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The level of oxidative stress and the expression of genes involved in DNA-damage signaling pathways in depressive patients with colorectal carcinoma

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Abstract

Objectives: This study investigated the connection among the oxidative stress, depression and expression of specific genes involved in DNA-damage signaling pathways in patients with colorectal carcinoma (CRC). **Methods:** A unique Dukes'C subset of patients with newly diagnosed colorectal adenocarcinoma were assessed using the Hamilton Depression Rating Scale (HAMD), Zung Self-rating Depression Scale (SDS), Zung Self-rating Anxiety Scale (SAS), Symptom Checklist 90 (SCL-90) and other multiple-item questionnaires. Oxidative-stress-related parameters in sera and the expression of genes were monitored during a pretreatment period. **Results:** Eighty-two eligibility cases were divided into 2 groups based on an HAMD score cutoff of 20: the mean score was 28.29 in Group A (depression, n=52) and 16.50 in Group B (nondepression, n=30). The serum total antioxidant capacity, catalase, and superoxide dismutase concentrations were lower in Group A, whereas those of nitric oxide and malondialdehyde were higher in Group A. Importantly, the 8-hydroxy-deoxyguanosine level was higher in Group A than in Group B (P<.05). Microarray analysis revealed that the expressions of p34, PA26, and ABL were higher in Group A, whereas those of HRAD51, CR6, and XRCC3 were higher in Group B. **Conclusion:** Oxidative stress is capable of causing neuronal toxicity via lipid peroxidation, DNA damage, and abnormalities of gene expression, and therefore is a possible pathogenic mechanism underlying depression in patients with CRC.

Keywords: Colorectal carcinoma; Depression; Oxidative stress; HAMD; DNA damage; 8-hydroxy-deoxyguanosine; Gene expression; p34; HRAD51

Introduction

The incidence of colorectal carcinoma (CRC) is high in China, adversely affecting both individuals and society as a whole. Approximately 95% of CRC is sporadic and believed to normally involve environmental agents and chronic inflammation [1,2]. There is recent evidence that oxidative stress is provoked in colorectal carcinogenesis [3]. Free radicals react with biological molecules to destroy the structure of cells, and reactive oxygen species are of particular interest in the research of oxidative damage and disease. Complex defense mechanisms involve enzymes such as superoxide dismutase, catalase, and glutathione peroxidase that have evolved to reduce reactive oxygen species levels [4]. However, low background levels of damage occur even in normal cells because free radicals have a tendency to escape the defense mechanisms.

The overproduction of reactive oxygen and nitrogen species can damage various biomolecules in humans —

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including DNA, lipids, and proteins [5] — so as to promote tumor formation. Because proteins and lipids are easily degraded and resynthesized, modification of DNA is considered to be the most important consequence of oxidative stress, and it can become permanent via the formation of mutations and other types of genomic instability. Most interest has been on measuring 8-hydroxy-deoxyguanosine (8-OHdG) as a sensitive biomarker for oxidative DNA damage [6]. Furthermore, the results of clinical studies have suggested that treatment with drugs can protect cells against oxidative damage by enhancing the cellular antioxidant activity and modulating cellular signal pathways [7,8].

Many groups have recently reported that depressive symptoms are associated with an increased risk of CRC [9], especially with specific factors such as chronic course, reduced social functional levels, suicidal ideation, and a poor prognosis. Severe symptoms may exert negative effects on coping and psychosocial adjustment, antitumor therapies, immunological function, and the quality of life [10,11]. Clinical depression is a fairly frequent condition that often causes significant additional suffering among patients with CRC. Moreover, the experience of unmet needs further elevates the level of depression [12]. Whilst recent data from several studies suggest that oxidative stress is involved in the biochemical mechanisms that underlie neuropsychiatric disorders in humans [13,14], increased oxidative damage, mitochondrial dysfunction, accumulation of oxidized aggregated proteins, inflammation, and defects in protein clearance constitute complex intertwined pathologies that conspire to kill neurons [13,15]. Clinically, this hypothesis has been supported by several recently published studies related to the efficacy of *N*-acetylcysteine, a glutathione precursor, in the treatment of various psychiatric disorders, such as schizophrenia and bipolar disorder [16,17].

Understanding the factors associated with this common psychiatric disorder might improve treatment outcomes. Hence, our study was designed to investigate the connection among oxidative stress, depression, and the expression of specific genes involved in DNA-damage signaling pathways in patients with CRC. Moreover, the factors of coping, distress, quality of life, and social support were assessed. Oxidative stress-related parameters in sera and the expression of genes were monitored during a pretreatment period.

Methods

Subjects

A unique Dukes'C subset of patients with newly diagnosed colorectal adenocarcinoma were enrolled between October 2005 and July 2007 in the Departments of Clinical Oncology and General Surgery, First and Second Affiliated Hospitals of Xi'an Jiaotong University. The definitive diagnosis was confirmed after immediate endoscopy-guided biopsy and subsequent histopathological examination. Eligibility criteria required that the patients be older than 18 years and able to speak Chinese. Patients with known confusion or who were judged too ill to participate were excluded from the investigation. None of the patients had central nervous system disease, uncontrolled infections, or other malignancies. The medical records were obtained by investigators through interviews, and each item in the psychological measurements was explained by a specialist physician prior to the investigation. This study was approved by the Xi'an Jiaotong University Ethics Committee and met international standards for patient confidentiality. Informed consents were obtained according to the Declaration of Helsinki after all subjects had been fully informed of the purpose of the study.

Psychological measurements

The Hamilton Depression Rating Scale (HAMD) [18] is a commonly used clinician-rated depression symptom rating scale that comprises 24 items rated on scales from 0 to 2, 0 to 3, and 0 to 4 (total score range: 0–75). The HAMD score reflects depression symptomatology that may be of clinical significance, rather than offering a strict diagnostic guideline. A HAMD index of at least 20 is generally considered to indicate the presence of depression. The HAMD was administered by experienced clinical raters certified with high interrater reliability and procedural integrity.

The Zung Self-rating Depression Scale (SDS) [19] and Zung Self-rating Anxiety Scale (SAS) [20] are commonly used self-evaluation instruments for measuring depressive and anxiety symptoms, respectively. The Quality of Life Questionnaire–Core 30 is the most frequently used health-related quality of life instrument and consists of 30 items related to the functioning and symptoms of cancer patients [21], including global health-related quality of life (QL), six other multi-item function scales, and nine single-item symptom scales. Social support was assessed by the patient's perception of support from their family and social members in Social Support Rating Scale (SSRS). The SSRS uses ten items to evaluate total social support objectively and subjectively, and its utility [22]. The Simple Coping Style Questionnaire (SCSQ) reflects the relationships between coping and psychosocial adjustment of patients [23], which the SCSQ assesses using 20 items on a two-point scale (active versus passive coping). The Symptom Checklist 90 (SCL-90) is a self-reported clinical symptom rating scale consisting of 90 questions [24]. Responses indicate the presence of symptoms associated with nine psychiatric constructs.

Analyses of oxidative-stress-related parameters

All participants were free of smoking and inflammatory and endocrinal dysfunctions for at least 2 weeks prior to obtaining baseline blood samples. The pretreatment blood samples were collected at 8 a.m. to avoid diurnal variations in blood components. Collected blood samples were