UNIVERSITI PUTRA MALAYSIA

PROTEIN EXPRESSION AND GENE ANALYSES OF HER2, NM23, AND K-RAS IN GASTRIC CANCER AND HELICOBACTER PYLORI-ASSOCIATED GASTRITIS

NURULHAFIZAH SAMSUDIN

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By

NURULHAFIZAH SAMSUDIN

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

January 2012

DEDICATION

I would like to dedicate my thesis to my beloved parents and family

Abstract of the thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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NURULHAFIZAH SAMSUDIN

January 2012

Chair: **Hairuszah Ithnin, MD, MPATH, AMM**

Faculty: **Faculty of Medicine and Health Sciences**

Gastric cancer is ranked as the fourth most common cancer worldwide and the seventh most common cancer in the Malaysian population. Due to its vague and nonspecific symptoms, over 80% of gastric cancer cases were detected in advanced stage, leading to poor survival rate in the patients. Increasing evidence have shown that studies on the molecular biology aspects of *Helicobacter pylori*-associated chronic gastritis, which is a precursor of gastric cancer, may improve the early diagnosis of gastric cancer. To date, the existing evidence, however, have yet to determine the specific molecular biomarkers that may assist in the diagnosis of early gastric cancer. This preliminary study was done to investigate the role of HER2, nm23 and K-Ras as possible molecular biomarkers in gastric cancer and *H. pylori*-associated chronic gastritis. A total of 32 cases of gastric cancer and 62 cases of *H. pylori*-associated chronic gastritis were analyzed using immunohistochemical staining to investigate the protein expressions of HER2, nm23

and K-Ras. Mutational analysis on 15 cases of gastric cancer and 10 cases of *H. pylori*-associated chronic gastritis with prominent alterations in protein expressions was performed using polymerase chain reaction and direct sequencing. Our study demonstrated significant increase in the protein expression of nm23 in 62.5% (20/32) of gastric cancer and 33.9% (21/62) *H. pylori*-associated chronic gastritis and K-Ras in 62.5% (20/32) of gastric cancer and 24.1% (15/62) of *H. pylori*-associated chronic gastritis using Mann-Whitney U test ($P < 0.05$). The HER2 was overexpressed in 25.0% (8/32) cases of gastric cancer. However, none of the *H. pylori*-associated chronic gastritis (0.0%; 0/62) showed HER2 positivity. Using Spearmann's rank correlation, age was significantly correlated with the nm23 expression in *H. pylori*-associated chronic gastritis ($P = 0.002$). Gender was significantly correlated with the K-Ras expression in gastric cancer ($P=0.026$). For the mutational analysis, no mutation was detected in the HER2 and K-Ras gene. Only one gastric cancer case (6.7%) showed a genetic variation with a C → A transition in the exon 1 of the nm23 gene. In conclusion, our findings suggest that nm23 and K-Ras may play role as possible early biomarkers in gastric cancers and precancerous lesions since significant increase was observed in their protein expressions. However, the absence or low incidence of mutations may indicate that mutations in HER2, nm23 or K-Ras gene have insignificant role in the progression of gastric cancer. Further studies should be performed to further elucidate the role of HER2, nm23 and K-Ras as biomarkers in gastric cancer.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Master Sains

EKSPRESI PROTEIN DAN ANALISIS GEN HER2, NM23, DAN K-RAS DALAM KANSER PERUT DAN *HELICOBACTER PYLORI*- GASTRITIS

Oleh

NURULHAFIZAH SAMSUDIN

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Kanser perut telah disenaraikan sebagai kanser keempat tertinggi di dunia dan kanser ketujuh tertinggi di kalangan penduduk Malaysia. Oleh kerana simptomnya yang samar dan tidak spesifik, lebih 80% kes kanser perut dikesan di peringkat akhir, membawa kepada kadar survival pesakit yang rendah. Peningkatan bukti yang menunjukkan bahawa kajian tentang aspek biologi molekul berkaitan *Helicobacter pylori*-gastritis kronik, yang mana merupakan prekursor kanser perut, boleh membantu dalam meningkatkan diagnosis awal kanser perut. Sehingga kini, bukti-bukti yang sedia ada, bagaimanapun, masih belum dapat menentukan biomarker molekular khusus yang boleh membantu di dalam diagnosis awal kanser perut. Kajian permulaan kami ini dilakukan untuk menyiasat peranan HER2, nm23 dan K-Ras sebagai calon biomarker molekular bagi kanser perut dan *H. Pylori*-gastritis kronik. Sebanyak 32 kes kanser perut dan 62 kes *H. Pylori*-gastritis kronik telah dianalisis menggunakan teknik immunohistokimia

untuk mengkaji ekspresi protein HER2, nm23 dan K-Ras. Analisis mutasi pada 15 kes kanser perut dan 10 kes *H. Pylori*-gastritis kronik yang menunjukkan perubahan yang jelas dalam ekspresi protein dilakukan dengan menggunakan teknik polimerase chain reaction dan sekuensing-langsung. Kajian kami menunjukkan peningkatan ketara di dalam ekspresi nm23 dalam 62.5% (20/32) kanser perut dan 33.9% (21/62) *H. Pylori*-gastritis kronik dan K-Ras dalam 62.5% (20/32) kanser perut dan 24.1% (15/62) *H. Pylori*-gastritis kronik berdasarkan analisa Mann-Whitney U ($P < 0.05$). Peningkatan ekspresi HER2 telah dilihat dalam 25.0% (8/32) kes kanser perut. Walau bagaimanapun, tiada kes *H. Pylori*-gastritis kronik yang menunjukkan kepositifan bagi HER2 (0.0%; 0/62). Berdasarkan analisa kolerasi Spermann, umur menunjukkan perkaitan jelas dengan ekspresi nm23 dalam *H.pylori*-gastritis kronik (P=0.002). Jantina menunjukkan perkaitan jelas dengan ekspresi KRAS dalam kanser perut ($P = 0.026$). Untuk analisis mutasi, tiada sebarang mutasi dikesan dalam gen HER2 dan KRAS. Hanya satu kes kanser perut (6.7%) menunjukkan variasi genetik dengan peralihan C →A dalam exon 1 bagi gen nm23. Sebagai kesimpulan, penemuan kami menunjukkan bahawa nm23 dan K-Ras mungkin memainkan peranan sebagai biomarker bagi kanser perut tahap awal dan juga luka tahap pra-kanser sepertimana yang telah diperhatikan dalam peningkatan ekspresi protein-protein tersebut. Walau bagaimanapun, kajian kami juga membuktikan bahawa ketiadaan atau kejadian mutasi yang rendah menunjukkan bahawa mutasi dalam gen HER2, nm23 atau K-Ras mempunyai peranan kurang penting dalam perkembangan kanser perut.Kajian lanjut perlu dilakukan bagi menjelaskan lagi peranan HER2, nm23 dan K-Ras biomarker dalam kanser perut.

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Thank you very much.

I certify that a Thesis Examination Committee has met on 26 January 2012 to conduct the final examination of Nurulhafizah binti Samsudin (Shamsuddin) on her thesis entitled "Protein Expression and Gene Analyses of HER2, NM23 and K-Ras in Gastric Cancer and *Helicobacter pylori*-Associated Gastritis" in accordance with the Universities and University College Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The committee recommends that the student be awarded the Master of Science.

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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 Master of Science**.** The members of the supervisory committee were as follows:

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DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been dully acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

NURULHAFIZAH SAMSUDIN

Date: 26 January 2012

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

g	Gram
***n*g**	Nanogram
µl	Microlitre
ml	Millilitre
cm	Centimetre
µm	Micrometer
bp	Base pair (nucleotide)
rpm	Revolutions per minute
°C	Degree Celsius
%	Percentage
<	Less than
>	More than
≥	Equal to or more than
±	Approximately
=	Equal to

/	Out of
-ve	Negative
+ve	Positive
et al.	And others
AJCC	American Joint Committee on Cancer
APC	Adenomatous polyposis coli
cagPAI	Pathogenicity island
CT	Computed tomography
CRC	Clinical Research Center, Malaysia
DNA	Deoxyribonucleotide acid
ECL	Enterochromaffin-like
EGFR	Epidermal growth factor receptor
EMR	Endoscopic mucosal resection
ERK	Extracellular regulated kinase
EUS	Endoscopicultrasonography
FFPE	Formalin-fixed, paraffin embedded
FISH	Fluorescence *in situ* hybridization

GANT	Gastrointestinal autonomic nerve tumor
GC	Gastric cancer
GIST	Gastrointestinal stromal tumors
GTP	Guanosine triphosphate
H. pylori	*Helicobacter pylori*
HER2	Human Epidermal Growth Factor Receptor 2
HIER	Heat induced epitope retrieval
HPCG	*H. pylori*-associated chronic gastritis
IARC	The International Agency for Research
K-Ras	V-Ki-ras2 Kirsten rat sarcoma viral oncogene
KSR	Kinase suppressor of Ras
MAPK	Mitogen-activated protein kinase
MEK	Methyl ethyl ketone
MSI	Microsatellite instability
NIH	National Institute of Health
nm23	Human nonmetastatic clone 23
OGDS	Oesophagogastroduodenoscopy

PCR	Polymerase chain reaction
PI3K-Akt	Phosphoinositide 3-kinase/Akt
PMNs	Polymorphonuclear leukocyte
QV	Quality value
Ras	Rat Sarcoma
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
SEER	The United States' Surveillance, Epidemiology, and End Results
TNM	Depth of tumor invasion; involvement of local or distant lymph nodes; M distant metastasis
UICC	Union for International Cancer Control
VacA	Vacuolating cytotoxin
WHO	World Health Organization

CHAPTER I

INTRODUCTION

1.1 Background

Gastric cancer refers to a malignant growth in the stomach. It may develop as a result of abnormal cell division due to mutations of certain genes, or a prolonged exposure towards carcinogenic agents. Based on the cellular origin of the growth, gastric cancer can further be classified into several types including gastric adenocarcinoma, gastric lymphoma and gastric sarcoma.

Gastric adenocarcinoma is the malignant growth that originates from the glandular cells of the stomach. Adenocarcinoma of the stomach accounts for approximately 90% of gastric cancer (Rotterdam & Enterline, 1989; Kelley & Duggan, 2003) and 10% of cancers worldwide (Ferlay *et al.*, 2004). It can be divided into two groups based on Lauren's classification: intestinal-type adenocarcinoma and diffuse-type adenocarcinoma (Lauren, 1965; Roukos *et al.*, 2002). The remaining of the percentage comprised of gastric lymphoma (about 2-7%) and gastric sarcoma (Rotterdam & Enterline, 1989). Gastric lymphoma originates from lymphoid cells, whereas, gastric sarcoma originates from mesenchymal tissues.

Gastric cancer is particularly common in countries like Korea, Japan, South America, Ukraine and Russian Federation (Bertuccio *et al.*, 2009). It is ranked as the

fourth most common cancer worldwide and is the seventh most common cancer affecting the local population in Malaysia (Parkin *et al.*, 2005; Malaysian Cancer Statistics., 2006). It is not as common as other types of cancer but it continues to carry high morbidity rate. Its nonspecific symptoms that resemble other benign gastric conditions such as vomiting, indigestion, and stomach discomfort often cause the cancer to develop undetected. Hence, more complex investigations are needed for proper diagnosis.

Individuals with high risk factor for gastric cancer include being male, elderly, cigarette smokers and patients suffering from chronic gastritis with intestinal metaplasia or pernicious anemia (Kelley & Duggan, 2003). In addition to that, long-term *Helicobacter pylori*-associated chronic gastritis is also believed to be a precursor of gastric cancer. The International Agency for Research on Cancer (IARC) has categorized *H. pylori* in Group 1 carcinogen (IARC, 1994). Its infection is allegedly responsible for 63% of all worldwide cases of non-cardia gastric cancer and may increase the incidence rate of gastric cancer by a factor of 6 (Parkin *et al.*, 2005). The infected normal tissue may progress into several intermediate stages like chronic gastritis, gastric atrophy, intestinal metaplasia, dysplasia and finally gastric cancer (Correa & Shiao, 1994: Milne & Offerhaus, 2010).

There is a need to search for biomarkers to allow the detection of cancer especially at early stage. This is proven important since in Malaysia alone, it is estimated that 82% of gastric cancer patients were diagnosed with Stage IV (Kandasami

et al., 2003). In general, for solid cancers such as gastric cancer, the prognosis and survival depends mainly on stage at diagnosis (Sant *et al.*, 2009). Analysis of gastric cancer biomarkers in patients with *H. pylori*-associated chronic gastritis may prove crucial since *H. pylori*-associated chronic gastritis is a precursor for gastric cancer and approximately 50% of the world population and 90% of the developing countries population are infected by the bacteria (World Cancer Report, 2008).

In this study, we analyzed Human epidermal growth factor receptor 2 (HER2), Nonmetastatic protein-23 (nm23), and v-Ki-ras2 Kirsten rat sarcoma viral oncogene (K-Ras) in gastric cancer and *H. pylori*-associated chronic gastritis. These proteins are involved in the Mitogen-activated protein kinase (MAPK/ERK) pathway and are responsible in facilitating and promoting cell division in normal tissue. In cancer, HER2 and K-Ras were found to have the ability to promote neoplasm due to their oncogenic properties (Juhl *et al.*, 1997: Gong *et al.*, 1999). Similarly, although nm23 protein has been recognized as a metastatic suppressor protein, a few studies have discovered its role in cancer progression and suppression of early step of carcinogenesis (Stahl *et al.*, 1991; Chow *et al.*, 2000). Hence, the aim of our study was to evaluate the status of HER2, nm23 and K-ras protein expression in gastric cancer.

The protein and genetic analysis of HER2, nm23, and K-Ras in gastric cancer have never been studied in Malaysian population. Moreover, previous findings have found that mutations in signalling components downstream of the MAPK/ERK pathway, such as mutations in HER2, nm23, and K-Ras, may slow or stop suppressive

therapy in gastric cancer (Roukos, 2010). Therefore, further understanding of HER2, nm23, and K-Ras is important since alterations in these proteins might have significant effects on gastric cancer progression and therapy.

From this study, analysis of protein expression may give some understanding on the role of *H. Pylori*-associated chronic gastritis as precursors for gastric cancer. In addition to that, genetic analysis of HER2, nm23, and K-Ras may provide some information on possible genetic alterations of these genes in gastric cancer. Correlation between protein and genetic analyses of these genes may provide some preliminary information that might be important for future research especially on diagnostic, prognostic and therapeutic biomarkers of gastric cancer.

In conclusion, molecular biomarker research on HER2, nm23 and K-Ras may open the possibility for early gastric cancer detection. Problem relating to gastric cancer is that due to late diagnosis of gastric cancer, patient survival rate is still relatively very low despite rapid improvements in cancer drugs and therapy. In fact, even with substantial increases in the cancer drugs or therapy, little is known about the effectiveness of the new treatment on different types of patients' genetics and backgrounds without the use of cancer biomarkers. Hence, in this study, we analyzed HER2, nm23 and K-Ras as possible biomarkers in gastric cancer. We hypothesize that the comparison of analyses on HER2, nm23 and K-Ras in gastric cancer cases with *H. pylori*-associated chronic gastritis cases could lead to the discovery of possible biomarkers for the detection of early gastric cancer.

1.2. Problem statement

The progression of *H. pylori*-associated chronic gastritis into gastric cancer, through several intermediate stages like gastric atrophy, intestinal metaplasia, and dysplasia, has been proposed long ago by Correa & Shiao (1994) and Milne & Offerhaus (2010). Many current studies are focusing on the molecular biomarkers for gastric cancer in order to understand the underlying factors that contribute to carcinogenesis. However, up until now, there is still no appropriate biomarker for early diagnosis of gastric cancer.

1.3. Research hypothesis

1.3.1 If HER2, nm23, and K-Ras have role as early molecular markers, then their protein expression should show significant increase in both gastric cancer and *H. pylori*-associated chronic gastritis.

1.3.2 If *H. pylori* infection has role in inducing activating mutation, then activating mutation may be the reason for HER2, nm23 and K-Ras overexpression.

1.4. Research Objectives

1.4.1 General objective:

To determine HER2, nm23, and K-Ras role as possible diagnostic biomarkers in gastric cancer.

1.4.2 Specific Objectives:

a. To determine protein expressions of HER2, nm23, and K-Ras using immunohistochemical analysis in gastric cancer and *H. pylori*-associated chronic gastritis.

b. To identify genetic alterations in HER2, nm23, and K-Ras by using gel electrophoresis and DNA sequencing in gastric cancer and *H. pylori*-associated chronic gastritis.

c. To correlate the protein expressions and genetic alterations of HER2, nm23, and K-Ras in gastric cancer and *H. pylori*-associated chronic gastritis.

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