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RELATIONSHIPS BETWEEN WNT-NOTCH-HIPPO SIGNALING PATHWAYS AND THEIR RELEVANCE TO COLORECTAL CANCER PATHOGENESIS

CHAI BOON LEE

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By

CHAI BOON LEE

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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RELATIONSHIPS BETWEEN WNT-NOTCH-HIPPO SIGNALING PATHWAYS AND THEIR RELEVANCE TO COLORECTAL CANCER PATHOGENESIS

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March 2018

Chair : Prof. Seow Heng Fong, PhD
Institute : Bioscience

Colorectal cancer (CRC) is a heterogeneous disease caused by progressive accumulation of multiple genetic alterations. Aberrant Wnt, Notch and Hippo signaling pathways commonly observed in CRC contributes to the pathogenesis of the disease. Crosstalk between these signaling pathways has previously been studied separately, but the relationship between these three signaling pathways has yet to be fully elucidated.

The objectives of this study are (1): to determine the abnormal biomolecule expression, and the possible relationship between Wnt, Notch and Hippo signaling pathways, and MSI status via immunohistochemical staining, (2): to determine the relationship of reduced APC immunoreactivity and APC truncation mutations via mutational analysis, and (3): to associate MSI with mutations by targeted exome sequencing.

Using Mann-Whitney U test, a significant difference between the CRC and apparently normal adjacent (ANA) tissue groups in immunohistochemical staining of cytoplasmic β-catenin, cytoplasmic APC, nuclear APC, p-GSK3β, DKK1, NICD1, Hes1, and cytoplasmic YAP was observed.

Biomolecule expression was associated with various pathological parameters using χ^2 test. Cancer stage was significantly associated with expression of nuclear β-catenin (p=0.013), Notch1 (p=0.005), NICD1 (p=0.011) and nuclear YAP (p=0.001), histological grade was significantly associated with expression of cytoplasmic β-catenin (p=0.013), membranous β-catenin (p=0.020) and PMS2 (p=0.014). Tumour infiltration stage (T) was significantly associated with expression of cytoplasmic β-catenin (p<0.005), cytoplasmic APC (p=0.038), Notch1 (p=0.007) and NICD1 (p=0.006). Metastasis (M) stage was significantly

associated with expression of nuclear β-catenin (p=0.049), and MSI was significantly associated with right sided tumour (p<0.005) and peritumoral lymphocytes aggregates (PLA) (p=0.032).

Using Spearman's rank test, novel correlation between Wnt, Notch and Hippo signaling pathways were discovered. Cytoplasmic β-catenin expression was negatively correlated with MSI status (p=0.002), p-GSK3β was positively correlated with FBXW7 (p=0.004), DKK1 was positively correlated with NICD1 (p=0.002), Hes1 (p=0.024) and nuclear YAP (p=0.019). NICD1 was positively correlated with cytoplasmic YAP (p=0.012), and Hes1 was positively correlated with nuclear YAP (p<0.005).

Mutational analysis of APC gene discovered two novel mutations (p.H1349L and p.K1350fs*4) whereas targeted exome sequencing discovered EGFR mutation in Malaysian CRC populations besides other common mutations in CRC.

In conclusion, nuclear β-catenin, Notch1 and NICD1 expression were discovered occurring at the early stage of CRC, while novel relationship between Wnt-Notch (DKK1-Hes1, DKK1-NICD1 and p-GSK3β-FBXW7), Wnt-Hippo (DKK1-NICD1) and Notch-Hippo (Hes1-nuclear YAP and NICD1-cytoplasmic YAP) signaling pathways were revealed in this study. This study also showed MSI was negatively correlated with cytoplasmic β-catenin expression.

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

HUBUNGAN ANTARA LALUAN ISYARAT WNT-NOTCH-HIPPO DAN RELEVAN MEREKA TERHADAP PATOGENESIS BARAH KOLOREKTAL

Oleh

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Barah kolorektal (CRC) adalah sejenis penyakit heterogenus yang disebabkan oleh pengumpulan perkembangan pelbagai perubahan genetik. Penyelewengan laluan isyarat Wnt, Notch dan Hippo yang biasa diperhatikan dalam CRC menyumbang kepada patogenesis penyakit. Penyilangan antara laluan-laluan isyarat ini telah dikajiselidik secara berasingan sebelum ini, tetapi hubungan antara ketiga-tiga laluan isyarat masih belum dijelaskan sepenuhnya.

Objektif kajian ini adalah (1): menentu pengekspresan biomolekul yang luar biasa, dan hubungan yang berkemungkinan antara laluan-laluan isyarat Wnt, Notch dan Hippo, dan status ketidakstabilan mikrosatelit (MSI) melalui kesan imunohistokimia, (2): untuk menentu hubungan kekurangan immunoreaktiviti APC dengan mutasi pemutusan *APC* melalui analisis mutasi, dan (3): untuk mencari hubung kait antara MSI dengan mutasi dari jujukan exom sasaran.

Dengan ujian Mann-Whitney U, perbezaan yang ternyata dapat diperhatikan antara kumpulan tisu-tisu CRC dan tisu-tisu bersebelahan yang kelihatan biasa (ANA) dalam kesan imunohistokimia β-catenin sitoplasma, APC sitoplasma, APC nukleus, p-GSK3β, DKK1, NICD1, Hes1, and YAP sitoplasma.

Pengekspresan biomolekul dihubung kait dengan pelbagai parameter patologi dengan menggunakan ujian χ^2. Peringkat barah berhubung kait secara ternyata dengan pengekspresan β-catenin nukleus (p=0.013), Notch1 (p=0.005), NICD1 (p=0.011) dan nukleus YAP (p=0.001), grad histologi berhubung kait secara ternyata dengan pengekspresan β-catenin sitoplasma (p=0.013), β-catenin membran (p=0.020) dan PMS2 (p=0.014), peringkat penyusupan tumor (T) berhubung kait secara ternyata dengan pengekspresan β-catenin sitoplasma (p<0.005), APC sitoplasma (p=0.038), Notch1 (p=0.007) dan NICD1 (p=0.006),

peringkat metastasis (M) berhubung kait secara ternyata dengan pengekspresan β-catenin nukleus (p=0.049) dan MSI berhubung kait secara ternyata dengan tumor bahagian kanan (p<0.005) dan pengumpalan limfosit peritumor (PLA) (p=0.032).

Dengan ujian Spearman's rank, hubungan baharu antara laluan-laluan isyarat Wnt-Notch-Hippo telah ditemui. Pengekspresan β-catenin sitoplasma adalah berkorelasi secara negatif dengan status MSI (p=0.002), p-GSK3β adalah berkorelasi secara positif dengan FBXW7 (p=0.004), DKK1 adalah berkorelasi secara positif dengan NICD1 (p=0.002), Hes1 (p=0.024) dan YAP nukleus (p=0.019), NICD1 adalah berkorelasi secara positif dengan YAP sitoplasma (p=0.012), dan Hes1 adalah berkorelasi secara positif dengan YAP nukleus (p<0.005).

Analisis mutasi gene *APC* telah menemui dua mutasi baharu (p.H1349L and p.K1350fs*4) manakala jujukan exom sasaran telah menemui mutasi EGFR dalam populasi CRC Malaysia selain mutasi-mutasi yang biasa dalam CRC.

Kesimpulannya, pengekspresan β-catenin nukleus, Notch1 and NICD1 ditemui berlaku pada peringkat awal CRC, manakala hubugan antara laluan-laluan isyarat Wnt-Notch (DKK1-Hes1, DKK1-NICD1 dan p-GSK3β-FBXW7), Wnt-Hippo (DKK1-NICD1) dan Notch-Hippo (Hes1-YAP nukleus dan NICD1-YAP sitoplasma) telah ditemui dalam kajian ini. Kajian ini juga menunjukkan MSI adalah berkorelasi secara negatif dengan pengekspresan β-catenin sitoplasma.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy . The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

µl	microliter
µM	microMolar
5-FU	5-fluorouracil
ADAM	A Disintegrin and metalloproteinase
AJCC	American Joint Committee on Cancer
AMPK	adenosine monophosphate-activated protein kinase
ANA	apparently normal adjacent
APC	Adenomatous Polyposis Coli
bp	base pair
BRAF	serine/threonine-protein kinase B-Raf
CIMP	CpG Island Methylator Phenotype pathways
CKI	casein kinase I
cm	centimeter
CRC	Colorectal cancer
C-terminal	Carboxy-terminal
DKK1	Dickkopf1
DNA	Deoxyribonucleic acid
EGFR	epidermal growth factor receptor
EMT	epithelial to mesenchymal transition
ERK	extracellular signal-regulated kinase
FBXW7	F-box and WD40 repeat domain-containing 7
FFPE	formalin fixed paraffin embedded
FOLFIRI	folinic acid (leucovorin), fluorouracil (5-FU), irinotecan (Camptosar)
FZD	Frizzled
HD	heterodimerization domain
Hes1	hairy and enhancer of split-1
IHC	immunohistochemistry
ILI	intratumoral lymphocytic infiltration
JAG	Jagged
kDa	kiloDalton
KRAS	Kirsten rat sarcoma viral oncogene homolog
LATS1/2	large tumor suppressor 1/2
LEF	lymphoid enhancer factor
LRP	Low-density Lipoprotein Receptor-Related Protein

MAPK	mitogen-activated protein kinase
MCR	mutation cluster region
mCRC	metastasis colorectal cancer
MLHs	MutL homologs
MMR	DNA mismatch repair
moAbs	monoclonal antibodies
MOB1	Mps One binder 1
mRNA	Messenger RNA
MSH6	MutS Protein Homolog 6
MSI	Microsatellite Instability
MST1/2	mammalian STE20-like protein kinase 1/2
NICD1	Notch Intracellular Domain 1
nm	nanometer
NRR	negative regulatory region
NRAS	neuroblastoma RAS viral (v-ras) oncogene homolog
N-terminal	Amino-terminal
OS	overall survival
PCP	Planar Cell Polarity
PDZ	Postsynaptic density 95, Discs Large, Zonula occludens-1
PEST	Proline/Glutamic acid/Serine/Threonine
p-GSK3β	phospho-Glycogen Synthase Kinase 3 beta
PI3K	phosphoinositide-3 kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PLA	peritumoral lymphocyte aggregates
PTEN	phosphatase and tensin homolog 10
PMS2	Postmeiotic Segregation Increased 2
RTK	receptor tyrosine kinase
SAV1	salvador family WW domain-containing protein 1
Ser	serine
TAD	transcriptional activation domain
TAZ	Transcriptional Coactivator with PDZ-binding Motif
TCF	T-cell factor
TEAD	transcriptional enhancer associate domain
Thr	threonine
TSG	Tumour Suppressor Gene
YAP	Yes-associated protein

β-TrCP	beta-transducin repeat–containing homologue protein
χ^2	Chi square

CHAPTER 1

INTRODUCTION

Colorectal cancer (CRC) is a malignancy of the colon and rectum. It is a large group of heterogeneous diseases classified under the same category where the most common groups are sporadic CRC, familial CRC and hereditary CRC. CRC arises from the epithelial cells lining of the colon and rectum. CRC begin with a growth of polyp from the inner wall of the colon and rectum. Overtime, some polyps develop into malignant tumours.

In 2012, nearly 1.4 million new cases of CRC were diagnosed around the world, making CRC the third most common cancer in the worldwide after lung and breast cancer. Of the new cases, around 50% was them were reported to be mortality cases (Ferlay et al., 2013). CRC has highest incidence rate in developed countries but the incidence rates is rising fast in countries undergoing rapid societal and economic changes particularly in Eastern Europe, Asia and South America (Center et al., 2009). The global incidence and mortality patters and trends in CRC can be categorized into 3 groups, namely, Group 1: increasing incidence and mortality, Group 2: increasing incidence but decreasing mortality, and Group 3: decreasing incidence and mortality (Arnold et al., 2016). It is expected in 2030, the global burden of CRC will increase by 60% to more than 2.2 million new diagnosis cases and 1.1 million deaths (Ferlay et al., 2013).

In Malaysia, colorectal cancer is the third most common cancer. The age-standardized incidence rates for colon cancer were 19.4 and 14.6 per 100,000 persons for men and women respectively. In year 2007 alone, 18219 new cancer cases were reported in Malaysia. Among which, CRC has the second highest incidence rate (12.3%), with a total of 2246 cases. The highest cases are reported in Chinese, followed by Malay then Indian. The ratio between male and female patients of CRC are 1.2 to 1. From the report cases, 31% and 32% were of stage III and stage IV respectively (Zainal & Nor Saleha, 2011). Majority of Malaysian CRC patients were diagnosed after age 50. The survival rate for CRC patients was 34.3% only and this is quite low compared to other developed countries (Ghazali et al., 2010).

The standard treatment for CRC is surgery. Chemotherapy is added in CRC advance stages or metastasis cases. The major cause of death for CRC patients is metastases in advance stages, primarily in liver and lung. Since the treatment for metastases CRC is not as effective as early stage of CRC, the survival rates for metastatic patients is not high.

Etiology of CRC is complex and heterogenous. Dietary, lifestyle factors, inherited and somatic mutations and local inflammation are among the more well-studied risk factors. High red meat and excessive alcohol consumption, smoking, and insufficient physical activity are among the most significant risk factors observed in CRC patients. A few mutated oncogenes and TSGs are observed in sizable fractions of CRC, namely, APC, p53 and KRAS. These genes plays an important role in the initiation, promotion and progression of CRC development.

Cells communicate through signaling. Signals received from cell surface travel to the nucleus through a route called signal transduction pathway. This pathway is complex where a group of molecules within a cell, pass down signals received from cell surface receptors to a series of biomolecules into the nucleus to elicit cellular actions. The transmission of signal can be amplified at any steps, thus generating a cascade of reactions downstream. Due to the complexity of this system, gene mutation of the biomolecules along the signal transduction pathway will lead to overexpression or reduce expression of the target genes. This is the case of many diseases including cancers.

Wnt signal signaling is a pivotal signaling pathway that plays a role in embryonic development of metazoan, regulating cell fate, proliferation, differentiation, polarity, and migration. This signaling pathway is also important in somatic cell maintenance and tissue regeneration after injury (Krausova & Korinek, 2013). There are three pathways of Wnt signaling, namely, the Canonical Wnt pathway, planar cell polarity (PCP) pathway and the Wnt-calcium (Wnt/Ca^{2+}) pathway (Croce & McClay, 2008).

The canonical Wnt signal is activated when Wnt glycoproteins bind to the transmembrane frizzled receptors and LRP 5/6 co-receptors. Following the binding of receptors, the Wnt signal is transduced to a protein complex, destruction complex, by associating with the Dishevelled (Dvl). The destruction complex consisted of APC, Axin, glycogen synthase kinase 3 (GSK-3) and β-catenin, which phosphorylated β-catenin for subsequent degradation when Wnt signaling is not activated. In the event where Wnt signal is transduced, β-catenin will dislodge from the complex becoming free β-catenin in cytoplasm. Accumulated cytoplasmic β-catenin then translocate into the nucleus can binds to TCF/LEF to activate gene transcription (Schneikert & Behrens, 2007).

In CRC, a common observation is overexpression of β-catenin in cytoplasm. This is the hallmark of aberrant Wnt signaling in CRC. One of the main factors that leads to accumulation of β-catenin is mutations of the APC gene. APC gene is considered as the gatekeeper gene in CRC tumourigenesis. The mutation of APC gene will lead to mutation in other genes. CTNNB1 gene mutation is another factor leading to overexpression of β-catenin protein but the frequency is low compared to APC gene mutations.

Notch Signaling Pathway is an important pathway in metazoan development that involves in various cellular processes including cell fate specification, proliferation, differentiation and apoptosis (Gazave et al., 2009). In normal intestine, notch signaling is crucial for the development and homeostasis of colon tissues. This signaling pathway controls the fate of the intestinal stem cell and determine differentiation of developing epithelial cells becoming either absorptive or secretory cell (Qiao & Wong, 2009).

Notch signaling is activated through cell to cell contact. When Notch receptors on cell membrane surface are bound by ligands from a neighbouring cell, the transmembrane Notch receptors are first cleaved by ADAM10/17 metalloproteases outside the cell membrane releasing the extracellular domain of the receptor. The second cleavage are performed by preselinin γ-secretase releasing enzyme releasing the intracellular domain (ICD). ICD then translocate into the nucleus and binds to the transcription factor RBPjκ to activate gene transcription.

Abnormal notch signaling was first discovered in a hematological tumours and later solid tumours. An interesting feature of notch signaling in various cancers is it can act as an oncogene or TSG depending on the cellular context, dose and timing (Maillard & Pear, 2003). This dual role of notch signaling was observed in CRC (Bolós et al., 2007). Activation of Notch signaling was initially discovered in human CRC (Reedijk et al., 2008). Later, reduced Notch activity was also observed in human clinical sample during CRC progression (Kim et al., 2012).

Hippo signaling pathway is highly a conserved signaling pathway in mammals. This pathway is essential in controlling organ size and regulating tissue homeostasis. In mammals, the core of Hippo signaling, MST1/2 is activated after interaction with SAV1. This activated complex then phosphorylates LATS1/2 and MOB1 independently before forming a complex. Activated LATS1/2 phosphorylates YAP and TAZ thus preventing their translocation into nucleus. In the event where YAP and TAZ are not phosphorylated, YAP/TAZ travel into nucleus then serve as coactivators for TEA-domain family member (TEAD) group to promote transcriptional activity.

One of the effectors of Hippo signaling, Yes-associated protein (YAP) plays a crucial role in promoting epithelial regeneration of intestine (Cai et al., 2010). In human clinical samples, overexpression of YAP was observed in CRC patients with shorter lengths of survival (Wang et al., 2013a; Wang et al., 2013b).

Crosstalk of signaling pathway occurs when one signaling pathway affects another. This phenomenon happens because the affected pathways share one or more common components. Crosstalk of signaling pathways is

important in biological system as this can enhanced the effects of signal transduced.

Human intestine is a complex biological system involving tight control of various signaling pathways to maintain the proliferation, differentiation and apoptosis of intestinal epithelial cells. The activation of both, Wnt and Notch signalings, are important in preserving the multipotency of progenitor cells in the intestinal crypts. When the progenitor cells lose Wnt signal, this population of cells will differentiate into absorptive cells. On the other hand, when progenitor cells lose the Notch signal, they differentiate into secretory cells (Crosnier et al., 2006). Hippo signaling is not involved in the development of intestine but was found to be an important player in sustaining the proliferation and maintenance of epithelial lining. A possible role between Hippo and Wnt signaling was discovered by Camargo *et al.*, where Hippo signaling might be able to inhibit Wnt signaling through the interaction of cytoplasmic YAP (Yes Associated Protein), effectors of Hippo signaling, with dishevelled, a protein connects Wnt signals from receptors to downstream effectors. In the event where YAP is activated in intestine, there will be an expansion of multipotent undifferentiated progenitor cells. When YAP was inactivated, progenitor cells resume the ability to differentiate (Camargo, Gokhale, Johnnidis, Fu, Bell, Jaenisch, et al., 2007).

In CRC, the most studied signaling pathway is the Wnt signaling pathway. This pathway has been well linked to other pathways such as TGFβ (Mishra et al., 2005), and ERK (Kim et al., 2007). In comparison, the study of relationship between Wnt signaling pathway with Notch and Hippo signaling pathways are relatively new and there is limited research. The crosstalk between Wnt-Notch, and, Wnt-Hippo has been published on cell biology and other diseases such as breast cancer, leukemia but the literature on colorectal carcinoma is limited. Furthermore, less attention has been given to study the relationship between Wnt-Notch and Wnt-Hippo signaling pathways in primary colorectal tumours. Understanding the crosstalk between Wnt, Notch and Hippo signaling will improve the understanding of pathogenesis of CRC. In addition, this information will be valuable in providing new insights for further investigation and new therapeutic strategies.

Microsatellite instability (MSI) is caused by impaired DNA mismatch repair (MMR). The defectiveness of MMR leads to genomic instability causing insertion and deletion in stretches of short tandem DNA repeats (microsatellites) as well as nucleotide substitutions throughout the genome (Thibodeau et al., 1993). In CRC, approximately 15% displayed MSH-H status. MSH-H tumours have two or more instable markers in the National Cancer Institute (NCI) recommends a microsatellite panel (NCI panel) consisting of two mononucleotide repeats (BAT26 and A4725) and three dinucleotide repeats (D5S346, D2S123, and D17S250). CRCs with MSH-H do not respond well to 5-fluorouracil (5-FU) based chemotherapy (Webber

et al., 2015). As a result, MSI status is considered as predictive biomarker in personalized treatment for CRC patients (Gatalica et al., 2016).

The crosstalk between Wnt-Notch, Wnt-Hippo and Notch-Hippo signaling pathways have been studied separately in CRC previously. However, the relationship between three signaling pathways study together was not examined. Therefore, elucidating the relationship between biomolecules of Wnt, Notch and Hippo signaling pathways are important for understanding the pathogenesis of CRC. The interaction between the main biomolecules in each signaling pathways (Wnt – APC and β-catenin, Notch – NICD1 and Hes1 and Hippo – YAP) would be interesting to study and might provide a better understanding to the relationship between theses signaling pathways.

The hypotheses of this study are:

1. Abnormal expression of biomolecules in Notch and Hippo signaling pathways occur at early stage of colorectal cancer.
2. Abnormal expression of biomolecules in signaling pathways are associated with MSI status of colorectal cancer.
3. YAP in Hippo signaling pathway is correlated with biomolecules of Wnt and Notch signaling pathways.

This study attempts to elucidate the relationship between three signaling pathways, Wnt-Notch-Hippo, simultaneously using clinical samples.

The objectives of this study are:

1. To determine the abnormal biomolecule expression of Wnt (Adenomatous Polyposis Coli (APC), β-catenin, p-GSK3β, DKK1), Notch (Notch 1, Notch Intracellular Domain 1 (NICD1), Hes 1, FBXW7) and Hippo (Yes-Associated-Protein (YAP)) signaling pathways between colorectal carcinoma tissues and apparently normal adjacent colon tissues.
2. To determine the possible relationship between Wnt, Notch and Hippo signaling pathways in colorectal carcinoma.
3. To determine microsatellite instability (MSI) status in colorectal carcinoma.
4. To determine the relationship of reduced APC immunoreactivity and *APC* truncation mutations.
5. To associate MSI with mutations in *KRAS, EGFR, PIK3CA, NRAS, p53, PTEN* and *BRAF* in colorectal cancer.

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