Evaluation Of K- Ras Mutation And Fas Tissue Expression In Common Neoplastic And Non Neoplastic Colonic Lesions

THESIS
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بسم الله الرحمن الرحيم

" سُبحَانَك لا عِلْمَ لَنَآ إلا مَا عَلمتَنَآ
إنكَ أنتَ العَلِيــمُ الحَكِيــمُ "

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Abstract: Colonic carcinoma including rectal carcinoma (Colo-Rectal Carcinoma) is one of the best studied conditions of multistage human carcinogenesis. K-Ras gene mutations are among the most common genetic alterations present in colorectal tumors. Ras genes codify for membrane-attached, small guanine triphosphate–bound proteins that play a key role in transduction of extracellular mitogenic signals. Ras mutations (mainly at codons 12, 13, and 61 of the K-Ras gene) that constitutively activate their function are present in a significant proportion of colorectal adenomas and carcinomas

The accumulation of such mutated protein can be detected by immunohistochemical staining in a significant proportion of cases. Apoptosis is a highly regulated cell suicide mechanism that is important for many biological processes, including embryonic development, response of tumors to cancer chemotherapy, and the pathogenesis of neurodegenerative diseases. The K-Ras has been recognized as a major oncogene involved in colo-rectal carcinogenesis arising from precancerous adenomatous changes and in randome cases.

Fas mediated apoptosis is involved in programmed cell death among cases of IBD, Bilharziasis, and CRC, with high expression in IBD which play an important role in the disease progression, and with low expression in CRC through which the tumor cells can escape the host immune reaction.

Key words: common colonic lesions, immunhistochemistry, K-Ras, Fas.

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List of Abbreviations

Ab.p	Abdominal pain
Ac.Bil.col.	Acute Bilharzial colitis
ACF	Aberrant crypt foci
APC	Adenomatous polyposis coli
APC	Avidinbiotin peroxidase complex
CC	Chronic constipation
CD	Crohn's disease
Ch.Bil.col.	Chronic Bilharzial colitis
Ch.d	Chronic diarrhea
CIMP	CpG island methylation phenotype
CpG	cytidine-phosphoguanosine
CRC	Colo-Rectal Carcinoma
DAB	Diaminobenzidine
DCC	Deleted Colon Cancer gene
EGF	Epidermal growth factor
FADD	Fas-associated death domain
FAP	Familial adenomatous polyposis
Hcz	Bleeding/rectum or haematochazia
Hcz+CC	Haematochazia with chronic constipation
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
IBD	Idiopathic inflammatory bowel disease
IGF	Intestinal Growth Factor
IGF-I and II	Insulin-like growth factors I and II
IHC	Immunohistochemical
LOH	Loss of heterozygosity
LP	Lamina propria
LPL	Lamina propria lymphocytes
MAPKs	Mitogene Activating Protein Kinases
MECC	Middle East Cancer Consortium
MLH1	Human MutL homologue 1
MSH2	Human MutS homologue 2
PBS	Phosphate buffered saline
SEER	US Surveillance, Epidemiology, and End Results Program
TBRI	Theodor Bilharz Research Institute
TCRs	T-cell receptors
TGF	Transforming growth factor
TILs	Tumor infiltrating lymphocytes
TNF	Tumour necrosis factor
TRADD	TNF receptor- associated death domain

UC	Ulcerative colitis
UC with dysp.	Ulcerative Colitis with dysplasia
UC without dysp.	Ulcerative Colitis without dysplasia
UPS	The ubiquitin–proteasome system

INTRODUCTION

Colonic carcinoma including rectal carcinoma (Colo-Rectal Carcinoma) is one of the best studied conditions of multistage human carcinogenesis *(Fearon and Vogelstein, 1990)*. K-Ras gene mutations are among the most common genetic alterations present in colorectal tumors. Ras genes codify for membrane-attached, small guanine triphosphate–bound proteins that play a key role in transduction of extracellular mitogenic signals. Ras mutations (mainly at codons 12, 13, and 61 of the K-Ras gene) that constitutively activate their function are present in a significant proportion of colorectal adenomas and carcinomas *(Capella et al., 1991 & Shibata et al., 1993).*

The Ras gene product has a key role in controlling cell growth and differentiation through its intrinsic GTPase (Guanine Tri-Phosphatase) activity *(Bos, 1989)*. It also seems to interact with pathways that regulate programmed cell death and with other oncogenes *(Vojtek and Cooper, 1995)* and may also play a part in drug resistance mechanism *(Sklar, 1988)***.**

K-Ras, one of three human Ras genes recognized, is reported to be mutated in about half of all patients with colorectal cancers *(Dix et al., 1994)***.**

The accumulation of such mutated protein can be detected by immunohistochemical staining in a significant proportion of cases *(Dix et al., 1994 & Smith et al., 1994)*

Apoptosis is a highly regulated cell suicide mechanism that is important for many biological processes, including embryonic development, response of tumors to cancer chemotherapy, and the pathogenesis of neurodegenerative diseases *(Wyllie, 1992).*

The cell surface receptor Fas (Apo-1; CD95) and its ligand (FasL) are known regulators of apoptosis in cells of the immune system.

The Fas system is involved in the peripheral deletion of autoimmune cells *(Debatin, 1994),* activation-induced apoptosis of T cells, and in cytotoxic T cell-mediated killing *(Alderson et al., 1995 & Brunner et al., 1995).*