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Retrospective Study

Correlation between TEX14 and ADAM17 expressions in elderly colorectal cancer tissues and neoplasm staging, invasion, and metastasis

Chen G *et al*. TEX14 and ADAM17 expressions in elderly CRC

Gun Chen, Ling-Hua Cong, Chi-Jiang Gu, Ping Li

Abstract

BACKGROUND

Colorectal cancer (CRC) stands as one of the most frequently encountered malignant tumors in clinical settings, with its incidence steadily escalating. Individuals aged 60 and above are particularly susceptible to CRC, presenting with a poorer prognosis and substantial hazards. Hence, the quest for pivotal indicators influencing the onset and progression of CRC holds significant implications for enhancing the prognosis of elderly patients. Proteins encoded by testis expressed gene 14 (TEX14) are imperative for spermatogenesis, necessitating intercellular bridges between germ cells. Anomalous expression of TEX14 has also been discovered to be associated with the proliferation and differentiation of certain tumor cells. Recombinant A disintegrin and metalloprotease 17 (ADAM17) is known as a membrane-bound protease that regulates cellular activities and signal transduction by hydrolyzing various substrate proteins on the cell membrane. Herein, we hypothesize that TEX14 and ADAM17 may serve as potential biomarkers influencing the staging, invasion, and metastasis of CRC.

AIM

This research intends to probe the correlation between TEX17 and ADAM17 profiles in the CRC tissues of the elderly and CRC staging, invasion, and metastasis.

METHODS

For a retrospective analysis, we gathered 86 elderly patients diagnosed pathologically with CRC between April 2020 and December 2023 as cases for our current study. For each patient, one sample of cancer tissue and one sample of adjacent normal tissue were harvested, respectively. Real-time fluorescence quantitative PCR measured the mRNA profiles of TEX14 and ADAM17 in both cancer and adjacent normal tissues. Immunohistochemistry ascertained the positivity rates of TEX14 and ADAM17 expressions in cancer and adjacent normal tissues. Clinical pathological features such as neoplasm staging, invasion, and metastasis for all patients were collected, and the association between TEX14 and ADAM17 expressions and clinical pathology was evaluated.

RESULTS

Vis-à-vis adjacent normal tissues, the mRNA profiles of TEX14 and ADAM17 in CRC tissues were dramatically heightened ($P < 0.05$). TEX14 and ADAM17 expressions in CRC tissues were higher than those in adjacent normal tissues ($P < 0.05$). The positivity rates of TEX14 and ADAM17 proteins in CRC tissues attained 70.93% and 77.91%, respectively. There were no substantial divergences in age, gender, pathological type, and tumor diameter between TEX14 and ADAM17 positive and negative patients ($P > 0.05$). Patients with higher tumor differentiation degree and deeper infiltration exhibited higher positivity rates of TEX14 and ADAM17 ($P < 0.05$). Patients with TNM stages ranging from III to IV displayed higher positivity rates of TEX14 and ADAM17 compared to those with stages I to II ($P < 0.05$). Patients with lymph node metastasis and distant metastasis presented with heightened positivity rates of TEX14 and ADAM17 vis-à-vis those without lymph node metastasis and distant metastasis ($P < 0.05$). The outcomes of multivariate logistic regression analysis confirmed that TEX14

and ADAM17 positive expressions were highly correlated with tumor staging, invasion, and metastasis ($P < 0.05$).

CONCLUSION

TEX14 and ADAM17 profiles were evidently elevated in the elderly CRC tissues, and their high expressions bore a relation to tumor staging, invasion, and metastasis.

Key Words: The elderly; Colorectal cancer; TEX14; ADAM17; Staging; Invasion; Metastasis

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Core Tip: This research retrospectively harvested clinical data from 86 elderly patients pathologically diagnosed with colorectal cancer, seeking to explore the impact of testis expressed gene 14 (TEX14) and A disintegrin and metalloprotease 17 (ADAM17) expressions in elderly colorectal cancer (CRC) tissues on tumor staging, invasion, and metastasis. The outcomes uncovered high expressions of TEX14 and ADAM17 in tumor tissues, which were highly correlated with tumor staging, invasion, and metastasis. This suggests that TEX14 and ADAM17 could serve as effective biomarkers for diagnosing and evaluating the progression of CRC in the elderly.

INTRODUCTION

Colorectal cancer (CRC) ranks as the world's third most prevalent lethal malignancy, causing approximately 900000 deaths annually and standing as the second leading cause of cancer-associated deaths worldwide[1,2]. It is widely believed that the onset of CRC is linked with advanced age. Elderly individuals are more prone to CRC due to improper dietary habits, declining bodily functions, and factors such as mucosal and

muscular atrophy of the colon, which dramatically increase the risk of intestinal mucosal cell mutations, stepping up the possibility of CRC[3]. With the recent advancements in medicine and the development of diagnostic and therapeutic techniques, the detection rate of CRC in its early stages has noticeably increased. Screening methods recognized today can conspicuously attenuate the incidence and mortality rates of CRC[4,5]. Surgery remains the dominating treatment modality for early-stage CRC, effectively achieved through tumor resection and lymph node clearance, thereby extending the survival period of elderly patients[6]. Nevertheless, in reality, most elderly colorectal cancer patients are often ineligible for surgical treatment due to factors such as advanced age, underlying health conditions, or tumor progression.

Multiple biomarkers assume crucial roles in the occurrence and progression of CRC, as well as in the proliferation, invasion, metastasis, and apoptosis of tumor cells. Testis expressed gene 14 (TEX14), a critical gene inextricably pertaining to reproductive cell stability, influences intercellular bridge function. Its DNA methylation is linked to the development of early-onset familial breast cancer[7,8]. Recombinant A disintegrin and metalloprotease 17 (ADAM17) belongs to the metalloprotease superfamily, located on chromosome 2q24.3, possessing a structural domain containing metalloenzyme activity. Tumor necrosis factor-alpha, epidermal growth factor receptor, and other cytokines are its common substrates, participating in the cleavage of various cell surface receptors, influencing cell growth, differentiation, and numerous physiological processes. In recent years, ADAM17 has been discovered to be a central regulatory hub in inflammation, immunity, and malignant tumor diseases, contributing to the occurrence and development of umpteen solid tumors[9]. Wilkinson *et al*[10] found that TEX14 was highly expressed in endometrioid carcinoma tissue based on the Cancer Genome Atlas. However, the expression of TEX14 in CRC tissue remains unclear. Additionally, studies have shown that compared to the expression level in normal colonic mucosa, ADAM17 is upregulated in CRC tumor specimens, and inhibiting ADAM17 can significantly suppress tumor cell growth[11].

Based on this, we speculate that TEX14 and ADAM17 may similarly play crucial roles in the formation and progression of CRC in the elderly. We harvested cancer tissues and adjacent normal tissues from 86 elderly patients and conducted experimental research to investigate the correlation between TEX14 and ADAM17 expressions in elderly colorectal cancer tissues and tumor staging, invasion, and metastasis.

MATERIALS AND METHODS

Study participants and inclusion criteria

We retrospectively gathered data from 86 elderly patients diagnosed with CRC by pathology between April 2020 and December 2023 as cases for our research. Among them, there were 45 males and 41 females, with ages ranging from 60 to 78 years and an average age of 66.73 ± 2.12 years. Pathological types encompassed 33 cases of tubular adenocarcinoma, 27 cases of villous adenocarcinoma, and 26 cases of papillary carcinoma. Tumor differentiation degrees comprised 34 cases of high differentiation, 25 cases of moderate differentiation, and 27 cases of poor differentiation. TNM staging consisted of 37 cases of stages I-II and 49 cases of stages III-IV. There were 53 cases with lymph node metastasis and 33 cases without it, as well as 46 cases with distant metastasis and 40 cases without it.

Inclusion criteria: Participants meeting the 8th edition colorectal cancer diagnostic criteria established by the American Joint Committee on Cancer[12] and clinically pathologically diagnosed with CRC; first-time onset cases; aged ≥ 60 years old; complete clinical and pathological data; no experiences of radiotherapy, chemotherapy, or other adjuvant treatments.

Exclusion criteria: Individuals with concurrent malignant tumor diseases; those with other digestive system diseases; individuals with hematological diseases or hemorrhagic disorders; those with infectious diseases; individuals with immune deficiencies or systemic immune diseases; individuals on long-term immunomodulatory therapy.

Sample collection

Tissue samples of tumors resected from the 86 patients and normal intestinal mucosal tissues approximately 5 cm away from the tumors were harvested, each preserved in liquid nitrogen for freezing to await further testing. To ensure the accuracy of sample collection and diagnosis, we opted for joint completion by two experienced pathologists.

Clinical data collection

A clinical data collection form was designed to record all patient clinical characteristics, including age, gender, pathological type, tumor diameter, differentiation degree, TNM staging, depth of invasion, lymph node metastasis, and distant metastasis, among other baseline conditions.

Methods

Real-time fluorescent quantitative PCR: An appropriate amount of tumor tissues and adjacent normal tissues were taken from liquid nitrogen, placed into a homogenizer, and thoroughly ground. Upon the addition of 1 mL of Trizol reagent, the samples were let sit for 5 minutes at room temperature (RT), followed by total RNA extraction from each tissue sample according to the instructions provided. Denaturing gel electrophoresis evaluated RNA integrity and purity. RNA underwent reverse transcription into cDNA. RT-PCR was implemented with the assistance of the Bio-Rad CFX96 quantitative PCR system and SYBR, as instructed by the supplier. PCR reaction conditions included: 30 seconds at 95 ℃, 5 seconds at 95 ℃, 30 seconds at 60 ℃, 10 seconds at 73 ℃, 40 cycles in total. β-actin was regarded as the internal parameter of TEX14 and ADAM17. The relative mRNA profiles of TEX14 and ADAM17 were computed as per the $2^{-\Delta\Delta Ct}$ method. Refer to Table 1 for specific primer sequences.

Immunohistochemistry and determination of outcomes: Appropriate amounts of tumor tissues and adjacent normal tissues were taken. After routine embedding in

paraffin, the sections were dewaxed and dehydrated in gradient ethanol. After being blocked using 3% H_2O_2 for 10 minutes to get the endogenous peroxidase inactivated, the sections were dealt with 0.01 mol/L sodium citrate buffer for microwave repair (pH = 6.0, 15 min). The slices, sealed with 5% bovine serum albumin for 20 minutes, were incubated along with the primary antibodies anti-TEX14, anti-ADAM17 (purchased from Abcam) at 4 °C overnight. On the next day, the goat anti-rabbit IgG (Abcam, ab109489, 1: 50, Cambridge, United Kingdom) was administered for 20 minutes' incubation at indoor temperature. Following PBS washing, DAB was harnessed for color development. Subsequent to hematoxylin redyeing, the sections were dehydrated and mounted for observation.

With PBS as a control, staining results were determined based on the staining of the tumor cell cytoplasm and cell membrane. Twenty high-power fields (× 400 magnification) were counted for immunohistochemical staining cells. Staining area: 0 points for staining area below 10%, 1 point for 10%-25%, 2 points for 25%-50%, 3 points for 50%-75%, and 4 points for above 75%; staining intensity: 0 points for no staining, 1 point for pale yellow, 2 points for brownish-yellow, and 3 points for brown. The sum of the scores for staining area and staining intensity was adopted as the total score. A total score of 0 suggested negative, 12 points denoted weak positive (+), 3 points indicated positive (++), and a total score of 5 or more demonstrated strong positive (+++).

Statistical analysis

SPSS 22.0 software came into use for statistical processing and analysis. Quantitative data were presented as mean ± SD, and *t*-tests were used. Categorical data were represented as percentages, and χ^2 tests were conducted. Multifactor analysis was verified *via* the logistic regression analysis, with statistical significance defined as $P < 0.05$.

RESULTS

Differences in TEX14 and ADAM17 mRNA profiles between CRC tissues and adjacent normal tissues

When compared to adjacent normal tissues, the mRNA profiles of TEX14 and ADAM17 in CRC tissues were vigorously elevated ($P < 0.05$), as shown in Table 2 and Figure 1. We speculated that the *TEX14* and *ADAM17* genes possibly partook in CRC occurrence and development, and their high expressions were likely to accelerate tumor growth and differentiation.

Divergence in TEX14 and ADAM17 protein expressions between CRC and adjacent normal tissues

Among 86 cases of CRC tissues, 61 cases were positive for TEX14 and 25 were negative, while 67 cases were positive for ADAM17 and 19 were negative. Among 86 cases of adjacent normal tissues, 23 cases were positive for TEX14 and 63 were negative, whereas 31 cases were positive for ADAM17 and 55 were negative. The positive profiles of TEX14 and ADAM17 in CRC tissues were higher than those in adjacent normal tissues ($P < 0.05$). The positivity rate of TEX14 protein in CRC tissues attained 70.93% (61/86), while the positivity rate of ADAM17 protein reached 77.91% (67/86), as displayed in Table 3.

Correlation between TEX14 protein expression and clinical pathology

Patients positive for TEX14 and those negative for TEX14 exhibited no remarkable differences in age, gender, pathological type, and tumor diameter ($P > 0.05$). Among patients with high tumor differentiation, 85.29% were positive for TEX14. In patients with TNM stages III-IV, 81.63% were positive for TEX14. Among patients with lymph node metastasis, 83.13% were positive for TEX14. For patients with infiltration depths of T3 and T4, 80.49% and 87.50%, respectively, were positive for TEX14. Among patients with distant metastasis, 80.43% were positive for TEX14. Hence, we observed that patients with higher tumor differentiation and deeper infiltration displayed higher positivity rates for TEX14 ($P < 0.05$). Patients with TNM stages III-IV had a higher

TEX14 positivity rate than those with stages I-II ($P < 0.05$). Patients with lymph node metastasis and distant metastasis exhibited higher TEX14 positivity rates than those without ($P < 0.05$), as denoted in Table 4. Our findings confirmed that the profile of TEX14 protein was correlated with the clinical pathological characteristics of elderly CRC patients, affecting tumor differentiation, infiltration depth, TNM staging, lymph node metastasis, and distant metastasis.

Correlation between ADAM17 protein expression and clinical pathology

Patients positive and negative for ADAM17 showed no conspicuous divergences in age, gender, pathological type, and tumor diameter ($P > 0.05$). Among patients with high tumor differentiation, 91.12% were positive for ADAM17. In patients with TNM stages III to IV, 87.76% tested positive for ADAM17. Among patients with lymph node metastasis, 86.79% were positive for ADAM17. For patients with infiltration depths of T3 and T4, 85.37% and 100%, respectively, were positive for ADAM17. Among patients with distant metastasis, 86.96% tested positive for ADAM17. Hence, patients with higher tumor differentiation and deeper infiltration exhibited higher positivity rates for ADAM17 ($P < 0.05$). Patients with TNM stages III-IV boasted a higher ADAM17 positivity rate than those with stages I-II ($P < 0.05$). Patients in the presence of lymph node metastasis and distant metastasis displayed heightened ADAM17 positivity rates than those without ($P < 0.05$), as illustrated in Table 5. From the above results, it can be inferred that the profile of ADAM17 protein was linked to the clinical pathological characteristics of elderly CRC patients. Moreover, ADAM17's positive expression influenced tumor differentiation, infiltration depth, TNM staging, lymph node metastasis, and distant metastasis.

Relationship between TEX14 and ADAM17 profiles and tumor staging, invasion, and metastasis

With tumor TNM staging, invasion degree, and metastasis status of elderly CRC patients as dependent variables, and TEX14 and ADAM17 expression as independent

variables, the binary variable assignment table is illustrated in Table 6. Multiple logistic regression analysis was implemented for the examination of the relationship between TEX14 and ADAM17 expressions and tumor staging, invasion, and metastasis. As evidenced by our research data, TEX14 positive expression was associated with higher TNM staging (OR = 3.343, 95%CI: 1.211-9.228, $P < 0.05$), deeper invasion (OR = 14.924, 95%CI: 2.152-103.491, $P < 0.05$), lymph node metastasis (OR = 5.018, 95%CI: 1.195-21.067, $P < 0.05$), and distant metastasis (OR = 6.203, 95%CI: 1.246-30.884, $P < 0.05$). Similarly, ADAM17's positive expression was correlated with higher TNM staging (OR = 4.963, 95%CI: 1.546-15.930, $P < 0.05$), deeper invasion (OR = 6.593, 95%CI: 1.366-31.813, $P < 0.05$), lymph node metastasis (OR = 2.659, 95%CI: 1.067-6.628, $P < 0.05$), as well as distant metastasis (OR = 7.980, 95%CI: 1.651-38.584, $P < 0.05$). Refer to Table 7. This denotes that high expressions of TEX14 and ADAM17 indeed influenced tumor staging, invasion, and metastasis in elderly CRC patients, promoting malignant progression of tumors in the elderly, and contributing to advanced tumor TNM staging, aggravated invasion, and metastasis.

DISCUSSION

Due to the lack of specific symptoms in the early stages of CRC, most elderly patients are diagnosed at an advanced stage, with late tumor staging, deeper invasion, conventional surgical treatment options often failing to achieve desirable outcomes, high surgical risks, poor postoperative recovery, and unfavorable prognosis. In clinical practice, it is necessary to combine the clinical and pathological characteristics of elderly patients to enhance treatment efficacy through adjuvant therapies such as chemotherapy, radiotherapy, and targeted therapy[13-15]. In advanced stages of elderly CRC, tumor cell proliferation is rapid, and invasion and metastasis exacerbate, accompanied by uncontrolled apoptosis. Studies have suggested that various genes such as *STC1*, *AKR1B1*, and *EMP1* are overexpressed in invasive tumor clusters of CRC, affecting local invasion and patient prognosis[16]. Finding biomarkers associated with TNM staging, invasion, and metastasis in elderly CRC patients is essential for

enhancing tumor screening and disease assessment, greatly aiding in improving prognosis and increasing expected survival duration for elderly patients.

TEX14, as a regulator of PLK1 protein, is an important regulatory mediator of kinetochore structure, function, and chromosome segregation fidelity during mitosis[17]. Recent studies have unraveled that TEX14-IT1 mediates the pr-proliferative and anti-apoptotic functions of transforming growth factor-beta in ovarian granular cells, and its mechanism involves inducing the transcription of TEX14-IT1 in an AMAD4-dependent pattern, exerting epigenetic regulatory effects[18]. Furthermore, in cancer diseases, the TEX14 rs302864 site can interact with SEPT4 rs758377, influencing specific molecular subtypes of breast tumors, thereby augmenting the risk of breast cancer[19]. ADAM17, as a type of multi-domain transmembrane glycoprotein, participates in the formation and release of pro-tumor progression-related ligands, thus affecting the malignant progression of various tumors[20-22]. Preceding studies have discovered that the expression level of ADAM17 pertains to the ability of human umbilical vein endothelial cells to form capillary-like networks when co-cultured with fibroblasts in three-dimensional matrix gel and scaffolds, and it can partake in the important process of angiogenesis by modulating the activation of matrix metalloproteinase 2[23,24]. In CRC, FHL2 dampens ADAM17 activity by regulating its plasma membrane localization. The interplay between FHL2 and ADAM17 in malignant colonic epithelial cells forms a complex that influences the occurrence and development of CRC[25].

Currently, there is scarce research on the functions of TEX17 and ADAM17 in the staging, invasion, and metastasis of CRC. To address this gap, our experiment explored this aspect. It turned out that TEX14 and ADAM17 expression levels in the tumor tissues of elderly CRC patients were significantly higher than those in adjacent normal tissues. Highly-expressed TEX14 and ADAM17 were associated with tumor differentiation, TNM staging, invasion depth, lymph node metastasis, and distant metastasis in elderly patients, standing as independent risk factors affecting the staging, invasion, and metastasis of tumors in elderly patients. Our experimental findings are aligned with those of Kumar *et al*[26], who found that multiple biomarkers such as SVIP,

BEND3, and TEX14 were abnormally expressed within breast cancer and could serve as efficacious indicators for early, non-invasive diagnosis and prognosis of breast cancer. Additionally, the study by Li *et al*[27] confirmed that exosomal ADAM17 could accelerate the formation of pre-metastasis niches by strengthening CRC vascular permeability, and eliciting cancer metastasis. Previous studies may have already revealed the key roles of these two genes in the development of CRC, possibly associated with tumor growth, invasion, and metastasis. By comparing our research results, the exact mechanisms of action of these genes in the pathophysiological processes of CRC can be further validated. The outcomes of our experiment may be related to the following reasons: TEX14 may suppress apoptosis of tumor cells endogenously by affecting the mitosis process of CRC cells, accelerating cell proliferation, invasion, and metastasis, thereby bolstering CRC malignancy[28]. Furthermore, ADAM17, as a connection point for cell-matrix interactions, interacts with integrin α5, degrading the cell basement membrane and extracellular matrix, giving rise to a decrease in the levels of adhesion molecules on the surface of CRC cells, making them unable to effectively exert a function in cancer cells' invasion and metastasis[29], ultimately exacerbating the malignant progression of tumors.

The clinical significance of these research findings is very important. By further investigating the relationship between the expression of TEX14 and ADAM17 in CRC patients and metastasis, attempts can be made to utilize these genes as potential therapeutic targets, providing a new direction for the treatment of CRC. Notwithstanding, this work also has certain limitations and shortcomings. Firstly, it is a retrospective study, which inherently has limitations. All data and information are derived from historical data of cases, which may result in incomplete information or selection bias, thus affecting the experimental findings. Additionally, this study only encompassed 86 patients, which is relatively small, and all samples were sourced from a single hospital, which may introduce institutional bias, influencing the external validity of the study outcomes and the credibility of its generalizability. In the future, we will

consider using carefully designed prospective studies combined with standardized data sampling to provide more robust evidence for our experimental results.

CONCLUSION

Overall, our findings corroborate the indispensable role of TEX14 and ADAM17 in the clinical diagnosis and prognosis assessment of elderly CRC individuals. They can serve as efficacious biomarkers for predicting disease progression and prognosis in patients. In clinical practice, when treating elderly CRC patients, it is essential not only to focus on common prognostic indicators and pathological results but also to strengthen the monitoring of TEX14 and ADAM17 markers. Future clinical research can further validate the value of these genes as potential diagnostic markers or therapeutic targets, providing new insights and possibilities for developing more effective treatment strategies.

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