Life Sciences 238 (2019) 116977

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Alterations in Eukaryotic Elongation Factor complex proteins (EEF1s) in cancer and their implications in epigenetic regulation

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ARTICLE INFO

Keywords:
Epigenetic regulation
Cancer
Histone modifiers
Eukaryotic elongation factors
EEF1 complex
Data mining

ABSTRACT

Aims: In the cell, both transcriptional and translational processes are tightly regulated. Cancer is a multifactorial disease characterized by aberrant protein expression. Since epigenetic control mechanisms are also frequently disrupted during carcinogenesis, they have been the center of attention in cancer research within the past decades. EEF1 complex members, which are required for the elongation process in eukaryotes, have recently been implicated in carcinogenesis. This study aims to investigate genetic alterations within EEF1A1, EEF1A2, EEF1B2, EEF1D, EEF1E1 and EEF1G genes and their potential effects on epigenetic regulation mechanisms.

Materials and methods: In this study, we analyzed DNA sequencing and mRNA expression data available on The Cancer Genome Atlas (TCGA) across different cancer types to detect genetic alterations in EEF1 genes and investigated their potential impact on selected epigenetic modulators.

Key findings: We found that EEF1 complex proteins were deregulated in several types of cancer. Lower EEF1A1, EEF1B2, EEF1D and EEF1G levels were correlated with poor survival in glioma, while lower EEF1B2, EEF1D and EEF1E1 levels were correlated with better survival in hepatocellular carcinoma. We detected genetic alterations within EEF1 genes in up to 35% of the patients and showed that these alterations resulted in down-regulation of histone modifying enzymes KMT2C, KMT2D, KMT2E, KAT6A and EP300.

Significance: Here in this study, we showed that EEF1 deregulations might result in differential epigenomic landscapes, which affect the overall transcriptional profile, contributing to carcinogenesis. Identification of these molecular distinctions might be useful in developing targeted drug therapies and personalized medicine.

1. Introduction

Cancer is a complex, multifactorial, heterogenous disease in which personal, demographic, genetic and epigenetic differences have significant importance. Therefore, it is crucial to develop personalized treatment approaches in order to achieve the most efficient cancer therapy with the least amount of side effects. Hence, it is critical to identify molecular biomarkers that could be useful in distinguishing personal differences between patients with the same disease. Carcinogenesis is a process, which is greatly contributed by the abnormalities in gene expression patterns within the cell. The aberrations in protein levels during cancer pathogenesis signifies the efficient completion of translation; the cellular process of synthesizing protein from mRNA templates [1,2]. Translation is a 3-phase process, composed of initiation, elongation and termination. The elongation phase is carried out by EEF1 and EEF2 complexes [3]. EEF1 complex subunits, namely EEF1A1, EEF1A2, EEF1B2, EEF1D, EEF1E1 and EEF1G, are responsible for binding to the aminoacyl-tRNAs and transferring them to the A-site of the ribosome [4]. In addition to this main function of EEF1 complex proteins, recent studies have also attributed them important implications in tumorigenesis mechanisms. For instance, elevated levels of EEF1A1 and EEF1A2 are associated with several different types of cancer [5–9]. Similarly, EEF1D upregulation has been linked to poor prognosis in medulloblastoma, epithelial-mesenchymal transition and tumor invasion in oral squamous cell carcinoma [10,11].

Establishment of differential gene expression patterns requires alterations to the accessibility of DNA in multi-cellular organisms. Eukaryotic DNA exists as a complex structure called chromatin, which results from the compaction of DNA wrapped around core histones H2A, H2B, H3 and H4, constituting the histone octamer. Chromosomes are composed of two structurally and functionally distinct regions called euchromatin and heterochromatin. While heterochromatin comprises tightly packed, gene-poor DNA stretches, euchromatin is loosely packed and transcriptionally active [12]. The transition between these two chromatin types provide gene activity regulation, orchestrated by DNA methylation, non-coding RNAs (ncRNAs) and RNA interference (RNAi), histone variants and post-translational histone modifications, which are collectively called epigenetic regulation

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https://doi.org/10.1016/j.lfs.2019.116977
Received 2 August 2019; Received in revised form 5 September 2019; Accepted 15 October 2019
Available online 19 October 2019

mechanisms. Histones can be post-translationally modified via processes such as methylation, acetylation, phosphorylation (reviewed in Ref. [13]). Histone modifications play crucial roles in modulating cellular functions such as transcription, DNA-damage repair, apoptosis and cell cycle regulation, by changing chromatin dynamics [14].

It is foreseeable that deregulation of EEF1 proteins in cancer, hence the dysregulation of the translational machinery, would have implications on the expression profiles of downstream genes, suggesting epigenetic regulation. However, although previous studies in the literature that focus on EEF1 complex proteins are valuable in terms of pointing out their prognostic significance, there are no studies up to date that investigate the genetic alterations, i.e. amplifications and mutations, within EEF1 genes, their potential effects on epigenetic regulation mechanisms and cancer pathogenesis. Therefore, in this study, we analyzed DNA sequencing and mRNA expression data available on The Cancer Genome Atlas (TCGA) across different cancer types to detect genetic alterations in EEF1 genes and investigated their potential impact on selected epigenetic modulators.

2. Methods

2.1. GEPIA analysis

GEPIA (http://gepia.cancer-pku.cn/index.html) is an online tool that provides differential expression analysis between tumor vs. normal samples based on the RNA expression data of 9.736 tumor and 8.587 normal samples from the Cancer Genome Atlas and the Genotype-Tissue Expression (GTEx) projects [15]. Dot plots and box plots of gene expression profiles of the selected genes across all tumor samples and paired normal tissues were generated on GEPIA. Furthermore, overall survival analysis based on Log-rank test with 95% confidence interval were performed to create survival plots. p-values were automatically calculated by the tool and p-values below 0.05 (%5) were considered significant.

2.2. cBioPortal analysis

The cBio Cancer Genomics Portal (http://cbioportal.org) is an open-access tool that provides mutation data, copy number alterations, microarray-based and RNA sequencing–based mRNA expression changes, DNA methylation values, protein and phosphoprotein levels based on the TCGA-derived data [16,17]. In order to study genetic alterations within EEF1-family genes in Brain Lower Grade Glioma (LGG) and Liver Hepatocellular Carcinoma (LIHC), we selected the respective TCGA datasets on the web interface and analyzed complete tumor samples that had mRNA, copy number alteration and sequencing data. The mutational status and alterations in gene expression of EEF1 genes were determined using the *OncoPrint* feature, which is a method to visualize multiple genomic alteration events by generating heatmaps. The Enrichments segment on the Portal allows users to compare mutations, copy number alterations and mRNA expression levels in a concept of altered genes. A gene is classified as altered in a specific patient if it is mutated, homozygously deleted, amplified, or its relative mRNA expression is less than or greater than a user-defined threshold [16]. In our analysis, we separated the patients into 2 groups (altered vs. unaltered) according to the alteration status of EEF1 genes and compared the expression levels of selected chromatin modulators. Box-plots were drawn using RNASeq V2 RSEM normalized expression values and statistical tests were automatically computed on the Portal. p-values below 0.05 (%5) were considered significant.

2.3. Oncomine Analysis

Oncomine (https://www.oncomine.org) allows differential expression analyses on sample groups and identifies genes that are over-expressed or down-regulated in disease subtypes and particular sample groups based on microarray data. Expression profiles of EEF1 mRNAs within tumor samples (cancer vs. cancer) were evaluated using p-values below 0.05 with at least a 2-fold change as thresholds.

2.4. STRING interaction network analysis

Predicted interactors of EEF1 proteins were analyzed on STRING database (https://version11.string-db.org) which computationally identifies direct (physical) and indirect (functional) associations between proteins.

3. Results

3.1. EEF1 proteins in tumor vs. normal tissue

In order to investigate alterations to the EEF1 complex proteins at the gene expression level in cancer, first, the expression profiles of EEF1A1, EEF1A2, EEF1B2, EEF1D, EEF1E1 and EEF1G across all tumor samples and paired normal tissues available on GEPIA online tool were analyzed (Supplementary Figures S1-6). Among the different types of cancer, many EEF1 proteins were found to be deregulated in Brain Lower Grade Glioma (LGG) and Liver Hepatocellular Carcinoma (LIHC), and this also correlated significantly with poor prognosis. Therefore, LGG and LIHC were selected for further analysis. We showed that EEF1A1, EEF1B2, EEF1D and EEF1G were significantly upregulated in glioma tumors compared to normal tissue, whereas EEF1A2 was downregulated (Fig. 1a and b). Similarly, EEF1A2, EEF1D and EEF1G mRNAs were found to be upregulated in hepatocellular carcinoma. EEF1E1 expression levels did not vary significantly between selected tumors or their matched normal tissues.

Next, using the same datasets, we analyzed the overall survival of glioma or hepatocellular carcinoma patients according to EEF1 protein levels. GEPIA analysis indicated that lower expression levels of EEF1A1 ($p < 0.01$), EEF1B2 ($p < 0.01$), EEF1D ($p < 0.05$) and EEF1G ($p < 0.01$) were correlated with shorter survival periods in glioma, which could also be linked with the poor prognosis of the disease (Fig. 2a). On the other hand, in hepatocellular carcinoma, lower expression levels of EEF1B2 ($p < 0.01$), EEF1D ($p < 0.05$) and EEF1E1 ($p < 0.05$) were correlated with better survival (Fig. 2b).

3.2. EEF1 proteins in cancer vs. cancer

Personalized medicine, which relies on detecting genetic and/or epigenetic differences between patients with the same disease, has great implications in optimizing medical treatment for each individual in diseases such as cancer [18]. In order to explore whether EEF1 proteins have the potential to be molecular biomarkers, we analyzed genetic alterations in and changes in the expression levels of these genes using DNA sequencing and mRNA expression data of 507 glioma and 360 hepatocellular carcinoma patients, available on The Cancer Genome Atlas (TCGA) through cBioPortal interface. We found that 26% of all glioma patients and 52% of all hepatocellular carcinoma patients had at least one genetic alteration (amplifications, deletions and point mutations) in EEF1 genes or deregulation of the EEF1 gene expression (data not shown). Among all the EEF1 complex subunits analyzed, EEF1D was identified as the most commonly altered gene within the patient groups studied, with 9% and 35% alteration percentages in glioma and hepatocellular carcinoma, respectively (Fig. 3a and b). In order to see whether the altered expression profiles of EEF1 genes within glioma and hepatocellular carcinoma is a common phenomenon that can be applied to other cancers, we performed Oncomine Analysis across different cancer types. Fig. 4 shows that all EEF1 proteins were to some extent up- or down-regulated in different cancer types, indicating differential expression patterns within the same disease.

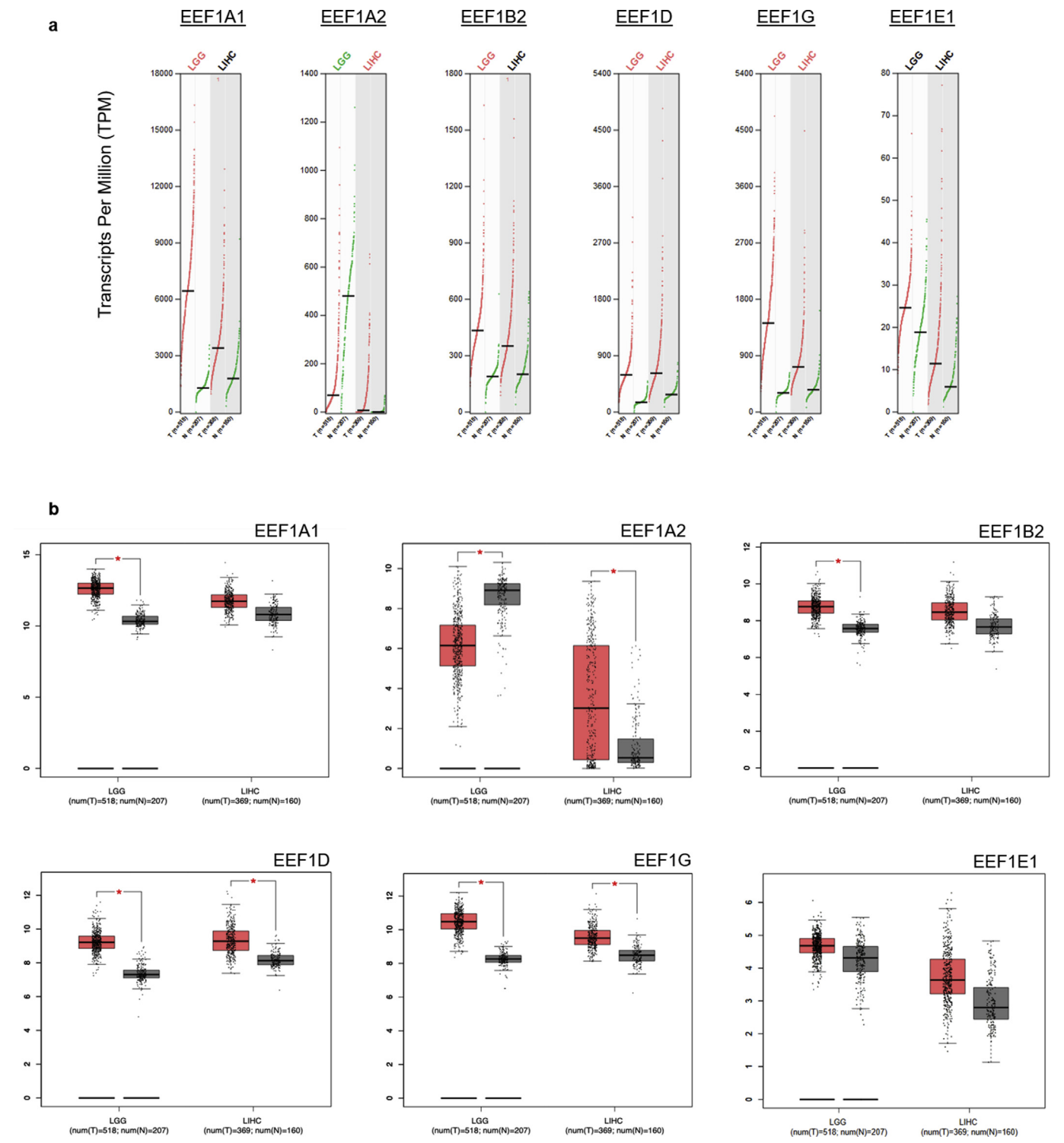

Fig. 1. Dot plots (a) and box plots (b) showing gene expression profiling of EEF1 genes. Each dot represents a distinct tumor (red) or normal (green) sample. If the cancer type is highlighted in red or in green, it indicates that the protein of interest is over-expressed or downregulated, respectively, in the tumor sample in comparison to the normal tissue. (LGG: Brain Lower Grade Glioma, LIHC: Liver Hepatocellular Carcinoma). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.3. EEF1 deregulation in relation to epigenetic regulation

When the heatmaps depicting EEF1 expression levels on a single patient basis in comparison to the genetic alterations were examined in detail, it was found that increased expression of EEF1 proteins were not directly reflected by the amplifications of the respective gene (Fig. 3a and b). In other words, most EEF1 upregulations were not based on genetic alterations, which suggests involvement of epigenetic mechanisms. In order to test our hypothesis that deregulation of EEF1 genes and their expression profiles might affect epigenetic mechanisms in cancer, we analyzed the expression levels of several histone modifying enzymes and chromatin modulators in relation to EEF1 alterations. We divided patients into two groups (altered vs. unaltered) according to the alteration status of EEF1 genes both in glioma and

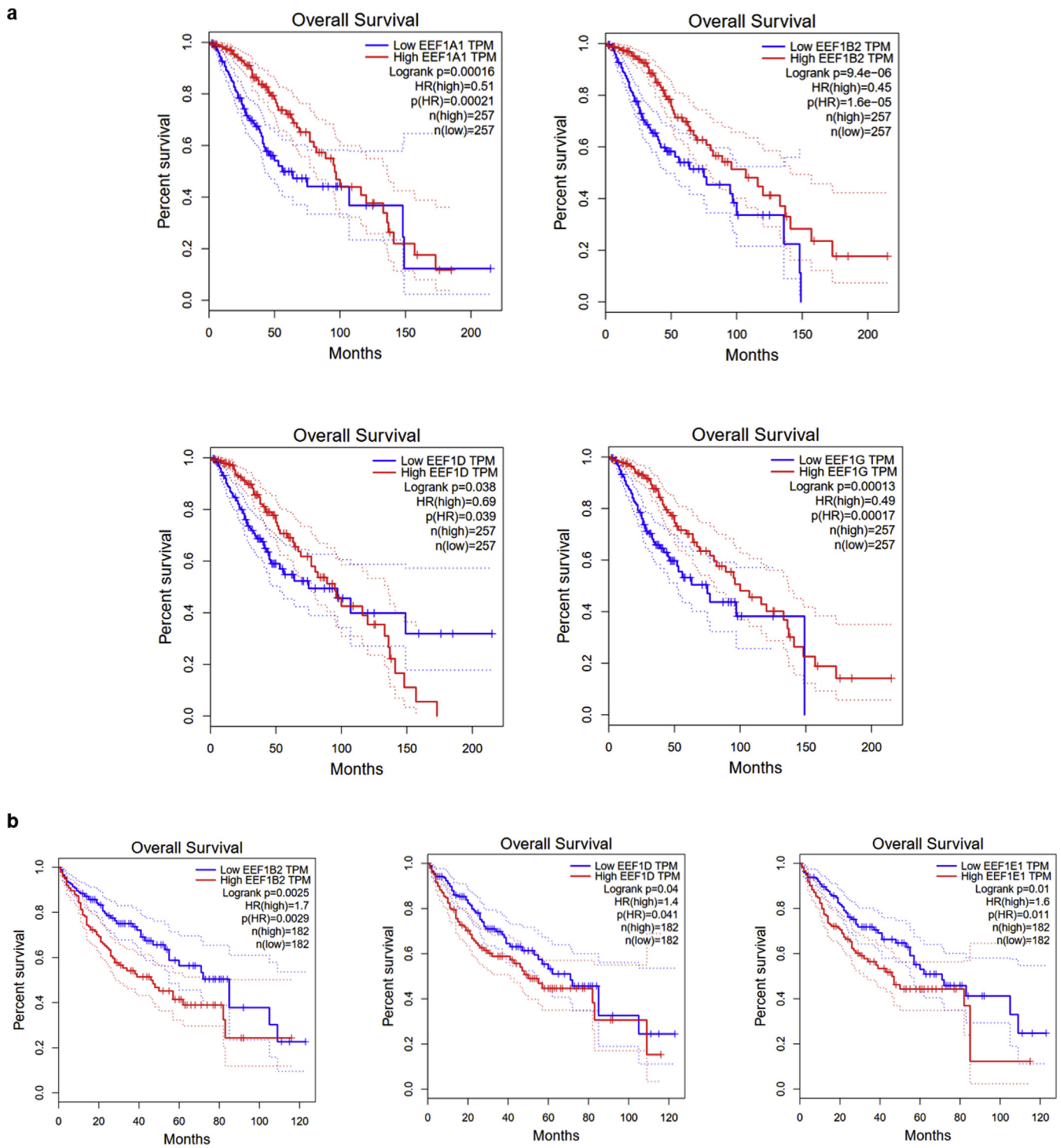

Fig. 2. Overall survival of glioma (a) and hepatocellular carcinoma (b) patients in relation to EEF1 protein levels. Only the proteins with a statistically significant effect on the overall survival are shown ($p < 0.05$).

hepatocellular carcinoma. If a patient carried at least one alteration within an EEF1 gene, the patient was included in the altered group. Fig. 5 shows that histone methyltransferases (HMTs) KMT2C, KMT2D and KMT2E, which are responsible for the methylation of histone H3 at Lysine 4 (H3K4me), were significantly down-regulated within the patient group with EEF1 alterations ($p < 0.001$). Similarly, the expression levels of histone acetyltransferases (HATs) KAT6A and EP300, which acetylate histones at H3K9ac and H4K16ac respectively, were significantly reduced in the EEF1 amplified group ($p < 0.001$). The patterns of altered gene expression followed the same trend both in glioma (Fig. 5a) and hepatocellular carcinoma (Fig. 5b).

3.4. Interaction partners of EEF1 proteins

In order to have a better understanding of the functional relevance of EEF1 proteins in cellular processes and epigenetic mechanisms, we performed STRING network analysis (Fig. 6). We found that EEF1A1, EEF1A2, EEF1B2, EEF1D and EEF1G interact closely, which is expected,

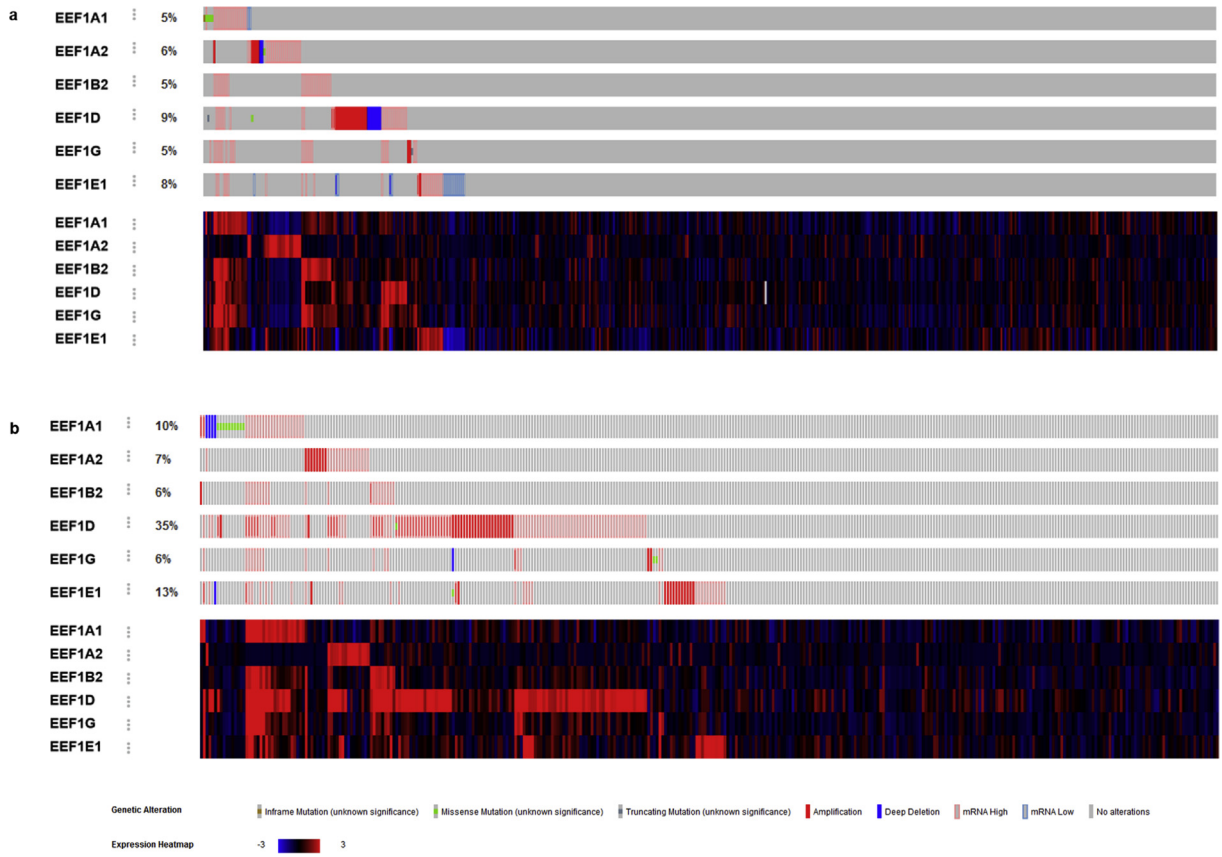

Fig. 3. Genetic alterations and gene expression profiles of EEF1 genes in glioma (a) and hepatocellular carcinoma (b) patients. Each bar represents one patient.

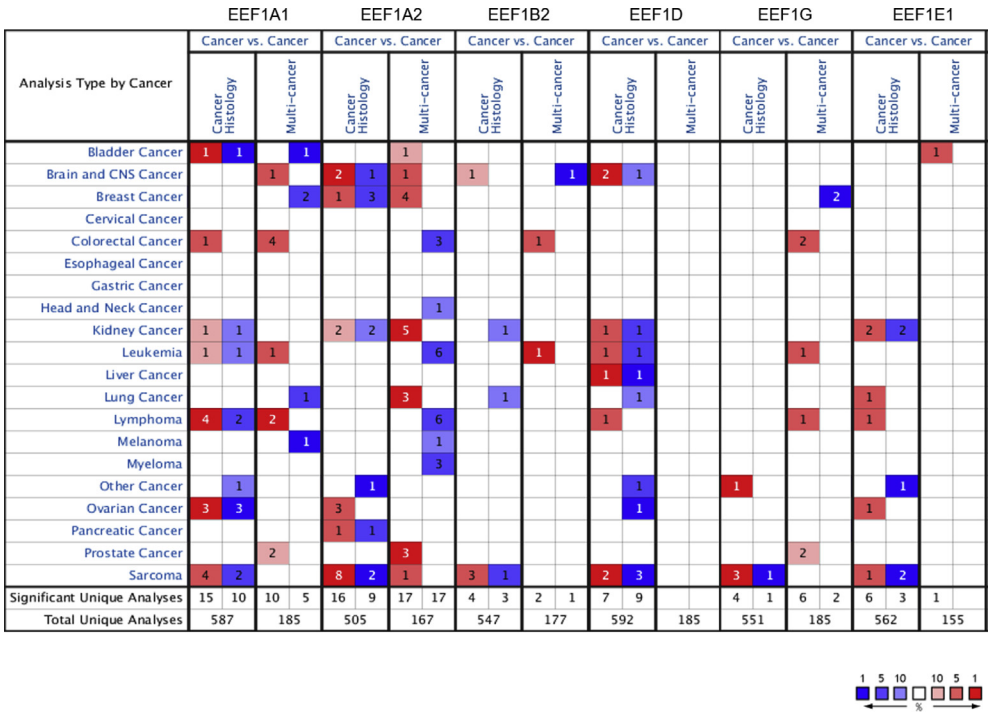

Fig. 4. EEF1 expression profiling across different tumor types. Red color indicates overexpression while blue color indicates downregulation. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

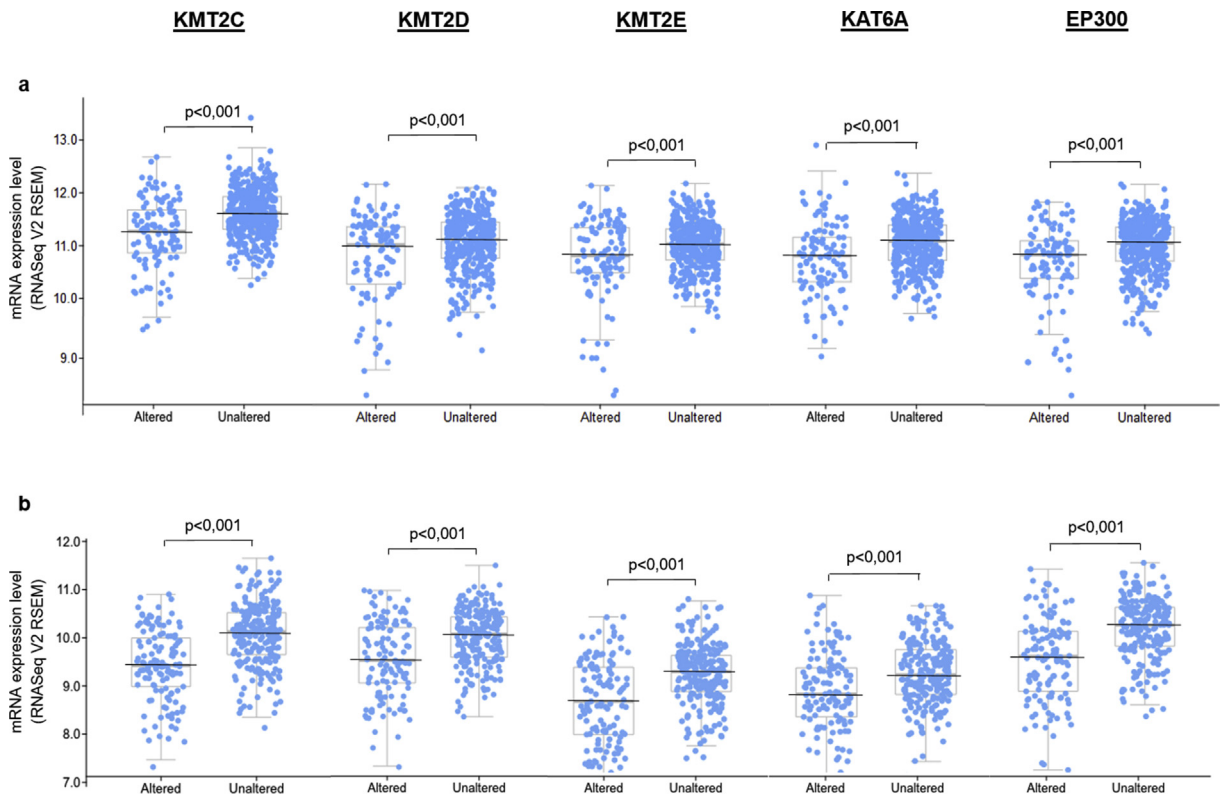

Fig. 5. Expression levels of selected HMTs and HATs in glioma (a) and hepatocellular carcinoma (b) patients with and without EEF1 genetic alterations (depicted as altered and unaltered, respectively). Only the proteins with a statistically significant difference between their expression levels in the EEF1-altered and unaltered groups are shown ($p < 0.001$).

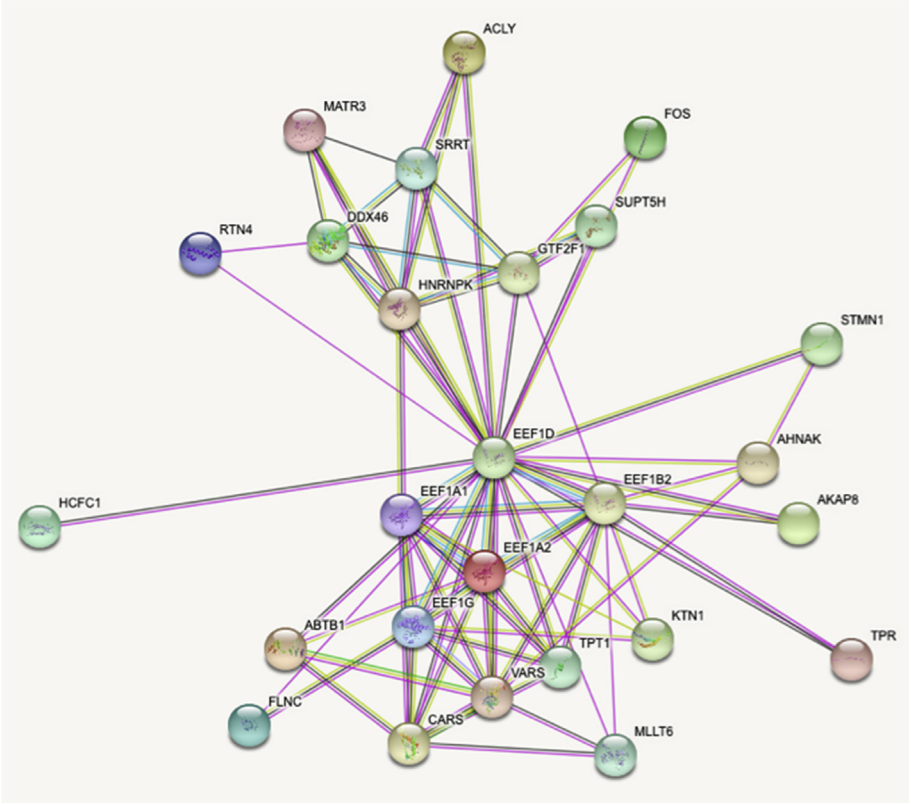

Fig. 6. Interaction partners of EEF1 proteins.

as they interact within the EEF1 complex and function together during translation. On the other hand, EEF1E1 was not among the top 25 interactors. The results showed that other interactors of EEF1 family proteins include factors ABTB1, FOS, HCFC1, TPT1, VARS, CARS, TPR, SUPT5H, DDX46, HNRNPK and AKAP8 that are involved in several cellular processes such as mRNA transport and processing, DNA damage response and chromosome condensation.

4. Discussion

In this study, we analyzed the genetic alterations in Eukaryotic Elongation Factor complex-1 (EEF1) genes and their gene expression profiles in TCGA datasets and compared them both in cancer vs. healthy tissues, as well as in cancer vs. cancer in order to evaluate their prognostic significance and potential as novel biomarkers for personalized medicine approaches. We have carried out an extensive analysis across 33 tumor types and found that gene expression profiles of EEF1 proteins are often deregulated in cancers, which is in line with previous studies in the literature. One interesting finding of our analysis was that although the expression of most EEF1s either increased significantly or slightly, EEF1A2 was downregulated in the tumor tissue compared to the normal tissue; contradicting the previous studies which suggest EEF1A2 is a potential oncoprotein [19]. EEF1A1 and EEF1A2 are isoforms that share more than 90% similarity in amino acid composition; however, they are implicated to have distinct, non-overlapping expression patterns [20]. Similarly, the two isoforms are suggested to play opposite functions during programmed cell death; EEF1A1 acts as a pro- and EEF1A2 as an anti-apoptotic protein, which could explain their tendency to behave differently in cancer [5,6,21]. Moreover, we performed overall survival analysis based on EEF1 protein levels in glioma and hepatocellular carcinoma patients and interestingly, we found that lower EEF1A1, EEF1B2, EEF1D and EEF1G levels were correlated with poor survival in glioma, while lower EEF1B2, EEF1D and EEF1E1 levels were correlated with better survival in hepatocellular carcinoma. This observation suggests that EEF1 complex proteins might have opposing implications in different cancer types, and is important as it corroborates our finding that EEF1s can be potential biomarkers that can be used for distinguishing between the patient-specific differences of individuals with the same disease.

Next, we explored molecular variations in EEF1 genes between patients with the same disease at both the DNA and mRNA levels and showed that all EEF1 genes were subjected to gene amplifications, mutations and mRNA up- or downregulations to some extent. More importantly, we found that, in most cases, the upregulation of EEF1 mRNA expression was independent of a genetic basis, that is, gene amplification; suggesting that their expression increased via epigenetic regulation mechanisms, possibly by alterations at the chromatin level. Likewise, we found that patients with deregulated EEF1 genes had lower levels of KMT2C, KMT2D, KMT2E, KAT6A and EP300 expression. These enzymes are responsible for setting histone marks H3K4me, H3K9ac and H4K16ac that are associated with loosely packed and transcriptionally active euchromatin [22,23]. Therefore, it is possible to think that patients with EEF1 alterations would have reduced global levels of H3K4me, H3K9ac and H4K16ac, consequently resulting in a more tightly packed, transcriptionally repressed global chromatin environment. As a result, there will be differences between the cancer patients with and without EEF1 alterations in terms of overall genomic landscape and transcriptional profile.

STRING network analysis showed that EEF1 proteins interact with several important proteins in the cell, which include those that play significant roles in cancer. These proteins include proto-oncogene c-Fos; ABTB1, which is implicated in PTEN-mediated cellular growth suppression [24]; HCFC1 which is involved in cell cycle regulation [25], TPT1 translationally-controlled tumor protein; VARS and CARS, which are tRNA ligases with proposed cancer-associated activities in glioma [26]; TPR, DDX46, SUPT5H and HNRNPK, which are all involved in mRNA transport and processing while HNRNPK alone also plays a role in p53-dependent DNA damage response [27]; AKAP8, which is required for chromosome condensation during cell division and enhances histone H3 lysine 4 methylation (H3K4me) mediated by histone methyltransferase KMT2B [28]. In addition to this long list, HCFC1 interacts with other H3K4 methyltransferases namely MLL and SET1 [29]. This link between EEF1 complex subunits and interactor proteins with chromatin-related functions further corroborate our finding that EEF1 deregulations can result in the establishment of differential epigenomic landscapes, affecting the overall transcriptional profile and consequently contributing to carcinogenesis.

5. Conclusion

Overall, our work is the first study to link eukaryotic elongation factor complex proteins (EEF1s) with interaction partners that have important roles in the cellular machinery and gene expression,and offer an explanation to the molecular alterations leading to carcinogenesis due to the deregulation of EEF1 proteins.

Author contributions

BBS performed the conceptualization of the study, data mining analyses, interpretation of the results, and writing of the manuscript.

Declaration of competing interest

The author declares no financial or non-financial conflict of interest.

Acknowledgements

The results published in this study are based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2019.116977.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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