Prognostic Value of Enolase Gene Family in Colon Cancer

Xiaohang Pan*  Huawen Wu*
Guofu Chen  Wenhuan Li

* Xiaohang Pan and Huawen Wu contributed equally

Corresponding Author: Wenhuan Li, e-mail: doctorliwenhuan@sina.com
Source of support: Departmental sources

Background: Colorectal cancer (CRC), the most common gastrointestinal cancer, is associated with high mortality rates. Enolase is a major enzyme present in the glycolytic pathway. However, the functional significance of the enolase (ENO) gene family in the pathogenesis of CRC has been unclear.

Material/Methods: The data associated with 438 CRC patients from The Cancer Genome Atlas database were extracted for analysis. Survival analyses with Cox regression was performed to construct a prognostic signature. We investigated the processes that underlies the correlation between ENO genes and overall survival (OS) using gene set enrichment analysis (GSEA). We then developed a connectivity map to identify candidate target drugs for CRC.

Results: The multivariate survival analysis showed that low expression of ENO2 and ENO3 had a significant correlation with longer OS. The joint-effects survival analysis indicated that the combined low expression of ENO2 and ENO3 was highly correlated with favorable OS. As indicated by the gene set enrichment analysis (GSEA), the ENO gene is involved in various biological pathways and has multiple roles. Potential pharmacological targets of ENO2 and ENO3 were constructed as well.

Conclusions: Low expression levels of both ENO2 and ENO3 were linked to a positive prognosis for CRC. Both ENO2 and ENO3 show promise as prognostic biomarkers for colon cancer patients.

MeSH Keywords: Colorectal Neoplasms • Phosphopyruvate Hydratase • Prognosis • Survival Analysis

Abbreviations: ENO – enolase; NSE – neuron-specific enolase; CRC – colorectal cancer; OS – overall survival; TCGA – The Cancer Genome Atlas

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/922980
Background

Colorectal cancer (CRC) is the most common gastrointestinal cancer and has high mortality. In the USA, the estimated incidence and mortality of CRC rank third among all cancers [1]. The 5-year relative survival rate for colorectal cancer patients is 65%. For patients with stage I or II disease, the 5-year relative survival rates are 91% and 82%, respectively, but the 5-year survival rate is only 12% for patients with stage IV disease. Moreover, the tumor stage has a strong association with CRC prognosis, and timely diagnosis and therapy improve overall survival (OS) rates [2].

Enolase is an important enzyme in the glycolytic pathway and is ubiquitous in organisms ranging from bacteria to mammals [3]. Enolase 1 (ENO1, α polypeptide, nonneuronal enolase), enolase 2 (ENO2, γ polypeptide, neuron-specific enolase), enolase 3 (ENO3, β polypeptide, muscle-specific enolase), and enolase 4 are members of the enolase gene family. ENO1 is associated with many cancers, including bladder cancer, gastric cancer, and colorectal cancer [4–6]. ENO2, which is also a neuron-specific enolase (NSE), is overexpressed in the serum of patients with small cell lung cancer [7]. NSE is the tumor marker of first choice for use in patients with small cell lung cancer [8]. Downregulation of ENO3 gene expression prevents the growth of cancer cells [9]. ENO4 is reported to be particularly important in spermatozoa [10]. However, the functional importance of ENO4 in the pathogenesis of cancer has been unclear. In the present study we assessed clinical data and ENO genes expressions of 438 CRC patients using publicly available data from the TCGA database.

Material and Methods

Data source

The medical data as well as the ENO levels of CRC patients were attained from The Cancer Genome Atlas (TCGA; https://cancergenome.nih.gov/). We created scatter plots of expression profiles of the ENO genes in CRC as well as normal colon tissue in the TCGA database.

ENO gene family correlation analysis and bioinformatics analysis

The co-expression analysis of ENO gene pathway and protein level expression was carried out with the use of GeneMANIA (www.genemania.org) [11], and functional bioinformatics analysis was performed in DAVID (david.ncifcrf.gov/tools.jsp) [12,13].

Survival analysis

We assessed the prognosis of patients with CRC based on OS. The associations between the expression of ENO genes in CRC and the OS of patients were assessed using Kaplan-Meier analysis, log-rank test, and the Cox proportional hazards regression after adjusting for not age, sex, and TNM stage.

Joint-effects survival analysis

Joint-effects analysis was used for the combination of significant ENO genes. The groups were developed by summarizing the chosen expression of ENO genes linked to better OS, worse OS, and other.

Table 1. Demographic and clinical data for 438 colon cancer patients.

| Variables | Patients (n=438) | No. of events (%) | MST (days) | HR (95% CI) | Log-rank P |
|-----------|-----------------|-------------------|------------|-------------|------------|
| Age (years) | | | | | | |
| <60 | 122 | 81.1 | 3039 | Ref. | 0.398 |
| ≥60 | 316 | 76.3 | 2535 | 1.223 (0.766–1.952) | 0.398 |
| Sex | | | | | | |
| Female | 204 | 78.4 | 2990 | Ref. | 0.545 |
| Male | 234 | 76.9 | 2320 | 1.131 (0.759–1.686) | 0.545 |
| TNM stage | | | | | | |
| I | 73 | 94.5 | 3234 | Ref. | <0.001 |
| II | 167 | 83.8 | 2838 | 2.24 (0.781–6.421) | <0.001 |
| III | 126 | 75.4 | 2856 | 4.068 (1.434–11.538) | 0.012 |
| IV | 61 | 49.2 | 1114 | 11.291 (3.980–32.026) | 0.012 |
| Missing | 11 | | | | |

MST – median survival time; HR – hazard ratio; CI – confidence interval.
We formulated a prognostic risk score for the ENO2 and ENO3 genes in CRC. We used nomograms to predict 1-, 3-, 5-, and 10-year survival to evaluate the correlation between ENO genes and OS in CRC patients [14].

**Gene set enrichment analysis (GSEA)**

The processes that underlie the correlation between the ENO genes and OS were investigated using GSEA. We performed biological pathway analysis in CRC with the ENO genes with the use of the reference c5 and c2 gene sets from the MSigDB, which made use of GSEA v.3.0 (http://software.broadinstitute.org/gsea/msigdb/index.jsp) [15]. The number of permutations was established at 1000. P<0.05 and FDR<0.25 were considered as having statistical significance.

**Pharmacological targets**

The genome-wide differentially expressed genes (DEGs), which include not just the upregulated but also the downregulated genes, together with the heatmaps and volcano plots, were attained with the use of edger [16]. Results with a fold change of >2 and P≤0.05 were used for analyses. Then, we chose target drugs from Connectivity Map (https://portals.broadinstitute.org/cmap/).
In addition, the chemical compositions of related drugs were obtained from PubChem Compound (https://www.ncbi.nlm.nih.gov/pccompound/). The visualization of GO terms was done using BinGO. Thereafter, the enrichment analysis was carried on DEGs using DAVID.

**Statistical analysis**

SPSS v.25.0 software (IBM, Chicago, IL, USA) was used for statistical analyses. The calculation of OS was carried out using Kaplan-Meier analysis and log-rank test. The evaluation of the
multivariate survival analysis was performed with log-rank P-values, hazard ratios (HR), and the calculation of the 95% percent confidence intervals (CIs) was done by Cox proportional hazards regression. P<0.05 was considered statistically significant.

**Results**

**Patients' clinical features**

The detailed clinical data attained from the TCGA concerning the 438 CRC patients are presented. Correlations between the clinical data and OS in the CRC patients are illustrated in Table 1 [17]. TNM stage had a significant association with OS (P<0.001; Table 1).

Scatter plots showing levels of ENO genes in CRC or normal colon tissue are shown in Figure 1. The median levels of ENO1, ENO2, and ENO3 were higher in CRC tissue than in normal colon tissue.

**ENO gene family correlation analysis and bioinformatics analysis**

Associations between expression of ENO genes in CRC were assessed using Pearson correlation coefficients (Figure 2A). Figure 2B shows the pathway and co-expression prediction for ENO1, ENO2, ENO3, and ENO4. ENO gene family co-expression was assessed at the protein level (Figure 2C). The biological roles of the ENO genes were assessed based on the biological process, together with the molecular function and cellular
component in GO pathway analysis. Findings associated with the KEGG pathway analysis are demonstrated in Figure 2D.

Effect of differential ENO gene expression on survival

Figure 3 shows the major results of univariate survival analysis. Low expression levels of ENO2 and ENO3 were significantly correlated with enhanced OS in CRC patients (P=0.003 and P<0.001, correspondingly). TNM stage was correlated with the prognosis of CRC patients (Table 1). Furthermore, the low expression levels of ENO2 (P=0.02) and ENO3 (P<0.001) were associated with a longer OS (Table 2).

A joint-effects framework was constructed for the various cohorts based on the expression of ENO2 and ENO3 (Table 3). Low expression levels of ENO2 and ENO3 were significantly correlated with longer OS (P<0.001; Figure 4).

Table 2. Prognostic survival analysis of ENO family genes.

| Gene expression | Patients (n=438) | No. of events (%) | MST (days) | Crude HR (95% CI) | Crude P | Adjusted HR (95% CI) | Adjusted P* |
|-----------------|-----------------|-------------------|------------|------------------|---------|----------------------|-------------|
| ENO1            |                 |                   |            |                  |         |                      |             |
| Low             | 219             | 76.7              | 2309       | Ref.             | 0.243   | Ref.                 | 0.840       |
| High            | 219             | 78.5              | 2933       | 0.788 (0.528–1.175) | 1.044 (0.689–1.580) |
| ENO2            |                 |                   |            |                  |         |                      |             |
| Low             | 219             | 83.1              | 3016       | Ref.             | 0.003   | Ref.                 | 0.020       |
| High            | 219             | 72.1              | 2311       | 0.543 (0.361–0.817) | 0.604 (0.395–0.923) |
| ENO3            |                 |                   |            |                  |         |                      |             |
| Low             | 219             | 85.8              | 3033       | Ref.             | <0.001  | Ref.                 | <0.001      |
| High            | 219             | 69.4              | 2365       | 0.439 (0.287–0.673) | 0.452 (0.292–0.699) |
| ENO4            |                 |                   |            |                  |         |                      |             |
| Low             | 219             | 79.0              | 2784       | Ref.             | 0.801   | Ref.                 | 0.685       |
| High            | 219             | 76.3              | 2566       | 1.052 (0.707–1.566) | 0.919 (0.611–1.382) |

* Adjusted for TNM stage. ENO – enolase; MST – median survival time; HR – hazard ratio; CI – confidence interval.

Table 3. Grouping according to ENO genes.

| Group patients (n=438) | Composition |
|------------------------|-------------|
| 1 127                  | Low ENO2+low ENO3 |
| 2 184                  | Low ENO2+high ENO3 |
| 3 127                  | High ENO2+low ENO3 |
|                        | High ENO2+high ENO3 |

ENO – enolase.

Figure 4. The joint-effects analysis of the influence of combined ENO gene expression on the OS with stratification on the basis of ENO2 and ENO3.

Nomogram of CRC prognostic risk score model

The nomogram confirmed not that tumor stage and ENO2 and ENO3 expression in CRC predicted prognosis and contributed the majority of risk (range, 0–100 points) for poor OS. All of the variables were awarded points on the basis of Cox
regression coefficients. The points were totaled, and the estimation of probability of survival made by drawing a vertical line (Figure 5).

**Gene set enrichment analysis (GSEA)**

We performed the GSEA analysis to investigate the biological mechanisms underlying the effects of ENO2 and ENO3 overexpression. KEGG pathway analysis showed that overexpression of ENO2 was positively correlated with cell adhesion (Figure 6A), focal adhesion (Figure 6B), natural killer cells (Figure 6C), MAPK signaling pathway (Figure 6D), VEGF signaling pathway (Figure 6E), and cancer pathways (Figure 6F). GO enrichment analysis showed that overexpression of ENO2 had a positive correlation with cell adhesion (Figure 7A), as well as endothelial cell migration (Figure 7B), lymphocyte apoptotic process (Figure 7C), BMP signaling pathway (Figure 7D), ERK1 and ERK2 cascade (Figure 7E), and insulin-like growth factor receptor signaling pathway (Figure 7F).
Pharmacological targets and drugs

We obtained DEGs with the use of edgeR. Pharmacological targets and drugs were attained from the Connectivity Map using the DEGs. The negatively correlated drugs constitute the latent pharmacological targets for ENO2 and ENO3 (Tables 4, 5). The heatmaps and volcano plots of these DEGs are demonstrated in Supplementary Figures 1–4. Supplementary Figures 5 and 6 show the chemical composition and the 2D structure of these latent target drugs. We performed enrichment analysis of the DEGs in DAVID. Supplementary Figure 7 and 8 show GO terms visualized by BinGO.

Discussion

We used data from TCGA to investigate correlations between the ENO gene expression levels in CRC, together with developing a risk score, including the medical factors as well as the expression patterns of ENO genes for the prediction of prognosis in patients with CRC. We found that expression levels of ENO2 and ENO3 were higher in CRC compared to the normal colon tissue. Survival analysis suggested that low ENO2 and ENO3 expression levels were strongly associated with longer OS. The joint-effects analysis of these genes showed their diagnostic value was better when combined than alone. We developed a nomogram based on clinical data, and ENO2 and ENO3 were used for the prediction of 1-, 3-, 5-, and 10-year OS of CRC patients. In exploring the underlying molecular processes, GSEA showed that over expression of ENO2 was positively correlated with cell adhesion, endothelial cell migration, focal adhesion, lymphocyte apoptotic process, natural killer cells, MAPK signaling pathway, VEGF signaling pathway, cancer pathways, BMP signaling pathway, ERK1 and ERK2 cascade, and insulin-like growth factor receptor signaling pathway. We assessed the pharmacological target drugs for ENO2...
and found 10 drugs – canadine, isomethene, amantadine, furazolidone, econazole, SR-95639A, vinburnine, Prestwick-857, quipazine, and N-acetylumamic acid – that might be latent targets for ENO2 in CRC treatment. Pharmacological target drugs for ENO3 were also determined, and 12 drugs – tetracycline, trimethobenzamide, cephaeline, rilmendine, 0317956-0000, levobunolol, cefamandole, diethylstilbestrol, indoprofen, quipazine, tiaprofenic acid, and terazosin – were found that may serve as latent targets with regard to ENO3 for CRC treatment. Further research on these latent target drugs are likely to support the growth of innovative strategies to treat CRC.

Enolase was discovered in 1934 by Lohman and Mayerhof in the course of investigating the conversion of 3-phosphoglycerate to pyruvate in muscle extracts [18]. Enolase reaction has a major status in the metabolic pathway of fermentation generally, besides the glycolytic pathway, together with catalyzing the development of phosphoenolpyruvate from 2-phosphoglycerate, the second of the 2 high-power intermediates, generating the ATP in glycolysis [19]. As indicated by the bioinformatics analysis of the current research work, the most evident molecular roles of ENO were phosphopyruvate hydratase activity, phosphopyruvate hydratase complex, and glycolytic process.

Enolase 2 (ENO2), which is also referred to as neuron-specific enolase (NSE), is a cell-specific isoenzyme of the glycolytic enzyme enolase, mainly expressed by mature neurons and cells of neuronal origin [8,20]. The major role of ENO2 in cancer is accelerating glycolysis, thereby supporting the augmented tumor cell metabolic requirements and making their proliferation possible [21]. ENO2 is a well-established tumor marker whose expression is modified in the development and progression of various cancers. ENO2 controls neuronal survival, coupled with the differentiation and neurite regeneration by means of the activation of the PI3K/Akt, as well as the MAPK/ERK signaling pathways, resulting in downstream regulation of the molecular

Figure 7. GSEA of ENO2 expressed in the colon cancer patients in accordance with the GO enrichment analysis (A–F).
and cellular mechanisms of cytoskeleton reorganization, as well as cell remodeling, activation of transcriptional factors, and regulation of the cell cycle [22,23]. Previous research suggested that ENO2 upregulates the glycolysis-related genes, together with enhancing the PI3K/Akt activity with the later glycogen synthase kinase3b (GSK-3b) phosphorylation, which induces cell proliferation and glycolysis in acute lymphoblastic leukemia [20]. In non-small cell lung cancer cells, an alternative splicing form of c-H-ras, p19ras was found to preferentially bind ENO2 and inhibit its enzymatic activity, leading to reduced cell proliferation [24]. Furthermore, ENO2 is overexpressed in breast epithelial cells exposed to the environmental contaminants arsenite and cadmium, strongly suggesting that the transformed cells are likely to attain the ability to express gamma-enolase to adapt to the increased metabolic requirements of a neoplastic state [25].

Similarity to other malignant neoplasms, CRC is characterized by changes in the cell signaling and metabolic pathways, including energy metabolism [26]. ENO2 was reported to be overexpressed in CRC [27]. Moreover, ENO2 was found to be significantly up-regulated in a metastatic colon cancer cell line, which indicated a likely correlation with the metastatic mechanism in vitro and in vivo [28]. Some studies showed that a lncRNA (LOC285629) is involved in CRC pathogenesis through direct or indirect association with ENO2 [29]. Other research indicated that ENO2 combined with other known CRC markers can distinguish early-phase malignant colorectal tumors from benign tumors [30].

In contrast to ENO2, there is little information on the role of ENO3 in cancer. Previous research demonstrated that down-regulation of ENO3 gene expression and, subsequent to that,
the encoded protein, are likely to inhibit the development of cancer cells [9]. The knockdown of ENO3 expression exhibited a selective anticancer effect in STK11 mutant cells in comparison with the STK11 wild-type cells [31]. Nevertheless, some research indicated that the effect of ENO3 varies among cancers. ENO3 protein levels were found to be lower in liver cancer tissues than in normal tissues [32].

Our study has certain limitations. First, the clinical information in the public databases was not detailed. Second, the patient data were from a single source. It is imperative to validate the prognostic significance of ENO genes in CRC by independent data containing full medical information. This was a bioinformatics investigation, and the majority results were created from the public database and bioinformatics analysis, lacking confirmation by in vitro and in vivo experiments.

In spite of these constraints, this study is, to the best of our knowledge, the first to report that the downregulation of ENO2 and ENO3 in colon cancer is correlated with a favorable prognosis, and that ENO2 and ENO3 are the latent prognostic biomarkers for patients with colon cancer. Further research is warranted on these latent target drugs to support development of innovative strategies to treat CRC.

**Supplementary Data**

**Conclusions**

We found that low expression levels of ENO2 and ENO3, individually and in combination, are correlated with a favorable prognosis in CRC. We also showed the various biological pathways and functions of the ENO gene, and potential pharmacological targets of ENO2 and ENO3 were constructed. Moreover, ENO2 and ENO3 show promise as prognostic biomarkers for patients with colon cancer.

**Acknowledgements**

The authors thank the contributors of TCGA for sharing their colon cancer survival data on an open access basis.

**Conflict of interests**

None.
**Supplementary Figure 1.** Heatmaps of ENO2 DEGs.
Supplementary Figure 3. Heatmaps of ENO3 DEGs.
Supplementary Figure 5. The chemical composition and 2D structure of potential target drugs for ENO2. (A) Canadine; (B) Isomehtepene; (C) Amantadine; (D) Furazolidone; (E) Econazole; (F) Sr-95639a; (G) Vinburnine; (H) Quipazine; (I) N-acetyl muramic acid.
Supplementary Figure 6. The chemical composition and 2D structure of potential target drugs for ENO3. (A) Tetracycline; (B) Trimethobenzamide; (C) Cephaeline; (D) Rilmenidine; (E) Levobunolol; (F) Cefamandole; (G) Diethylstilbestrol; (H) Indoprofen; (I) Quipazine; (J) Tiaprofenic acid; (K) Terazosin.
Supplementary Figure 7. The GO terms visualized by BinGO for ENO2.
Supplementary Figure 8. The GO terms visualized by BinGO for ENO3.
DATABASE ANALYSIS

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