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Nomor : 88/UN4.20/PL.09/2016 06 Januari 2016
Lamp. : 1 (satu) exp.
Perihal : **Penerimaan Proposal Penelitian Lanjutan untuk Pendanaan Tahun 2016.**

Yth. Ketua Tim Peneliti
Hibah Desentralisasi dan Kompetitif Nasional Tahun 2016
Universitas Hasanuddin
di
Makassar.

Dengan hormat, merujuk surat Direktur Riset dan Pengabdian Masyarakat, nomor 3287/E5.2/PL/2015 tanggal 31 Desember 2015 perihal seperti pada pokok surat, kami ucapkan Selamat Atas Dilanjutkannya Penelitian Saudara.

Sehubungan dengan hal tersebut, kiranya Saudara (Daftar Terlampir), **segera mengunggah proposal penelitian yang dimaksud melalui SIMLITABMAS** untuk diproses lebih lanjut.

Atas perhatian dan kerjasama Saudara disampaikan terima kasih.

Ketua,

Prof. Dr. Ir. H. Sudirman, M.Pd
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1. Rektor Unhas
2. Wakil Rektor I Unhas
3. Ketua Dewan Riset LPPM Unhas

NO	Perguruan Tinggi	NIDN	Nama	Skema	Judul
312	Universitas Hasanuddin	0012054502	SJAMSUDDIN RASYID	MP3EI	Model Peningkatan Produktivitas Lahan Kering-Kritis melalui Teknologi Integrasi Corn-Beef dengan Zero Waste di Kabupaten Pinrang Provinsi Sulawesi Selatan.
313	Universitas Hasanuddin	0010087107	SUHARDI	MP3EI	Penyediaan Kadar Air Tanah secara Alami dan Menekan Erosi dengan Penerapan Teknologi Zero Run-off untuk Mendukung Budidaya Tanaman Kakao secara Berkelanjutan
314	Universitas Hasanuddin	0029126302	SUMBANGAN BAJA	Ipteks	PENGEMBANGAN SISTEM USER FRIENDLY INFORMASI GEOSPASIAL PEWILAYAHAN KOMODITAS (SUFIG-WILKOM) UNTUK MENDUKUNG PROGRAM BANGUN DESA
315	Universitas Hasanuddin	0003076003	SYAMSU ALAM	Unggulan PT	ANALISIS MODEL DAN STRATEGI PENGEMBANGAN USAHA DAN PERAN SEKTOR INFORMAL DI SULAWESI SELATAN (Kasus Usaha Sektor Informal di Kota Makassar dan Kota ParePare)
316	Universitas Hasanuddin	0023095202	SYAMSUDDIN HASAN	Ipteks	PENINGKATAN PRODUKTIVITAS PADANG PENGGEMBALAAN KRITIS MELALUI PEMANFAATAN BIOLOGICAL NITROGEN FIXATION (BNF) DAN INTRODUKSI SAPI POTONG DI KABUPATEN SIDRAP PROVINSI SULAWESI SELATAN
317	Universitas Hasanuddin	0030037403	UPIK ANDERIANA MISKAD	KLN	IDENTIFY AND ANALYZE MOLECULAR MARKERS IN THE PROGRESSION AND METASTASIS OF COLORECTAL CANCER; Evaluation of Protein Regenerating Liver-3 (PRL-3) as an emerging marker of carcinogenesis and its interact with other markers (Integrin β1, E Cadherin, MMP2, MMP9, VEGF A, VEGF C and EGFR)
318	Universitas Hasanuddin	0002036004	WAHYU HARYADI PIARAH	Unggulan PT	Rancangbangun Prototipe Mesin Pendingin Mini berbasis ELemen Peltier sebagai Pompa Kalor tanpa Refrigeran
319	Universitas Hasanuddin	0017117505	YUSNITA RIFAI	Ipteks	Pemodelan molekul dan analisis hidrolisis in vitro dan in vivo senyawa sintetik MMEO inhibitor Glioma
320	Universitas Andalas	0011075012	ABDI DHARMA	Hibah Pasca	EKSPLORASI POTENSI DAN APLIKASI MIKROALGA SEBAGAI SUMBER PANGAN, PAKAN DAN BIOENERSI

SURAT KETERANGAN TANGGUNGJAWAB MUTLAK

Yang bertandatangan di bawah ini :

Nama : dr. Upik Anderiani Miskad, S.Ked., Ph.D
Jabatan : Ketua Pelaksana/Dosen Fak. Kedokteran Unhas

Menyatakan bahwa :

1. Saya telah menerima dana tahap II Program Penelitian Tahun 2016 tahun 2016 sebesar Rp. 45.600.000,- (Empat Puluh Lima Juta Enam Ratus Ribu Rupiah) dan menggunakannya sesuai dengan peruntukannya.

2. Saya bertanggungjawab penuh atas pengelolaan administrasi keuangan kegiatan tersebut sesuai dengan peraturan perundang-undangan yang berkaitan dengan pengelolaan keuangan pemerintah yang berlaku dan berdasarkan persetujuan anggaran sebagaimana yang dituangkan dalam surat perjanjian kerjasama antara Pejabat Pembuat Komitmen Riset dan Pengabdian Masyarakat Direktorat Jenderal Penguatan Riset dan Pengembangan Kementerian Riset dan Pendidikan dengan Ketua LP2M Universitas Hasanuddin tentang "Pelaksanaan Pekerjaan Program Penelitian Tahun 2016" No. 019/SP2H/LT/DPRM/II/2016 tanggal 17 Februari 2016 untuk kegiatan "Identify and Analyze Molecular Markers in the Progression and metastasis of colorectal cancer
3. Evaluation of protein regenerating Liver-3 (PRL-3) as an emerging marker of carcinogenesis and its interact with other markers (Integrin B1, E Cadherin, MMP".

4. Bersedia menyampaikan laporan keuangan secara rutin kepada Pejabat Pembuat Komitmen selaku pemberi dana dan Lembaga Penelitian dan Pengabdian Kepada Masyarakat Unhas sebagai institusi penanggungjawab kegiatan.

5. Bersedia diperiksa oleh aparat pemeriksa fungsional bilamana diperlukan.

Mengarsipkan semua dokumen keuangan secara tertib dan teratur.

Demikian surat keterangan tanggungjawab mutlak ini dibuat dengan sebenarnya untuk dipergunakan seperlunya.

Makassar, Januari 2017
Ketua

dr. Upik Anderiani Miskad, S.Ked., Ph.D

Code/ Field of Science: 306/ Basic Medical Science

FINAL REPORT

INTERNATIONAL RESEARCH COLLABORATION

AND SCIENTIFIC PULICATION

IDENTIFY AND ANALYZE MOLECULAR MARKERS IN THE PROGRESSION AND METASTASIS OF COLORECTAL CANCER

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4. Prof. Alfred Lam, MD, PhD (Griffith University Australia)

HASANUDDIN UNIVERSITY

2016

HALAMAN PENGESAHAN

Judul	: IDENTIFY AND ANALYZE MOLECULAR MARKERS IN THE PROGRESSION AND METASTASIS OF COLORECTAL CANCER;Evaluation of Protein Regenerating Liver-3 (PRL-3) as an emerging marker of carcinogenesis and its interact with other markers (Integrin 1, E Cadherin, MMP2, MMP9, VEGF A, VEGF C and EGFR)
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ABSTRACT

Background: Colorectal cancer is the third most common malignant neoplasm worldwide. PRL-3 (phosphatase of regenerating liver-3/PTP4A3) was reported participates in the progression of colorectal cancer and play a role in epithelial to mesenchymal transition by down regulate the expression of E- cadherin.

Aims: To clarify the molecular mechanisms that involved in colorectal cancer development and progression, we investigate the expression of PRL-3, MMP2, VEGF, EGFR and E-Cadherin in colorectal cancer and correlate the expression with the clinicopathologic parameters.

Methods: Expression of PRL-3, MMP2, VEGF, EGFR and E-Cadherin in colorectal cancer in 76 colorectal cancer specimens were detected by immunohistochemistry.

Results: Among colorectal cancer specimens examined, there were 30 (39.5%) well differentiated, 36 (47.4%) moderately differentiated and 10 (13.2%) poorly differentiated CRC. There were a significant correlation between histological grading and PRL-3 ($p=0.044$), MMP2 ($p=0.040$), E-cadherin ($p=0.039$), VEGF (0.020) and EGFR (0.009)expression, respectively. The expression of PRL-3 was significantly correlated with the expression of MMP2 ($p<0.001$), VEGF ($P<0.001$), EGFR ($p<0.001$), and E cadherin in colorectal cancer ($p=0.003$). The result showed that the higher PRL-3 expression the more frequent of MMP2, VEGF and EGFR expression but the lower/ abnormal expression of E-cadherin in colorectal cancer.

Conclusions: These study strongly suggest that PRL-3 may play a role to up regulate the expression of MMP2, VEGF and EGFR, and in other hand down regulate the expression of E cadherin in the development and progression of colorectal cancer.

Key words: PRL-3, MMP2, VEGF, EGFR, E-Cadherin, colorectal cancer, Immunohistochemistry

CHAPTER I

INTRODUCTION

I.1 BACKGROUND

Colorectal cancer is the third most common malignant neoplasm worldwide (Shike M, 1990) and the second leading cause of death due to cancer in the United States (Winawer SJ, 1997). In Indonesia, colorectal cancer is an emerging public health problem and currently ranks among the three highest cancers (Murdani, 2012). In Makassar, South Sulawesi Indonesia during 2010-2011, the incidence of colorectal cancer is increasing and recorded as the most common malignant cancer in Makassar according the pathology based data.

Lack of a colonoscopy screening and lifestyle changes might contribute to it. Diet is clearly implicated in the origin of colorectal cancer, with risk factors for the disease including reduced consumption of vegetables, fiber, and starch and increased consumption of red meat and animal fat. Several hypotheses have been developed to explain these associations (Bruce WR, 2000). High consumption of meat was found in Makassar population since the famous food in Makassar is a meat soup containing mostly gut. Although this lifestyle may contribute to many disease including cancer, but there is no study about correlation between dietary style and development of colorectal cancer in this population.

In the last few decades, there is an increasing interest towards the contribution of genetic-environment interaction in colorectal carcinogenesis. Some studies have indicated that CRC might develop through several different pathways; the three major routes are chromosomal instability (CIN), microsatellite instability (MSI), and inflammatory pathways. An earlier study on clinical epidemiology of CRC in Indonesia showed that the majority of patients were diagnosed between 45 and 50 years old, with a mean age around 47 years old. It is affect more younger population compare to other countries reported. Study on molecular carcinogenesis in colorectal cancer among Indonesian population is still few and need more study to elaborate clinical and pathological as well as molecular marker in colorectal cancer (Murdani, 2012). Despite recent advances in diagnostic and therapeutic measures develop, the prognosis of colorectal cancer patients with distant metastasis still remains poor. In

addition, not a few colorectal cancer patients suffer from the unexpected development of occult metastases, especially in the liver and lung, after the curative resection of their primary tumors. Commonly in Indonesia, the patient with colorectal cancer come to see the clinician when the condition is alredy advanced stage. Mortality rate of colorectal cancer quite high and related to metastasis. Therefore, it is necessary to clarify the molecular mechanisms involved in metastasis and to identify the specific biomarkers of colorectal cancer metastasis. To identify the consistent genetic alterations associated with the transition from primary colorectal cancers to liver metastases, (Saha *et al.* 2001) performed global gene expression profiles using a serial analysis of gene expression approach and found that *PRL-3* (*phosphatase of regenerating liver-3/PTP4A3*) was frequently overexpressed in the liver metastases studied, but expressed at lower levels in primary tumors and normal colorectal epithelium. Recently PRL-3 was reported participates in invasion, migration, metastasis and angiogenesis (Miskad UA, 2004, 2007), but the cascade and which molecular interact with this protein still need to identify.

I.2. RESEARCH RECORD

We started to study this PRL-3 gene and protein in 2003 and alredy published several paper in International journal, cited by other researchear. On the first time, we just checked the expression of PRL-3 protein in gastric cancer. It has been found that this gene has correlated with progression and metastasis of gastric cancer using sample from Japanese population. In Indonesia, gastric cancer is very few compared with colorectal cancer. Surgical operation with gastric cancer is limited. Meanwhile incidence of colorectal cancer increasing in Indonesian population. To the next future, we use colorectal cancer cases to understand the molecular mechanism of PRL-3.

I.3. RESEARCH OBJECTIVE

To understand the molecular mechanism of PRL-3 induce metastasis in colorectal cancer.

1. To identify the expression of PRL-3 gene and protein in colorectal cancer (primary tumor and metastasized colorectal cancer to lymphonode and liver).

2. To identify the expression of MMP2, VEGF, EGFR and E-Cadherin in colorectal cancer.

3. To correlate the expression of PRL-3 with PRL-3, MMP2, VEGF, EGFR and E-Cadherin in colorectal cancer.

4. To analyse the expression of all these protein and clinicopathological parameters of colorectal cancer.

I.4. RESEARCH SIGNIFICANCE

Understanding the oncogenic mechanism of colorectal cancer, may provide the information about novel molecular marker for aggresivenes colorectal cancer, define prognosis and it may provide a new candidate therapeutic target for colorectal cancer. It will influence management of colorectal cancer. The last decade has witnessed exciting new strategies for the diagnosis and treatment of colon cancer, enabling improved patient survival. With the advent of molecular modeling and new tools that predict recurrence, the future will bring more individualized treatment, which ideally will result in improved outcomes.

I.5. OUTPUT/ TARGET

1. Publish research in International Seminar and publish qualified paper in international journal.

2. Extend International collaboration to expand more qualified research.

CHAPTER II

LITERATURE REVIEW

II.1 COLORECTAL CANCER

Colorectal cancer is the third most common type of cancer diagnosed in the United States and is the third most common cause of cancer-related death (Shike M, 1990). The majority of cases are sporadic, with hereditary colon cancer contributing up to 15% of all colon cancer diagnoses.

There are many known risk factors for sporadic CRC, including nonmodifiable and modifiable variables. Preventive measures should be targeted at tobacco use, dietary habits, and weight control. The inflammatory bowel disease (IBD) population is the second major category of patients at increased risk of CRC. The 2 main syndromes accounting for the inherited cases are hereditary nonpolyposis colon cancer (HNPCC) and familial adenomatous polyposis (FAP). The prevalence of HNPCC, is estimated to be 2% to 5%. The syndrome is caused by a germline mutation in 1 of 6 currently identified DNA mismatch repair (MMR) genes: *hMSH2, hMLH1, hPMS1, hPMS2, hMSH3*, and *hMSH6*. Inactivation of these genes leads to the development of short repeats of DNA, known as microsatellites; 90% of the mutations in the MMR genes are found specifically in *hMSH2* and *hMLH1*. Patients with HNPCC have an 80% lifetime risk of developing CRC. HNPCC is differentiated from sporadic colon cancer by a distinctive clinical picture. The average age of cancer diagnosis is much earlier (ie, 47 y vs 63 y), and there is a pattern of both metachronous and synchronous colon cancers, in addition to a high association with other primary tumors (eg, endometrial, ovarian, gastric, small bowel).

Initiation of colon cancer screening in the average-risk patient is indicated at age 50; however, current screening guidelines do not clearly define the optimal modality to perform screening. Sporadic colon cancer is believed to develop from benign lesions that deteriorate into carcinoma over a period of time, thus providing a window for early detection and treatment with the goal of lowering mortality. Between 1975 and 2000, the incidence of colon cancer decreased by 22%, with half of that volume attributed to screening and half to risk-factor modification and improved treatment. The screening methods for CRC are

differentiated between detection and prevention. Fecal occult blood testing (FOBT) and stool DNA testing are methods that detect malignant disease, whereas computed tomography (CT) colonography, sigmoidoscopy, and colonoscopy can detect premalignant lesions (Winawer SJ, 1997).

Sporadic CRC is postulated to follow the adenoma–carcinoma sequence, precipitated by cumulative genetic mutations. Point mutations, altered DNA methylation, gene rearrangements, amplifications, and deletions comprised the most common mutational events that led to 3 described pathways leading to tumorigenesis: (1) gain of function (oncogene activation); (2) loss of function (tumor suppressors/apoptotic pathways); and (3) epigenetic alterations (DNA methylation patterns) (Sarah et al, 2011). CRC is diagnosed either after routine screening or prompted by the onset of new symptoms. Symptoms in CRC are nonspecific and vague, and may include a change in bowel habits, weight loss, abdominal pain, and fatigue. More specific symptoms such as obstruction, bleeding, or perforation may occur, prompting an urgent surgery. The goal of preoperative imaging is to accurately stage patients.

The critical component that determines prognosis in colon cancer remains the pathologic stage (**Table 1**). The variation in survival between early- and late-stage colon cancer underscores the importance of screening and early diagnosis. One well-known biomarker, carcinoembryonic antigen (CEA), is traditionally used postoperatively to monitor for recurrence. It has been suggested that preoperative CEA be incorporated into the TNM staging system for CRC (Sobin LH, 1997).

Table 1: TNM Staging System for Colorectal Cancer

Primary tumor (T)	
T_x	Tumor cannot be assessed
T_{is}	Carcinoma in situ
T_1	Tumor invades submucosa
T_2	Tumor invades muscularis propria

T_3	Tumor invades subserosa
T_4	Tumor directly invades adjacent organs/structures or through the visceral peritoneum

Regional lymph nodes (N)	
N_x	Lymph nodes cannot be assessed
N_0	No lymph node metastases
N_1	Metastases in 1-3 lymph nodes
N_2	Metastases in ≥4 lymph nodes

Distant metastases (M)	
M_x	Metastases cannot be assessed
M_0	No distant metastases
M_1	Distant metastases present

Stage	**TNM classification**	**5-year survival (%)**
I	T_1, T_2	>90
IIA	T_3, T_0	87.5
IIB	T_4, T_0	71.5
IIIA	T_1, T_2, N_1	87
IIIB	T_3, N_1	68.7
IIIC	T_3, T_4, N_1, N_2	47-50
IV	Any T, M_1	27

CHAPTER III

RESEARCH METODOLOGY

III.1. MATERIALS

Tissue samples. 76 paraffin-embedded surgical specimens of primary human colorectal carcinomas, lymph node metastases and liver metastasis were collected from Hasanuddin University Hospital and Wahidin Sudirohusodo Hospital. Informed consent was obtained from all patients. They consisted of men and women with an age range variably. Tumor size was divided in to two group according to maximum diameter. Histological type was classified as follows: well-differentiated tubular adenocarcinoma, moderately differentiated tubular adenocarcinoma, poorly differentiated adenocarcinoma, and mucinous adenocarcinoma. Depth of carcinoma invasion was classified as follows: *T1*, mucosa (m) and submucosa (sm); *T2*, muscularis propria (mp) and subserosa (ss); *T3*, serosa-exposed (se); *T4*, serosa-infiltrating (si). Extent of lymph node metastasis was classified as follow: *N0*, no evidence of lymph node metastasis; *N +* metastasis to lymph nodes; M+ metastasis to Liver.. Limphatic invasion, venous invasion and tumor stage was also defined for clinicopathological features.

Blood Samples. Blood samples from patient with colorectal cancer were collected. These samples were storage in -80 degrees C.

III.2. METHODS

Immunohistochemistry

Consecutive 4 μm sections were cut from each block, deparaffinized with xylene and rehydrated with graded ethanol solutions in deionized distilled water. Serial sections were subjected to hematoxylin and eosin staining to determine histological diagnoses and the remaining sections were processed for the immunohistochemical study. Immunohistochemical staining was performed using the streptavidin-biotin-peroxidase method with labeled streptavidin-biotin (LSAB; Dako, Kyoto, Japan). Briefly, the sections were placed in a glass box filled with 10 mmol/L citrate buffer (pH 6.0), and were autoclaved for 15 min at 125°C. The sections were allowed to cool in the box at room temperature (24°C) for 60 min before being immersed for 15 min in 0.3% H_2O_2 to block endogenous

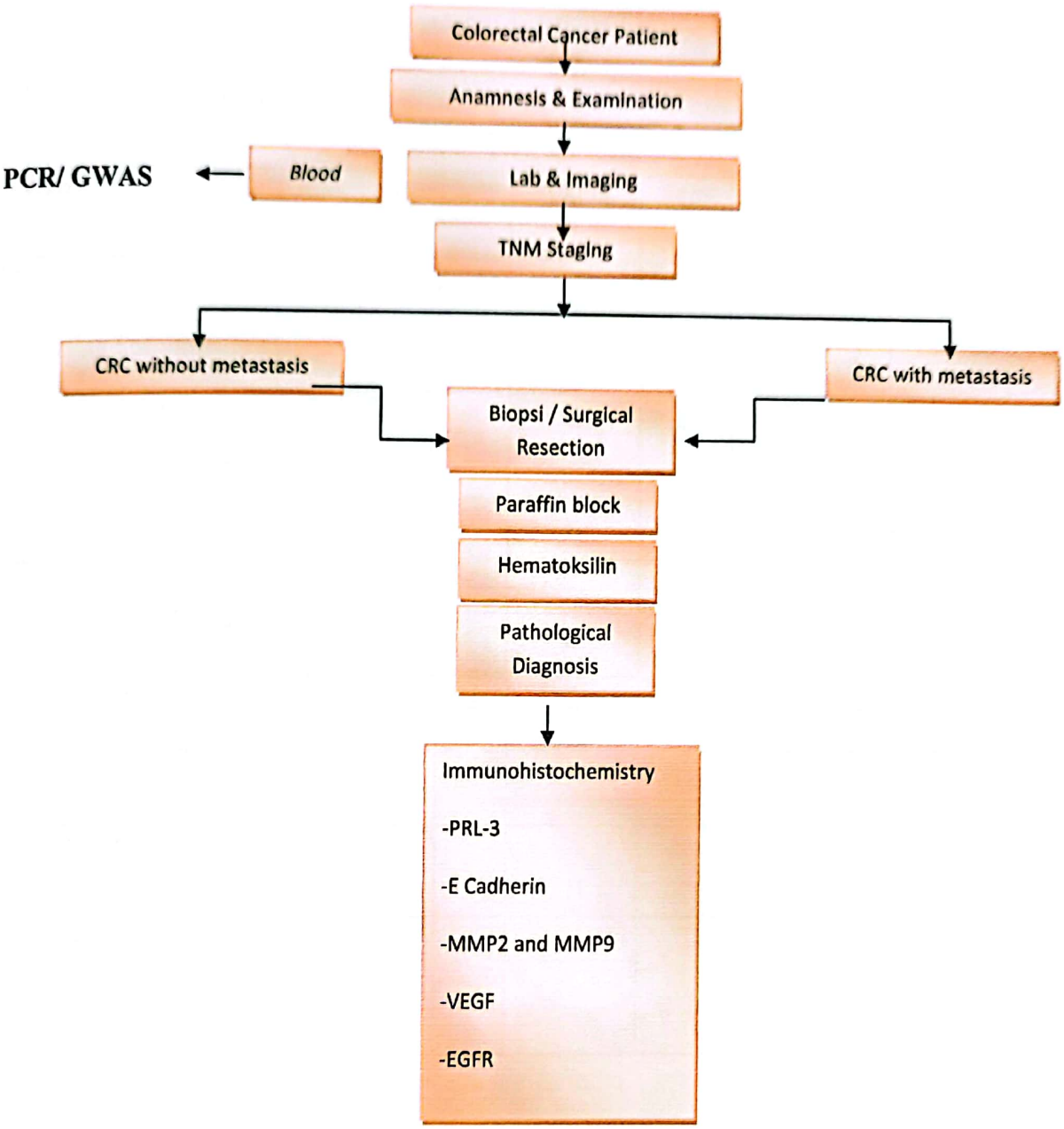
peroxidase, and then for 30 min in avidin-biotin blocking solution to block avidin in the tissue. The monoclonal antibodies, anti-**PRL-3** (1 : 100 dilution, Attogen Bio, anti **E cadherin** antibody (DAKO), anti **MMP2** antibody (R &D), anti **MMP9** antibody (R & D), anti **VEGF** antibody (DAKO) and anti **EGFR** antibody (DAKO) were applied to sections and incubated overnight at 4°C in a moist chamber. Subsequently, sections were biotinylated with goat antirabbit IgG for 30 min and streptavidin conjugated to horseradish peroxidase (DAKO, Kyoto, Japan) for 30 min. Chromogenic fixation was carried out by immersing the sections in the solution of 3,3-diamino-benzidine tetrahydrochloride (DAB) at room temperature (24°C) for 10 minutes until a distinct reaction product was evident microscopically. The sections were then counterstained with Mayer's hematoxylin. Negative control sections were incubated without primary antibody.

Immunoreactivity of antibodies were graded according to the number of stained cells and the staining intensity in individual cells as follows: -, almost no positive cells; +, less than 50% of tumor cells showed weak immunoreactivity; ++, less than 50% of tumor cells showed strong immunoreactivity; +++, over 50% of tumor cells showed strong immunoreactivity. Grades – and + were regarded as weak expression and grades ++ and +++ were regarded as strong expression. Smooth muscle fibers which have strong immunoreactivity were used for internal controls of positive immunoreaction. Immunostaining was evaluated independently by three independent observers who were unaware of the clinical and histological diagnoses, and all of the sections were scored twice to confirm the reproducibility of the results. (Miskad UA, 2004, 2007).

Statistical Analyses.

The relationships between the results of the immunohistochemical study and clinicopathological variable were tested by chi-square test. $p < 0.05$ was regarded as statistically significant.

III. 3. DIAGRAM OF OPERATIONAL RESEARCH



CHAPTER IV

RESEARCH SCHEDULE

VI. 1 RESEARCH SCHEDULE

Month	May	June	July	August	Sept	Oct	Nov	Dec
Preparation	X							
Collecting Specimen		X	X	X	X	X	X	
DNA extraction and Tissue Block Paraffin, Processing and Sectioning				X	X	X	X	X
Immunohistochemistry				X	X	X	X	
Documentation	X	X	X	X	X	X	X	X
Data analyses							X	X
Writing paper								X
Presentation Publication							X	X

DISCUSSIONS

Protein tyrosine phosphatase PRL-3 has been reported to be associated with human colorectal cancer progression. The phosphatase of regenerating liver 3 (PRL-3) protein belongs to the family of tyrosine phosphatases, together with PRL-1 and PRL-2. These proteins have unique COOH-terminal prenylation motif, and involved in a major reaction for the cell, i.e., dephosphorylation of tyrosine residues deactivating enzymes. Although its physiological role is poorly investigated, literature data suggest that PRL-3 takes part in development of tumor and in neoformation, i.e., migration, metastasizing, and angiogenesis.[4-6] However, factors that regulate PRL-3 expression as well as its enzymes are not well known, and researchers are still searching for pathways and processes associated with the protein involvement. Still a few studies have revealed a link between PRL-3 and proteins responsible for cytoskeleton rebuilding. Regulation of cell adhesion is another mechanism of the protein in the promotion of cancer cell growth and invasion.[11,18,19] In this study, we detected the expression of PRL-3 had higher rates of positive expression in poorly differentiated than moderately and well differentiated. Although not just poorly can be metastasized, but this tumor grading reflect the worse prognosis than well or moderately differentiated. We found the significant correlation between high expression of PRL-3 and histological grading of CRC. These results suggest that PRL-3 may play a crucial role in development and differentiation of colorectal cancer.

E-cadherin, a transmembrane adhesion molecule has a function to maintain intercellular adhesiveness. Abnormal expression or decreased expression of E-cadherin cause loss of cell to cell contact, can lead to the detachment of cancer cells from the primary tumor mass and thus increase their invasiveness to stroma and vessels. In this study, expression of E-cadherin

was abnormal and decreasing in cancer area comparing with non neoplastic area. E-cadherin positivity rate was more frequent decrease in tumor with poorly differentiated than moderately and well differentatied. It suggests that abnormal and decreased expression of E-cadherin play a role in progression and tumor differentiation.

PRL-3 seems to be particularly responsible for the development and migration of cancer cells. Wang et al. have been the first to suggest the involvement of PRL-3 in epithelial mesenchymal transition (EMT).[20] They have put forward the hypothesis that PRL-3 activates the Akt pathway through direct inhibition of PTEN (inhibitor for PI3K), which results in GSK-3β inactivation. Then, Liu et al. have presented evidence for PRL-3 involvement in EMT via cadherin-related signaling pathway. Most likely, PRL-3 plays a major role in direct inhibition of the expression of E-cadherin and CDH22 [21]. In our study, we analyzed the immunohistochemical correlation between the expression of PRL-3 and E-cadherin in colorectal cancer and observed a correlation between increased PRL-3 expression and abnormal E-cadherin expression ($P = 0.003$), which indicates that they may interact. We revealed a correlation of positive PRL-3 and abnormal E-cadherin with colorectal cancer. It is likely that an abnormal expression of E-cadherin and an overexpression of PRL-3 are associated with the loss of cell junctions and loosening of cells in this histological type. Thus, PRL-3 and E-cadherin seem to exert an extremely significant effect on the progression of colorectal cancer. We also revealed that PRL-3 expression correlated significantly with the expression of MMP2, VEGF and EGFR. Our findings are compatible with previous studies.[20-22]

In conclusion, these study strongly suggest that PRL-3 may play a role to up regulated expression of MMP2, VEGF, EGFR and down regulate the expression of E-cadherin in the development and progression of colorectal cancer.

PRL-3 might be considered as a new indicator for malignant potential and as a potential therapeutic target in cases of colorectal carcinoma.PRL-3, MMP2, VEGF and EGFR might be a novel molecular marker for aggressive colorectal cancer.

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