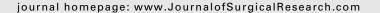


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COMP gene coexpresses with EMT genes and is associated with poor survival in colon cancer patients



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ABSTRACT

Background: About 1.2 million new cases of colon cancer (CC) and 0.6 million deaths are reported every year, establishing CC as an important contributor to worldwide cancer morbidity and mortality. Although the overall incidence and mortality of CC have declined over the past 3 decades, the number of early-onset colon cancer ([EOCC], patients <50 y old) continues to rise alarmingly. These young patients are often diagnosed at a more advanced stage and tend to have poor survival. Our recently published data showed that the cartilage oligomeric matrix protein (COMP) is overexpressed in early-onset colon cancer patients. COMP is also reported in several cancers to coexpress with epithelial-mesenchymal transition (EMT) transcription factors. Given the role of EMT in cancer metastasis and cell invasion, we assessed the correlation between COMP gene expression and EMT gene expression in CC, and COMP's relationship to patient survival.

Methods: mRNA expression of COMP was compared to that of EMT markers using the UCSC Cancer Genomics Browser. Survival analysis was performed using the UCSC Xena Browser for cancer genomics.

Results: Expression analysis revealed coexpression of COMP with the EMT markers CDH2, FN1, VIM, TWIST1, TWIST2, SNAI1, SNAI2, ZEB1, ZEB2, POSTN, MMP2, MMP9, and COL1A1. Samples that were more mesenchymal had higher expression levels of COMP and EMT markers, thus suggesting a potential role of COMP in EMT. Patients with increased COMP expression presented with poorer overall survival compared to patients with no change or reduced COMP expression (P = 0.02).

Conclusions: These findings reveal COMP as a potential biomarker for CC especially in more aggressive CC and CC in young patients, with a likely role in EMT during tumor metastasis and invasion, and a contributing factor to patient survival.

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Introduction

Every year, there are 1.2 million new cases of colon cancer (CC) and 0.6 million deaths, establishing CC as an important contributor to worldwide cancer morbidity and mortality. 1 In the United States, 49,690 new CC cases were expected to be diagnosed in men and 47,530 in women in 2018.² Although the overall incidence and mortality of CC have declined over the past 30 y in both men and women,³ the number of early-onset colon cancer (EOCC), in individuals younger than 50 y, continues to rise alarmingly.4 In our previous study using the Surveillance, Epidemiology, and End Results Program Cancer Registries database, we demonstrated that the incidence of CC has continuously increased in every age group (5-y intervals) from 20 to 49 y, with the most impressive increase seen within the age group 40-44.5 The majority (70%-80%) of EOCC cases are sporadic and not attributed to any hereditary cause. 4,6-8 These EOCC tumors tend to have more aggressive features like mucinous, poorly differentiated histopathology, and signet ring morphology and are often diagnosed at a more advanced stage. 4-6,9 Moreover, trends toward poorer survival are frequently being seen in EOCC patients. 10 Currently, the exact mechanism for these differences between early- and late-onset patients is unknown and could be multifactorial.

Our recently published genomic studies showed that sporadic EOCC expressed unique genes when compared to lateonset colon cancer (LOCC). One of the genes uniquely overexpressed in EOCC patients was the cartilage oligomeric matrix protein (COMP). 11 COMP is normally expressed in cartilage and plays a role in chondrogenesis. 12 Interestingly, analysis of COMP expression in prostate and breast cancer showed coincident expression of several transcription factors known to mediate epithelial-mesenchymal transition (EMT), 13,14 which is a cellular process that is characterized by cell separation and invasion. During EMT, epithelial cells lose polarity and cell-tocell adhesion, and gain migratory and invasive properties to become mesenchymal cells.¹⁵ It is typically involved in embryonic development, heart valve formation, and other developmental processes. However, EMT has also been implicated in cancer, specifically with increased tumor cell invasion and metastasis.¹⁶ As EMT is associated with both metastasis and cell invasion, this supports an imperative need to study the role of COMP in EMT and CC. In this study, we demonstrated a correlation between COMP gene expression and the expression of some key EMT genes and showed that the overexpression of COMP is associated with poor survival in CC patients.

Methods

Ethics statement

This study does not involve any human subjects. It utilizes the publicly available deidentified The Cancer Genome Atlas (TCGA) data set. TCGA makes available data sets concerning various cancers including colon adenocarcinoma data set (The Cancer Genome Atlas-Colon Adenocarcinoma) used in this study. This data set contains data on the expression levels of 17,814 genes in tumorous tissue and in normal tissue.

Data set

The Cancer Genome Atlas-Colon Adenocarcinoma cohort was used in our studies. ^{17,18} Normal colon tissues and tumor samples with null values were excluded from the analysis. Only "Primary Tumor" sample types, resulting in 286 samples of the original 461 were used for further analysis. Age, sex, and tumor stage distribution for these selected primary tumor samples are summarized in Table 1.

Gene expression

Gene expression data were obtained from the TCGA-COAD database using the UCSC Cancer Browser (https://xenabrowser.net/heatmap/).¹⁹ Data visualization and interpretation was performed using the UCSC Xena Platform for cancer genomics.²⁰ Expression levels analyzed by the IlluminaHiSeq platform are shown as log 2 (norm_countx + 1) transformed RSEM normalized count.

The epithelial-to-mesenchymal signature was characterized by the following gene expression equation: =FN1 + VIM + ZEB1 + ZEB2 + TWIST1 + TWIST2 + SNAI1 + SNAI2 + CDH2 - CLDN4 - CLDN7 - TJP3 - MUC1 - CDH1. A higher resulting EMT scores represent mesenchymal states, whereas lower scores represent epithelial states. Samples were sorted on an epithelial-mesenchymal spectrum.

Pearson's/Spearman's rank rho coefficients were calculated and two-dimensional correlation scatter plots were obtained using the UCSC Cancer Browser Interface (https://xenabrowser.net). Positively and negatively correlated expressions between COMP and EMT genes are shown in Tables 2 and 3, respectively.

	Table 1 – Age, sex, and tumor stage distriused TCGA-COAD data set.	ibution of the
Ī	Gender	
	Male	54.4%
	Female	44.3%
	Age at initial diagnosis	
	Average	68 ± 13
	Minimum	31
	Maximum	90
	Tumor stage	
	Not reported	4.0%
	I	19.5%
	II	6.0%
	IIA	28.9%
	IIB	2.0%
	III	2.7%
	IIIA	1.3%
	IIIB	13.4%
	IIIC	9.4%
	IV	8.7%
	IVA	3.4%
	IVB	0.7%

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