistical evidence for quantification of change in expression levels of MTERF1 and TEFM

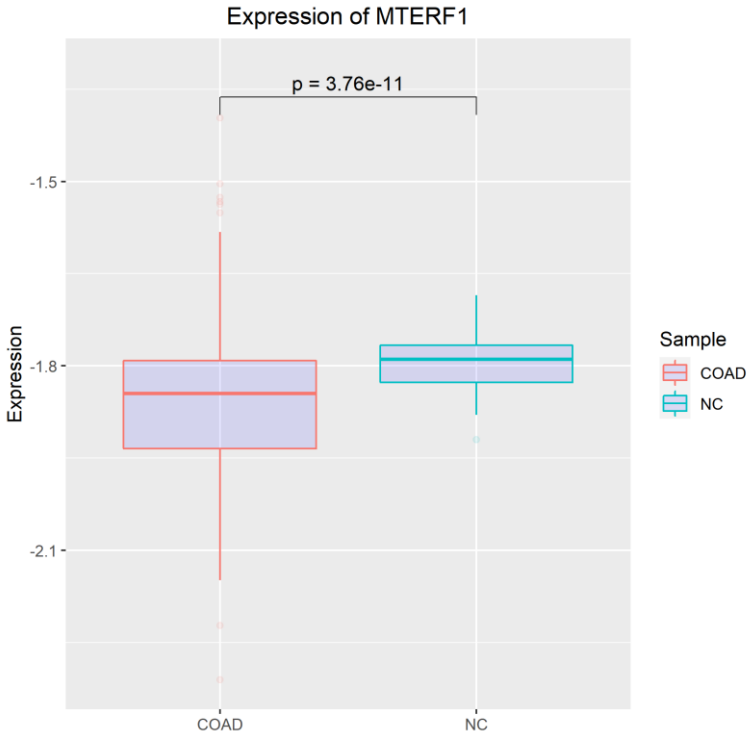

Figure 3

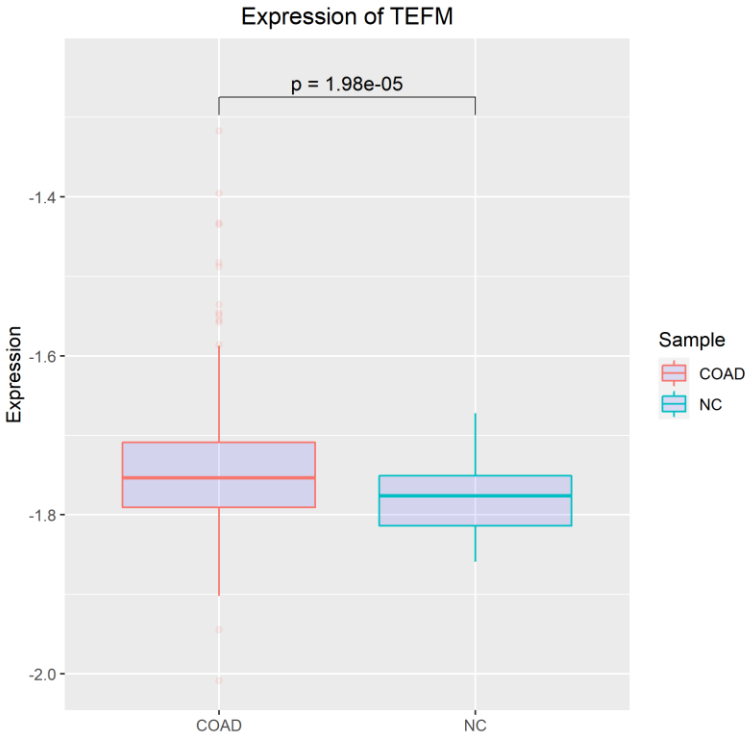

Figure 4

Figure 3 & 4 Quantification of alteration in expression of TEFM and MTERF1.The box-plots show the median expression of MTERF1 and TEFM with the Prognostic values that signify the difference between normal (NC) colon tissue sample and Colon cancer tissue sample (COAD). NC= 50 (Normal Colon tissue samples) COAD = 300 (Colon cancer tissue samples)

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5.3 Varied expression of MTERF1 and TEFM enhances the overall survival of COAD patients

The present study used survival curve analysis from the open source database – The Human Protein Atlas to evaluate the prognostic values of MTERF1 and TEFM in patients with COAD and the results were as follows:-

1) Overall survival of colon cancer affected patients increased when the expression of TEFM was highly

expressed and also the when the expression of TEFM was high the 5 year survival probability was 71% where as 5 year survival probability was 60 percent when expression of TEFM was low.

2) Overall survival of colon cancer affected patients increased when the expression of MTERF1 was less and also the when the expression of MTERF1 was high the 5 year survival probability was 57% where as 5 year survival probability was 60 % when expression of MTEF1 was low.

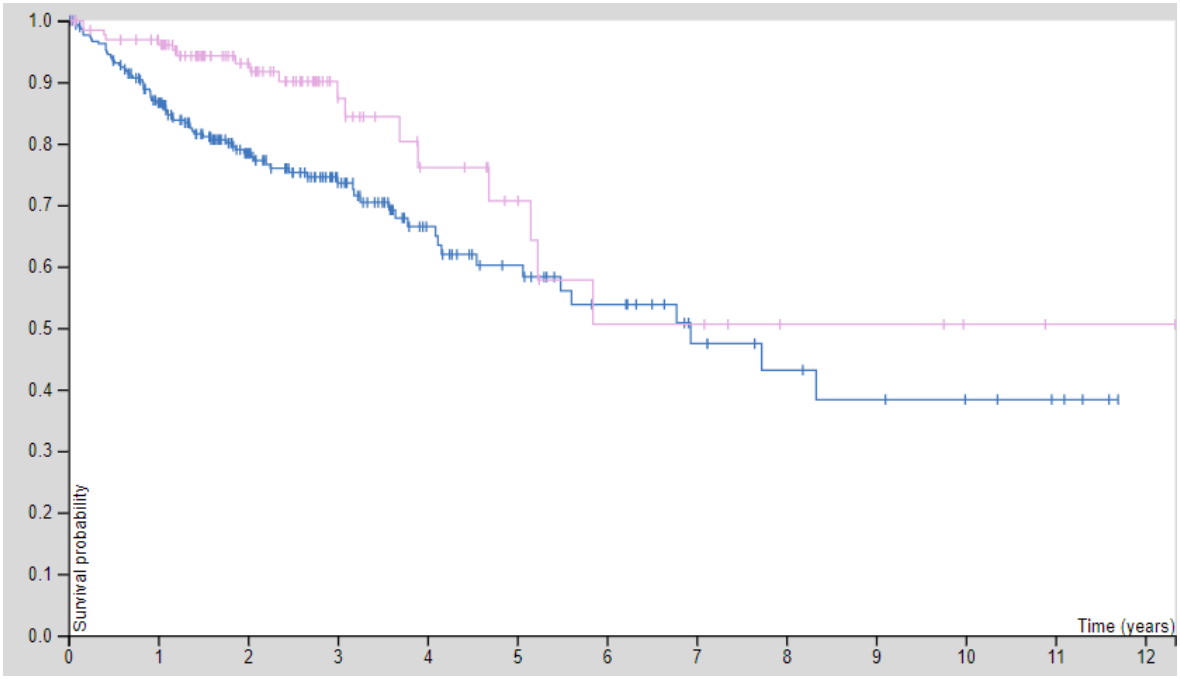

Figure 5: Shows the survival curve analysis and the overall survival rate in COAD patients when the expression of TEFM varies from high to low.

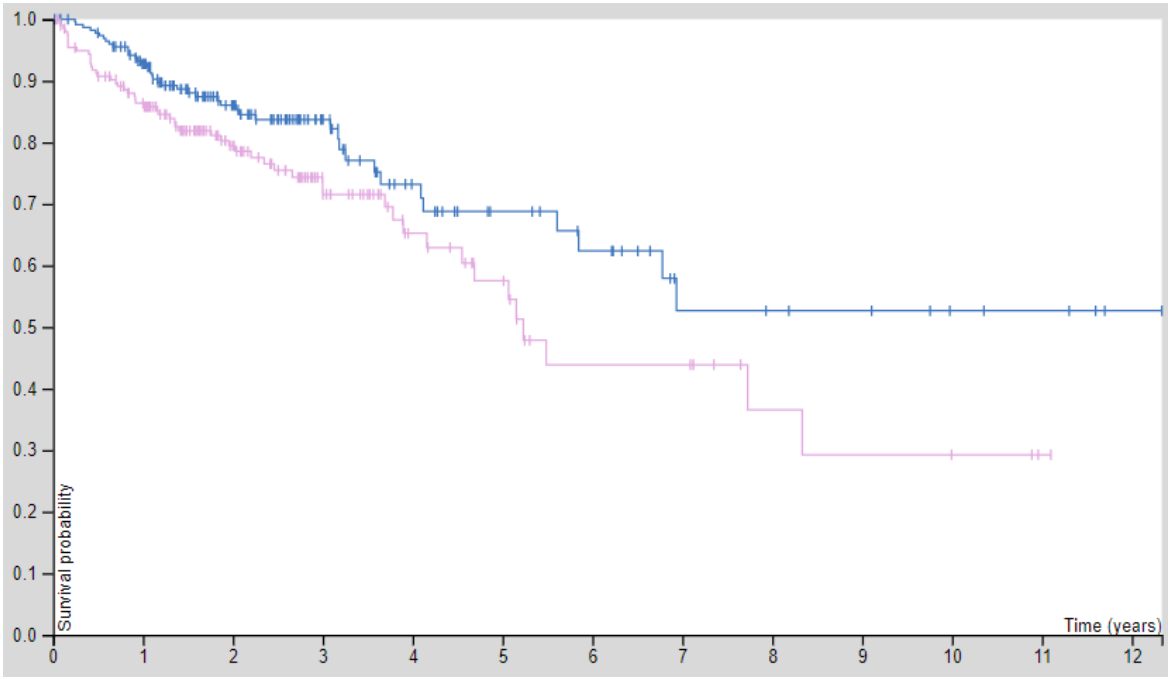

Figure 6: shows the survival curve analysis and the overall survival rate in COAD patients when the expression of MTERF1 varies from high to low.

6. Discussion

This research was performed using bioinformatics tools and statistical datasets that were collected and used from the TCGA database, a total of 350 samples data out of which 50 normal tissue samples and 300 patient tissue sample data were taken from the database to analyze the mRNA expression of different proteins associated with the mitochondrial genome and mitochondrial transcription. Previous research on MTERF1 and TEFM already show a promising result as they can be used as prognostic biomarkers in different types of cancer(43,44), but no prior art was found for their role in colon adenocarcinoma.

According to the results that were found during this study, it can be inferred that the change in expression levels of MTERF1 and TEFM are significantly co related to the overall survival rate in patients suffering from colon adenocarcinoma, Possible explanation that can be given for this kind of result is that the change in expression levels of these regulatory factors of mitochondrial transcription may be involved in some molecular process that might be improving the overall status of normal cells as well as the cancer cells. MTERF1 and TEFM both are invovled in regulation of mitochondrial genome which is the primary source of energy as the proteins produced by the mitochondrial genome are invovled in oxidative phosphorylation and hence energy production, Because of the above state processes and factors their might be a possible explanation for their significant prognostic values in colon adenocarcinoma patients which makes them probable early stage biomarkers that can be used to predict the overall survival at early stages of colon cancer.

The Present study only focuses on bioinformatics and statistical analysis, and the conclusion of this study may require additional biological experiments and analysis to accurately justify the potential underlying molecular biology mechanism.

7. Conclusion

7.1 Summary

The present study was conducted for finding the prognostic roles of TEFM and MTERF1 in Colon cancer affected patients. TCGA database was used to download 350 samples transcript per million data for analyzing the expression levels of 50 normal colon tissue samples and 300 cancer affected tissue samples , R studio, an open-source software was used to build the heat-map and box-plots for visualization and quantification of changes in mRNA expression levels of TEFM and MTERF1 in which it was observed that there were significant differences in expression levels of mRNA expression for TERFM and MTERF1 between normal and cancer affected patients. The prognostic values indicate that these genes can act as biomarkers for early prognosis of colon cancer patients.

7.2 Evaluation

The results from the study show that the prognostic values of MTERF1 and TEFM are significant and can be used as early prognosis of colon cancer in COAD patients which was the main objective of the present study.

7.3 Future work

The current study lacks a large number of patient data that can be improved when the patient data will be available. Increasing the sample size of the data might increase the efficiency of the study done. Mitochondrial genome has always remain elusive when it is related to cancer and the current study can be further done for more number of mitochondrial transcription factors in search for proper biomarkers for early colon cancer prognosis which might help in generating specific therapeutics against the mitochondrial transcription factors that will increase the overall survival of cancer patients. Additional wet lab experiments can be done for confirmed Prognostic values such as gene knock out tests, RT-PCR tests and DNA micro array analysis.

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