Immunohistochemical Expression of Debiquitinating Enzyme OTUB1 in Colorectal Carcinoma

Thesis

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List of Abbreviations

Abbrev.	Full-term
AFAP	**:** Attenuated Familial Adenomatous Polyposis
AFP	**:** Alpha Fetoprotein
AJCC	**:** American Committee for Cancer
AMACR	**:** Alpha Methyl Acyl Coenzyme A Racemase
APC	**:** Adenomatous Polyposis Coli
API	**:** Asian/Pacific Iskander
ATP	**:** Adenosine triphosphate
β-HCG	: Beta Human chorionic gonadotropin
BMPR1A	**:** Bone Morphogenetic Protein Receptor, type IA
BRAF	**:** B-Raf Proto-oncogene, Serine/threonine Kinase
CAP	**:** College of American Pathologists
CDX2	**:** Caudal Type Homeobox 2
CEA	**:** Carcinoembryonic Antigen
CHRPE	**:** Congenital Hypertrophy of the Retinal Pigment Epithelium
CIMP	**:** CpG Island Methylation Pathway
CIN	**:** Chromosomal Instability Pathway
CK	**:** Cytokeratin
CpG	**:** 5'—C—phosphate—G—3'
CRC	**:** Colorectal Cancer
DAB	**:** Diaminobenzidine
DM	**:** Diabetes Mellitus
DNA	**:** Deoxyribonucleic Acid

DUBs : Deubiquitinating Enzymes
E : Enzyme
EMT : Epithelial Mesenchymal Transition
EMVI : Extramural Venous Invasion
EpCAM : Epithelial Cell Adhesion Molecule Gene
FAP : Familial Adenomatous Polyposis
GI : Gastrointestinal
GRAIL : Gene Related to Anergy In Lymphocytes
H&E : Haematoxylin and Eosin
HDI : Human Development Index
HNPCC : Hereditary Nonpolyposis Colorectal Cancer
HPS : Hyperplastic Polyposis Syndrome
HPs : Hyperplastic Polyps
IBD : Personal History of Inflammatory Bowel Disease
IGF : Insulin-like Growth Factor
IHC : Imunohistochemistry
IL : Interleukin
IMVI : Intramural Venous Invasion
IRR : Incidence Rate Ratio
IRS : Immunoreactivity Score
JAMMs : JAMM/MPN Domain Associated Metallopeptidases
JPS : Juvenile Polyposis Syndrome
KRAS : Kirsten Rat Sarcoma-2 Virus Oncogene
LKB1 : Liver Kinase B1
LOH : Loss of Heterozygosity
M : Metastasis

MANEC : Mixed Adenoneuroendocrine Carcinoma

MAP : MUTYH Associated Polyposis

MCPIP : Monocyte Chemotactic Protein Induced Protein

MINDY : Motif Interacting with Ub-containing Novel DUB Family

MJD : Machado-Joseph Disease Protein Domain Proteases

MLH1 : MutL Homolog 1

MMR : Mismatch Repair Gene

MSH2 : MutS Protein Homolog 2

MSH6 : MutS Homolog 6

MSI : Microsatellite Instability

MSI-H : Microsatellite Instability-High

MSS : Microsatellite Stable

MUC1 : Mucin 1 Cell Surface Associated

MUC2 : Mucin 2 Cell Surface Associated

MUC5AC : Mucin 5AC

MUTYH : MutY Homolog

N : Node

NEC : Neuroendocrine carcinomas

NF-Kb : Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells

NOS : Not Otherwise Specified

NS : Non-significant

OTUB1 : OTU domain-containing ubiquitin aldehyde-Binding protein

OTUs : Ovarian Tumor Domain Containing Proteases

P	**:** Probability
PDC	**:** Poorly Differentiated Clusters
PIK3CA	**:** Phosphatidylinositol-4, 5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha
PJS	**:** Peutz-Jeghers Syndrome
PMS2	**:** Postmeiotic Segregation Increased 2
PNI	**:** Perineural Invasion
PSC	**:** Primary Sclerosing Cholangitis
S	**:** Significant
SD	**:** Standard Deviation
SES	**:** Socioeconomic Status
SMAD4	**:** Mad-related protein4
SPS	**:** Serrated Polyposis Syndrome
SPSS	**:** Statistical Package for Social Science
SSA/Ps	**:** SSA and Sessile Serrated Polyp
SSAs	**:** Sessile Serrated Adenomas
STK11	**:** Serine/threonine kinase 11
T	**:** Tumor
TGF-β	**:** Transforming Growth Factor-β
TNM	**:** Tumor Node Metastasis
TP53	**:** Tumor Protein p53
TSAs	**:** Traditional Serrated Adenomas
UB	**:** Ubiquitin
UCHs	**:** Ubiquitin Carboxy-terminal Hydrolases
UICC	**:** Union Internationale Contre Cancer
UPP	**:** Ubiquitin Proteasome Pathway

USA **:** United States of America

USP22 **:** Ubiquitin Specific Protease 22

USPs **:** Ubiquitin Specific Proteases

VEGF **:** Vascular Endothelial Growth Factor

VI **:** Venous Invasion

WHO **:** World Health Organization

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Introduction

Worldwide, Colorectal cancer (CRC) is by far the most common malignancy of the gastrointestinal tract ranking the third most commonly diagnosed malignancy in men while the second most common cancer in women and the fourth leading cause of cancer death according to 2012 GLOBOCAN database. More than two-thirds of all cases and about 60% of all deaths occurred in countries with a high or very high human development index (HDI) ***(Arnold et al., 2017).***

CRC is positively associated with human development with estimated rate about six to seven times higher in very high HDI compared to low HDI regions in both sexes. With an etiology linked to lifestyle and environment, including changes in dietary and metabolic factors. Therefore CRC can be considered a clear marker of developmental transition ***(Fidler et al., 2016).***

CRC diagnosis rates are highest in Australia and New Zealand, with the lowest rates foundin Western Africa***(Ferlay et al., 2013).***

CRC in Egypt, as most of developing countries, has lower incidence than that of western countries with sedentary lifestyle. In Egypt, it is the sixth most common cancer constituting about 4% of total cancers in both sexes ***(Zeeneldin et al., 2012).***

CRC is generally thought of as a disease of older persons, with more than 90% of patients being diagnosed after the age of 55 years. It is well known, however, that CRC also affects a young population. Recent studies suggested that as many as 7% of patients who developed CRC were under 40 years of age, and this incidence keeps increasing ***(Berut et al., 2013).***

The epidemiology of CRC in developing countries differs from that of developed countries. CRC in developing countries including Egypt is usually characterized by low incidence, young age of onset and left-sided location ***(Zahir et al., 2014).***

El-Bolkainy et al. (2006) referred to the difference in the site of CRC distribution between developed and developing countries, for instance in USA, rectal carcinoma constituted 25% of all CRC while in Africa it is 50%.

In most Western populations, the average lifetime risk for CRC is in the range of 3–5%. However, this risk almost doubles in individuals with a first-degree family member with CRC who was diagnosed at 50–70 years of age; the risk triples if the first-degree relative was <50 years of age at diagnosis ***(Kuipers et al., 2015).***

More than 50% of patients with CRC will develop metastatic disease to their liver over the course of their life, which ultimately results in death for more than two thirds of these patients. Currently, hepatic resection of CRC liver