UNIVERSITI PUTRA MALAYSIA

ASSOCIATION OF DNA METHYLATION STATUS, GENE AND PROTEIN EXPRESSION OF HER FAMILY IN COLORECTAL ADENOCARCINOMA

ROSFAYATI BINTI OTHMAN @ JAFFAR

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ASSOCIATION OF DNA METHYLATION STATUS, GENE AND PROTEIN EXPRESSION OF *HER* FAMILY IN COLORECTAL ADENOCARCINOMA

By

ROSFAYATI BINTI OTHMAN @ JAFFAR

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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ASSOCIATION OF DNA METHYLATION STATUS, GENE AND PROTEIN EXPRESSION OF *HER* FAMILY IN COLORECTAL ADENOCARCINOMA

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ROSFAYATI BINTI OTHMAN @ JAFFAR

October 2020

Chairman : Associate Professor Norhafizah binti Mohtarrudin, PhD
Faculty : Medicine and Health Sciences

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cancer in Malaysia. Despite advanced therapies, many cases of recurrence and resistance have been reported. Surgery is only applicable for early diagnosed CRC cases. Reliable biomarkers are very crucial for early diagnosis, prognosis and therapeutic target. Overexpression of *HER* family members (*EGFR*, *HER2*, *HER3* and *HER4*) has been associated with oncogenic transformation via DNA methylation of the promoter regions. Aberrant DNA methylation of *HER* family members has been implicated in carcinogenesis of CRC mainly through the regulation of gene expression. This study aimed to determine the DNA methylation status and gene expression of *HER* family members in CRC cell lines and in formalin-fixed paraffin embedded (FFPE) samples as well as the protein expression of *HER* family members in FFPE samples. The associations of DNA methylation status, gene and protein expression of these genes in FFPE samples were also determined. Fifty-nine archival FFPE CRC cases with the adjacent normal colon tissues were retrieved. The selected tissues were micro-dissected manually prior to RNA and DNA extraction. Gene expression and DNA methylation status of *HER* family members were evaluated by qPCR and MSP technique respectively. Protein expression was determined using immunohistochemistry (IHC) technique. Prior to FFPE, the same procedures were performed on CRC cell lines i.e. HT-29, HCT116, Caco-2 and CCD 841 CoN (normal colon) with treatment of 5'-aza-2'-deoxytidine (5-aza-dC) and 5-fluorouracil (5-FU). Upregulation of *HER* family members were discovered in all CRC cell lines with *HER3* recorded significant expression ($p<0.0001$). *EGFR* and *HER3* were hypomethylated whereas *HER4* was hypermethylated in CRC cells. Downregulation of all genes were observed in several CRC cell lines after treatment with only *HER3* shows significant result ($p<0.001$). *EGFR*, *HER2* and *HER3* remained unmethylated after being treated with 5-FU and *HER4* was unmethylated after treatment with 5-aza-dC. Overexpression of EGFR (54.2%, p-value=0.021), *HER2* (52.5%, p-value=0.022), and *HER3* (42.4%, p-value=0.077) and hypomethylation of *EGFR* (81.4%) and *HER3* (91.5%) were discovered in FFPE CRC tissues. Positive proteins expressions of *EGFR*

(42.4%), *HER2* (11.9%), *HER3* (47.5%) and *HER4* (57.6%) were seen in FFPE tissues. However, no significant association was found between DNA methylation, mRNA levels and protein expression of *HER* family members. Aberrant DNA methylation pattern of *HER3* showed significant association with tumour differentiation (p-value=0.035) and tumour location (p-value=0.007). Even though our data suggest that there is no significant relationship between DNA methylation and mRNA expression, the aberrant regulation and hypomethylation of these genes strongly suggest the important role of these genes in tumourigenesis of CRC. Hypomethylation facilitates the activation of these genes which promotes oncogenic cell growth, loss of imprinting or genomic instability and subsequently promotes carcinogenesis and progression of CRC. Therefore, *HER* family has a potential as prognostic factors and therapeutic target for CRC. The genes are very promising candidates for the identification of new biomarkers. However, further investigation on DNA hypomethylation is required.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

HUBUNG KAIT ANTARA STATUS METILASI DNA, EKSPRESI GEN DAN PROTEIN BAGI FAMILI *HER* PADA ADENOKARSINOMA KOLOREKTAL

Oleh

ROSFAYATI BINTI OTHMAN @ JAFFAR

Oktober 2020

Pengerusi : Profesor Madya Norhafizah binti Mohtarrudin, PhD
Fakulti : Perubatan dan Sains Kesihatan

Kanser kolorektal (CRC) merupakan kanser ketiga paling kerap berlaku di seluruh dunia. Manakala di Malaysia, CRC merupakan kanser kedua paling kerap terjadi. Walaupun terdapat banyak kemajuan dari segi terapi, masih terdapat banyak kes ulangan dan resistan dilaporkan. Pembendahan hanya berkesan pada kes yang didiagnos pada peringkat awal. Ekspresi berlebihan bagi ahli famili *HER* (*EGFR*, *HER2*, *HER3* dan *HER4*) mempunyai hubungkait dengan transformasi onkogenik melalui proses metilasi DNA pada bahagian promoter. Penyimpangan metilasi DNA yang berlaku pada ahli famili *HER* telah memberi implikasi dalam karsinogenesis CRC melalui regulasi ekepresi gen. Oleh itu, penyelidikan ini dijalankan bertujuan untuk menentukan status metilasi DNA dan ekspresi gen bagi ahli famili *HER* pada sel dan tisu terendam formalin-parafin (FFPE) CRC. Ekpresi protein pada tisu FFPE juga dikenalpasti. Hubungkait antara status metilasi DNA, gen dan protein bagi famili *HER* pada tisu FFPE juga ditentukan. Sebanyak lima puluh sembilan tisu FFPE CRC bagi kes CRC bersama dengan tisu normal yang berdekatan telah diperolehi. Tisu-tisu yang telah dipilih telah menjalani proses diseksi-mikro secara manual sebelum ekstraksi RNA dan DNA dijalankan. Ekspresi gen dan status metilasi DNA bagi ahli famili *HER* telah dinilai dengan menggunakan teknik tindak balas rantaian polimerase kuantitatif (qPCR) dan metilasi spesifik PCR (MSP). Ekspresi protein ditentukan menggunakan teknik immunohistokimia. Sebelum itu, kaedah yang sama telah digunakan pada sel CRC yang terdiri daripada HT-29, HCT 116, Caco-2 dan sel normal, CCD 841 CoN. Sel-sel ini juga menjalani rawatan dengan menggunakan 5'-aza-2'-deoksitidin (5-aza-dC) dan 5-flurourasil (5-FU). Regulasi aras tinggi telah dikesan bagi ahli keluarga *HER* pada sel CRC dengan *HER3* merekodkan ekspresi yang signifikan ($p<0.0001$). *EGFR* dan *HER3* didapati terhipometilasi manakala *HER4* telah terhipermetilasi pada sel CRC. Regulasi aras rendah telah diperhatikan pada sel CRC selepas rawatan dengan hanya *HER3* yang menunjukkan keputusan yang signifikan ($p<0.001$). *EGFR*, *HER2* dan *HER3* pula kekal terhipometilasi selepas menjalani rawatan dengan 5-FU dan *HER4* juga telah terhipometilasi selepas rawatan dengan 5-aza-dC. Ekspresi berlebihan pada *EGFR* (54.2%, nilai-p=0.021), *HER2* (52.5%, nilai-p=0.022), dan *HER3* (42.4%,

nilai-p=0.077) dan hipometilasi pada *EGFR* (81.4%) dan *HER3* (91.5%) telah dikesan pada tisu FFPE CRC. Ekspresi positif pada protein EGFR (42.4%), HER2 (11.9%), *HER3* (47.5) dan *HER4* (57.6%) telah dikenalpasti pada tisu FFPE. Walau bagaimanapun, tiada hubungkait yang signifikan dikesan antara metilasi DNA, aras mRNA dan protein bagi famili *HER*. Corak metilasi aberan bagi *HER3*, menunjukkan hubungkait yang signifikan dengan pembezaan (nilai-p=0.035) dan lokasi tumor (p-value=0.007). Walaupun data-data ini menunjukkan tiada hubungkait yang signifikan antara metilasi DNA dengan ekspresi mRNA, namun, penyimpangan regulasi dan hipometilasi bagi gen-gen ini telah membuktikan kepentingan peranan gen-gen ini dalam proses tumorigenesis CRC. Hipometilasi telah membantu pengaktifan gen-gen ini sekaligus menyebabkan pertumbuhan sel onkogenik, kehilangan peneraan dan ketidakstabilan genomik. Hal ini telah menyumbang kepada proses karsinogenesis dan perkembangan CRC. Oleh itu, famili *HER* mempunyai potensi besar sebagai faktor prognostik dan sasaran terapeutik bagi CRC. Gen-gen ini merupakan calon harapan untuk proses identifikasi penanda-bio baru bagi CRC. Walau bagaimanapun, penyelidikan lanjut bagi hipometilasi DNA amatlah diperlukan.

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Norhafizah binti Mohtarrudin, MBBS, MPath
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Malina binti Osman, MComm. Health
Associate Professor (Medical)
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Norshariza binti Nordin, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Seow Heng Fong, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

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Name and Matric No: Rosfayati binti Othman @ Jaffar, GS36716

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LIST OF ABBREVIATIONS

ºC	degree celcius
µm	micromemeter
µl	Microliter
5-aza-dC	5-aza-2'-deocytidine
5-FU	5-fluoro Uracil
AJCC	American Joint Committee on Cancer
AKT	A serine/theorine kinase (protein kinase B)
APC	adenomatous polyposis coli
ATCC	American Type Culture Collection
β-catenin	beta catenin
β-ME	beta-mercaptoethanol
BAX	beta cell lymphoma 2-Associated X
BCL6B	B-cell chronic lymphocytic leukimia/lymphoma 6 member 6
BEST	Biomarkers, EndpointS, and other Tool
BRCA1	breast cancer 1
C-terminal	carboxy terminal
CA9	carbonic anhydrase 9
CDKN2A	cyclin-dependent kinase inhibitor 2A
cDNA	complimentary deoxyribonucleic acid
CEA	carcinoembryonic antigen
CG	cytosine guanine
CIN	chromosomal instability
CLDN4	claudin-4
cm	centimeter
c-Met	c-mesychymal to epithelial transition

COX2	cyclooxygenase-2
CRC	colorectal cancer
CT scan	computed tomography scan
CXCL14	C-X-C motif chemokine ligand 14
DAC	5-aza-2'-deocytidine
ΔΔCt	delta delta cycle threshold
DIRAS	distinct subgroup of the RAS family
DMEM	Dulbecco's modified Eagle's medium
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DNase	deoxyribonuclease
DNMT3L	DNA methyltransferase 3-like
DNMTs	DNA methyltransferases
DPX	dibutylphthalate polystyrene xylene
e-HIS	electronic hospital information system
ECD	ecdysoneless homolog
EGF	epiregulin growth factors
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMEM	Eagle's minimum essential medium
ErbB	epidermal growth factor receptor
ErbB2	epidermal growth factor receptor 2
ErbB3	epidermal growth factor receptor 3
ErbB4	epidermal growth factor receptor 4
EREG	epiregulin
ERK	extracellular signal-regulated kinases (ERK)

FBS	fetal bovine serum
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FIT	fecal immunohistochemical test
FOBT	fecal occult blood test
FOLFOX	folinic acid, fluorouracil, oxaliplatin drugs
gDNA	genomic deoxyribonucleic acid
gFOBT	guaiac fecal occult bood test
GSTM1	glutathione S-transferases mu 1
GSTP1	glutathione S-transferase pi 1
GSTs	glutathione S-transferases
GSTT1	glutathione S-transferases theta 1
HER	human epidermal growth factor related
HER1	human epidermal growth factor related 1
HER2	human epidermal growth factor related 2
HER3	human epidermal growth factor related 3
HER4	human epidermal growth factor related 4
HNSCC	head and neck squamous cell carcinoma
HOXA	homeobox A
HOX1	homeobox proto-oncogene 1
HOXA10	homeobox proto-oncogene 10
HRG	heregulin
IGF-1R	insulin-like growth factor 1 receptor
IHC	immunohistochemistry
JAK/STAT	janus kinase / signal transducer and activator of transcription
JKEUPM	Ethics Committee for Research Involving Human Subjects, Universiti Putra Malaysia

KRAS	kirsten rat sarcoma viral oncogene homolog
LCC	left colon cancers
LIFR	leukemia inhibitory factor receptor
LV	leucorovin
mAbs	monoclonal antibodies
MAPK	mitogenic-activated protein kinase
MEK	mitogen-activated protein kinase
MGMT	O(6)-methylguanine-DNA methyltransferase
miRNAs	microRNA
MLH	mutl homolog
MLH1	mutL homolog 1
MOH	Ministry of Health
mRNA	messenger ribonucleic acid
MSH2,	mutS homolog 2
MSH6	mutS homolog 6
MSI	microsatellite instability
MSP	methylation specific polymerase chain reaction
MTHFR	methylenetetrahydrofolate reductase
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
MTR	methione synthase
MYC	MYC Proto Oncogene
NAT1	N-acetyltransferase 1
NRG	neuregulin
NSAIDS	non-steroid anti-inflammatoty drugs
NSCLC	non-small cell lung cancer
NTC	non-template control

OD	optical density
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PET	positron emission tomography
PI3K	phosphatidylinositol-3-kinase
PITX2	paired-like homeodomain 2
PMS1	postmeiotic segregation increased 1
PMS2	postmeiotic segregation increased 2
PTEN	phosphatase and tensin homolog
qPCR	quantitative polymerase chain reaction
RAF	rapidly accelerated fibrosarcoma
Ras	rat sarcoma
RB1	retinoblastoma 1
RCC	right colon cancer
RNA	ribonucleic acid
RTKs	receptor tyrosine kinases
SEER	Surveillance, Epidemiology and End Results
SMAD	S mothers against decapentaplegic
SPSS	statistical packages for social sciences
SRC	sarcoma
STAT	signal transducer and activator of trasncription
TBE	Tris/Borate/EDTA
TCF	T-cell factor
TGF-α	tumour growth factor alpha

TGFbetaRII	tumour growth factor beta receptor 2
TKD	tyrosine kinase domain
TKIs	tyrosine kinase inhibitors
TKR	tyrosine kinase receptor
TME	total mesorectal excision
TNM	tumour-node-metastasis
TP53	tumour protein 53
UK	United Kingdom
uPA	urokinase-type plasminogen activator
US	United States
UV	ultra violet
V	Volt
v/v	Volume/volume
VEGF	vascular endothelial growth factor
VHL	von hippel-lindau
w/v	weight/volume
WHO	World Health Organization
Wnt	wingless-related integration site

CHAPTER 1

INTRODUCTION

1.1 Research Background

Colorectal cancer (CRC) is considered as one of the main deadly cancer in many parts of the world. CRC ranks as the third most common cancer among men and second among women (Siegel et al., 2019). In the United States (US), there are projected to be more than 147 000 individuals will be newly diagnosed with CRC (Siegel et al., 2020). The number of new cases is estimated to surge up to 2.5 million cases after year 2030 (Dekker et al., 2019).

In previous years, CRC has been thought to be less common in Asia. However, due to the changes in lifestyle and becoming more westernized, the incidence rates of CRC are increasing year by year in this region (Allemani et al., 2015; Arnold et al., 2017; Koo et al., 2012). The incidence of CRC increases by two to four-fold in China, Japan and Singapore (Allemani et al., 2015; Jiricny & Nyström-Lahti, 2000; Sung et al., 2015). According to V et al. (2014), Asia had the highest proportions of incident and mortality of CRC cases per 100 000 populations in the world.

In Malaysia, CRC is the second type of malignancy that inflicts Malaysian men and third in women (Veettil et al., 2017). The number of CRC cases is highest among Chinese, followed by Malays, and Indians (Hassan et al., 2016; Shah et al., 2014).

CRC emerges as a results of genetic and/or epigenetic modifications in colonic epithelial cells during tumourigenesis (Kim et al., 2010). These alterations contribute to abnormal expression of genes during carcinogenesis. Epigenetics involves "chromosome modifications without changing the sequence of DNA; resulting in a heritable and stable phenotype" (Berger et al., 2009).

The most common epigenetic changes in human tumour is DNA methylation in specific gene promoters. DNA methylation is the "covalent addition of methyl group to the 5'-position of cytosine in the sequence context 5'CG-3' of the DNA molecule without changing the specific sequence of the gene" (Bestor, 2000; Kulis & Esteller, 2010). DNA methylation is essential in many physiological processes. However, aberrant DNA methylation leads to various pathologic changes including carcinogenesis through regulation of gene expression (Galamb et al., 2016; Verma & Kumar, 2017).

Determination of DNA methylation of a specific gene is very useful in the identification of a new biomarker responsible for carcinogenesis. The biomarkers are very valuable in detecting the pre-cancerous tumour that might progress into cancer, selecting the candidates for chemotherapy, aiding in disease prognosis and detecting cancer tissue that cannot be diagnosed by current imaging technique.

1.1.1 HER Family

HER (Human Epidermal Growth factor Related) family is a tyrosine kinase receptors subfamily. The *HER* family is also known as *ErbB* family consists of *EGFR* (*ErbB1* or *HER1*), *ErbB2* (*HER2*/Neu), *ErbB3* (*HER3*) and *ErbB4* (*HER4*) (Bublil & Yarden, 2007; Roskoski, 2014). *HER* receptors are essentials in cell growth, differentiation, proliferation, apoptosis, invasion, survival, and migration (Seshacharyulu et al., 2012; Wee & Wang, 2017; Yarden & Pines, 2012; Zhang et al., 2016). Epigenetic studies have shown that the aberrant promoter methylation of tyrosine kinase receptors is related to cancer development and progression (J. Datta et al., 2008; Sarkar et al., 2013). Abnormal expression of this family receptor which is mostly overexpression has been linked to various types of human tumours via abnormal signalling of *HER* pathway (Byeon et al., 2017; Hynes & MacDonald, 2009; Wang, 2017).

Alterations due to methylation in the promoter of the tyrosine kinase receptors have been linked to tumour development and progression (Hynes & MacDonald, 2009; Kushwaha et al., 2016; Thuan & Phuong, 2017). DNA methylation of HER family members were detected in non-small cell lung cancer (NSCLC), breast and head and neck cancer (Das et al., 2010; Szmida et al., 2015). In fact, according to Dricu (2012), epigenetic modifications in tyrosine kinase receptors might be one of the factors causing acquired resistance to conventional cancer therapy.

This study aimed to identify the DNA methylation of tyrosine kinase receptors specifically *HER* family and their effect on gene expression in primary colon adenocarcinoma.

1.2 Problem Statement

Over recent decades, intense efforts have been carried out to identify genetic and epigenetic changes that occur during colorectal cancer tumourigenesis. Even though many cancer therapies have been developed to treat CRC, considerable proportions of cancer patients respond poorly to therapy and the number of resistance cases increases year by year. This factor is the major obstacle in the treatment of CRC.

Surgery is proven to be very effective to remove the tumours (Fuzi et al., 2015). But it is only applicable for cases which were diagnosed at early stage and relapse often occurs in some cases. In addition, CRC is mostly asymptomatic until it progresses to

advanced stage. Almost 25% of CRC cases are diagnosed at late stage with metastases which causes difficulties in curative surgical control (Keum & Giovannucci, 2019; Sánchez-Gundín et al., 2018). In Malaysia, most of CRC patients presented late compared to developed countries (Law et al., 2009; Lim, 2014). It might be caused by risk factors including genetic inheritance, lack of awareness on cancer warning signs and poor national screening program in our country (Lim, 2014; Su et al., 2013).

The current biomarkers available are not suitable for population-wide screening purposes (Soreide et al., 2009). Therefore, identification of reliable tumour biomarkers for early detection and therapeutic targets is critically important to alleviate the number of cases and mortality rates of CRC in Malaysian population.

Moreover, epigenetic alterations of tyrosine kinase receptors leads to resistance to conventional cancer therapy (Dricu, 2012). Therefore, more studies focusing on aberrant DNA methylation of tyrosine kinase receptors should be carried out due to low number of research available on this issue. Majority of available studies only focus on DNA methylation of *EGFR* especially in CRC (Montero et al., 2006; Scartozzi et al., 2011). A limited number of studies have been conducted highlighting the other members of *HER* family. Moreover, Yonesaka et al. (2011) reported that patients with CRC who have developed resistance to cetuximab-based (anti-EGFR) therapy also show *HER2* amplification, and have increased levels of heregulin (HRG) which induces *HER3* signalling.

In addition, currently, the number of molecular studies on CRC in Malaysian populations is low. Most of previous studies were conducted in Western populations with diverse disease features and genetic make-up compared to Malaysian.

Most of the research involving gene expression especially in biomarker discovery used fresh frozen tissue or blood samples. However, over 400 million of FFPE samples are stored worldwide and are expected to increase annually (Sah et al., 2013). FFPE specimens provide many advantages which include easy handling, low cost and suitable for large scale applications (Perlmutter et al., 2004). Paraffin blocks serve as excellent starting materials for vast amount of research. FFPE has been proven to be useful in several molecular researches (Espinal et al., 2017; Jacobson et al., 2011; Torrente et al., 2011; Zhang et al., 2017). More molecular studies are required to show that FFPE specimens are useful not just for morphology studies.

1.3 Hypothesis

The hypothesis of this study was listed as follows:

1. DNA methylation and gene expression of *HER* family members are identified in colorectal adenocarcinoma cell lines and FFPE samples and there is association between DNA methylation, gene and protein expression of HER family members in colorectal adenocarcinoma.

1.4 Objectives

1.4.1 General objective

The general objective of this study was listed as follows:

1. To determine the association of DNA methylation status, gene and protein expression of *HER* family in colorectal adenocarcinoma.

1.4.2 Specific objectives

The specific objectives of this study were listed as follows:

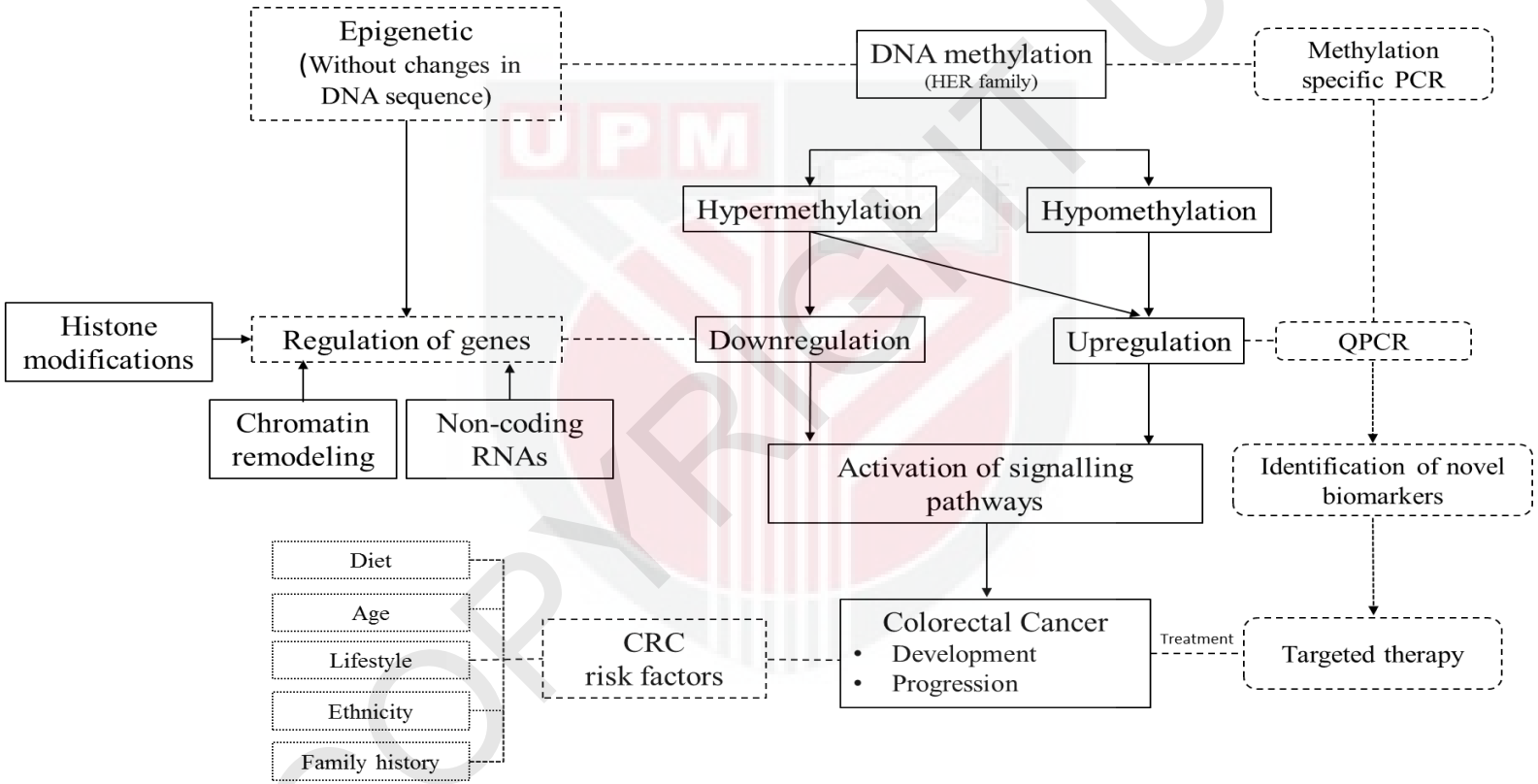
1. The determine the mRNA levels and DNA methylation of *EGFR*, *HER2*, *HER3* and *HER4* in colorectal adenocarcinoma cell lines before and after treatment with 5-aza-2'-deocytidine (5-aza-dC) and 5-fluorouracil (5-FU).
2. To determine the association between mRNA levels with DNA methylation status of *EGFR*, *HER2*, *HER3* and *HER4* in FFPE colorectal adenocarcinoma tissues.
3. To identify the association of mRNA levels and DNA methylation status of *EGFR*, *HER2*, *HER3* and *HER4* with demographic parameters (age, gender and race) and clinicopathological characteristics (Dukes' staging, tumour differentiation/grade, tumour location, lymph node metastasis, diabetes mellitus, hypertension, smoking and family history).
4. To identify the association between mRNA levels and DNA methylation status with protein expression of *EGFR*, *HER2* and *HER3* in FFPE colon adenocarcinoma tissues.
5. To identify the association between mRNA levels-DNA methylation status and protein expression of *HER* family (*EGFR*, *HER2*, *HER3*) in FFPE colon adenocarcinoma tissues.

1.5 Significance of Study

Currently, epigenetics is one of the fastest-growing areas in the molecular study. Epigenomic approaches will improve our knowledge regarding the roles of certain genes in tumourigenesis.

Therefore, identification of DNA methylation of *EGFR*, *HER2*, *HER3* and *HER4* in this study suggested their vital role in CRC development. The findings will provide better understanding of *HER* family. It also may serve as new alternatives to targeting *HER* signalling pathway in the treatment of CRC. The integration of epigenetics with genetic data will be beneficial in the establishment of new biomarkers for prognosis, early diagnosis and therapy of CRC. Hopefully, the risk and cost for unsuccessful treatment can be reduced.

1.6 Research conceptual framework



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