EXPRESSION OF CATHEPSIN D IN COLORECTAL CARCINOMA
Immunohistochemical and Histopathological Study

Thesis

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By

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ABSTRACT

Colorectal cancer is one of the leading causes of cancer death in both developed and developing nations. It is the third most common type of cancer and the second leading cause of cancer death in the Unites State. The current study included fifty cases of colorectal carcinomas studied histologically, and immunohistochemically for Cathepsin D expression. Cathepsin D expression was observed in 90% of cases in tumor cells and in 92 % of cases in peritumoral stromal cells of colorectal carcinomas. All cases of mucinous and signet ring cell carcinoma and 87.2% of adenocarcinomas showed Cathepsin D positive immunostaining. Statistically significant relationship was detected between Cathepsin D expression in cancer cells and histologic grade but not with lymph node metastasis or stage, however, statistically significant relationship was detected between Cathepsin D expression in peritumoral stromal cells and depth of tumor invasion and , lymph node metastasis. In addition, statistically significant relationship was detected between Cathepsin D immunostaining pattern in tumour cells and histologic grade as in more poorly differentiated tumors, there was a diffuse cytoplasmic staining while in better differentiated tumors there was apical staining pattern reflecting loss of cellular polarization in cancer cells. Therefore, it is suggested that Cathepsin D may be used as a prognostic marker in detection of invasiveness and metastatic potential in colorectal carcinomas and it will be necessary to carry out similar studies on a larger sample size and look for correlations between Cathepsin D expression and survival rate.

Key words: Colorectal carcinoma, adenocarcinoma, mucinous, signet ring, Cathepsin D.

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List of Abbreviations

ACF	:	Aberrant crypt foci
AJCC	:	American Joint committee on Cancer
APC	:	Adenomatous polyposis coli
BAX	:	Bcl 2 associated X protein
BCL 2	:	B cell lymphoma 2
BMI	:	Body mass index
CAP	:	Collage of American Pathologist
CD	:	Crohn's disease
CEA	:	Carcinoembryonic Antigen
CK	:	Cytokeratin
CRC	:	Colorectal Carcinoma
CRM	:	Circumferential margin
DAB	:	Diaminodenzidine
DCC	:	Deleted in colon cancer
DNA	:	Deoxy ribonucleic acid
DPC 4	:	Tumor suppressor gene
EC	:	Enterochromaffin
ECM	:	Extracellular matrix
EGF	:	Epidermal growth factor
ELISA	:	Enzyme linked immunosorbent assay
FAP	:	Familial adenomatous polyposis
GH	:	Growth hormone
GLUT 1	:	Glucose transporter 1
HCG	:	Human Chorionic gonadotropins
H & E	:	Hematoxylin and Eosin
HGD	:	High-grade dysplasia
HIV	:	Human immunodeficiency virus
HMLH 1	:	Mismatch repair genes
HNPCC	:	Hereditary Non Polyposis Colorectal Carcinoma
HP	:	Hyperplastic polyps
ICAM 1	:	Intercellular Adhesion Molecule 1

IEN	:	Intraepithelial neoplasia
IGF 1	:	Insulin like growth factor 1
Ig A	:	Immunoglobulin A
K RAS	:	Oncogene
LGD	:	Low grade dysplasia
LN	:	Lymph node
M6Pr	:	Mannose 6-phosphate receptor
MSI	:	Microsatellite instability
MUC	:	Mucin
NEC	:	Neuroendocrine carcinoma
NET	:	Neuroendocrine tumour
P 53	:	Tumour suppursor gene
PJS	:	Peutz-Jeghers syndrome
PP	:	Pancreatic Polypeptide
P value	:	Propability value
PYY	:	Peptide Tyrosine Tyrosine
RERs	:	Replication errors
SCC	:	Squamous cell carcinoma
SMAD 4	:	Tumour suppursor gene
SPSS	:	Statistical Product for Services Solution
SSA	:	Sessile serrated adenoma
TSA	:	Traditional serrated adenoma
TNF	:	Tumour necrosis factor
UC	:	Ulcerative colitis
UICC	:	Union International Contre Le Cancer
US	:	United States
WCRF/AICR	:	World Cancer Research Fund/American Institute for Cancer Research
WHO	:	World Health Organization

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INTRODUCTION

Colorectal cancer is the third most common type of cancer and the second leading cause of cancer death in the Unites States (**Calonge et al., 2008**). It ranks fourth in frequency in men and third in women all over the world (**Parkin et al., 2005**).

In Egypt, the Cancer Pathology Registry of National Cancer Institute of Cairo University showed that during the years 2003-2004, colorectal cancer occupied the first rank among digestive system's malignancies (15.78%) and the fifth rank among all total cancers (4.34%) (**Mokhtar et al., 2007**).

The prognosis of patients with colorectal carcinoma is mainly dependant on the staging systems which represent a combination of the criteria of local extent and lymph node involvement, whether ones uses the original scheme proposed by Dukes or any of the modifications that have been subsequently advanced (American Joint Committee category IIA) (**Rosai J, 2004**).

Selection of the most beneficial treatment regimens in colorectal cancer remains a challenge and is hindered by a lack of predictive and prognostic markers. In recent years, research on a global scale has attempted to define subsets of prognostic markers to determine the aggressiveness of the disease and the like hood of recurrence after surgery (**Wilson et al., 2007**).

The metastatic process in cancer depends on the invasion of the tumor cells to the surrounding matrix and penetration of the basement

membrane to reach the systemic circulation. These steps of degradation and membrane passage are used to be basically controlled by tumor associated proteolytic enzymes. These include endopeptidases, matrix metalloproteinase and cathepsins (**Tetu et al., 2001**).

Cathepsin D is known to be a lysosomal acid protease that is mainly included in intracellular protein catabolism and is inducible by estrogens. Therefore, many investigators have studied intensively the role of Cathepsin D in breast carcinomas. These studies have suggested that the expression of Cathepsin D is correlated with the invasion and metastasis of breast carcinomas, but several studies done to investigate the role of Cathepsin D expression in predicting prognosis or invasive potential in colorectal carcinoma revealed conflicting results (**Yilmaz et al., 2003**).

Several studies have reported a wide range of Cathepsin D and their antigen expressions patterns in colorectal tumours with the development of the disease stage, suggesting the use of Cathepsin D as a prognostic tumor marker in colorectal cancer (**Sebzda et al., 2005**).

AIM OF THE WORK

The current work consists of histopathological and immunohistochemical studies on colorectal carcinoma (CRC) designed to assess and investigate:

1. The expression of Cathepsin D in the different histologic types of colorectal carcinoma.
2. Assess the role of Cathepsin D in predicting progression, invasive and metastatic potential of colorectal carcinoma.