Department of Obstetrics and Gynaecology

The University of Hong Kong

Research Activities 2017

The Department

The Department of Obstetrics and Gynaecology consists of 14 academic staff. In addition, there are 12 postdoctoral fellows/research officers/scientific officers and 28 research postgraduate students including 24 PhD and 4 MPhil students. The Department works closely with the Hospital Authority staff in providing clinical service at the Queen Mary Hospital and Tsan Yuk Hospital. Besides teaching undergraduates and providing clinical service, the Department is actively involved in research. The Hospital Authority staff also takes part in teaching medical students and conducting research. There are ample opportunities for graduate students to pursue a research postgraduate degree.

The Department is a tertiary referral centre in Hong Kong for patients with complicated gynaecological problems, endocrine problems, subfertility, gynaecological malignancies, high-risk pregnancies and prenatal diagnosis. The Department runs an assisted reproduction programme and a territory wide prenatal diagnosis laboratory. Because of the expertise in these areas, we have a large number of referrals and there are ample opportunities for clinical and applied research. The laboratories are fully set up for real-time PCR assay, immunoassay, sperm function assay, computer assisted sperm analysis, embryo and stem cell culture, embryo micromanipulation, cryopreservation of biological specimens including sperms, embryos and tissues, molecular biology techniques including gene transfer and automatic DNA sequencing, image analysis, prenatal diagnosis procedures and protein purification. Within the Department, there are altogether 18 PhDs (16 from the University and 2 from the Hospital Authority) who can provide laboratory support in the provision of clinical service as well as basic scientific research. Therefore, adequate support and supervision can also be provided for basic academic research. Indeed there has been an increase in emphasis in recent years in basic research using techniques in molecular biology.

The Department is actively engaged in research in the areas of gynaecological oncology, reproductive medicine, perinatology and prenatal diagnosis. The number of high impact publications has increased progressively in recent years and the Department is well known internationally for some of these research areas. The Department is actively collaborating with other institutions locally, nationally and internationally. The Department has been successful in attracting research grants. The amount of grants awarded has increased progressively in the last few years. Additional funding is also obtained from the supplementary account of the Department. This ensures that there is adequate funding for research activities in the Department.

In this booklet, our research activities and the relevant staff are described. Students interested in pursuing a research degree in the Department can get further information from our research postgraduate coordinator Prof. William S.B. Yeung (Fax: 852-28550947, email: wsbyeung@hku.hk).

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Head of Department

Professor Sharon Cameron, External Examiner of Licensing Examination 2017

20 November, 2017

Staff of University of Hong Kong 2017

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Chair Professor

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Dr. T.H.Y. Leung, BSc *HKUST*; MPhil *CUHK*; PhD *HK*

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Dr. P.W.S. Ma, MBBS *HK*; MRCOG; FHKCOG; FHKAM (O&G); Cert HKCOG (Urogynaecology) up to 3 Jul 2017

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Dr. H.M.C. Chan, MBBS *HK*

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Dr. K. Wong, MBBS *HK*

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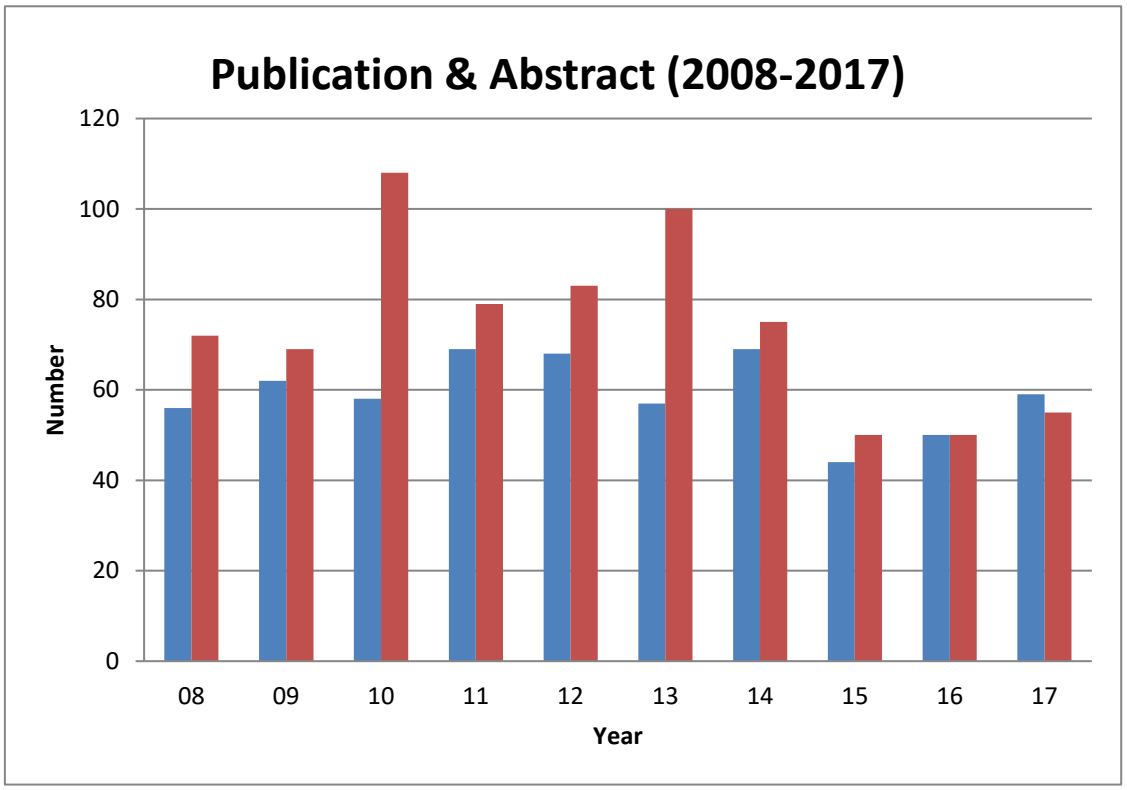
Dr. E.Y.L. Lau, BSc *Hull*; PhD *HK*


Publication & Abstract (2008-2017)
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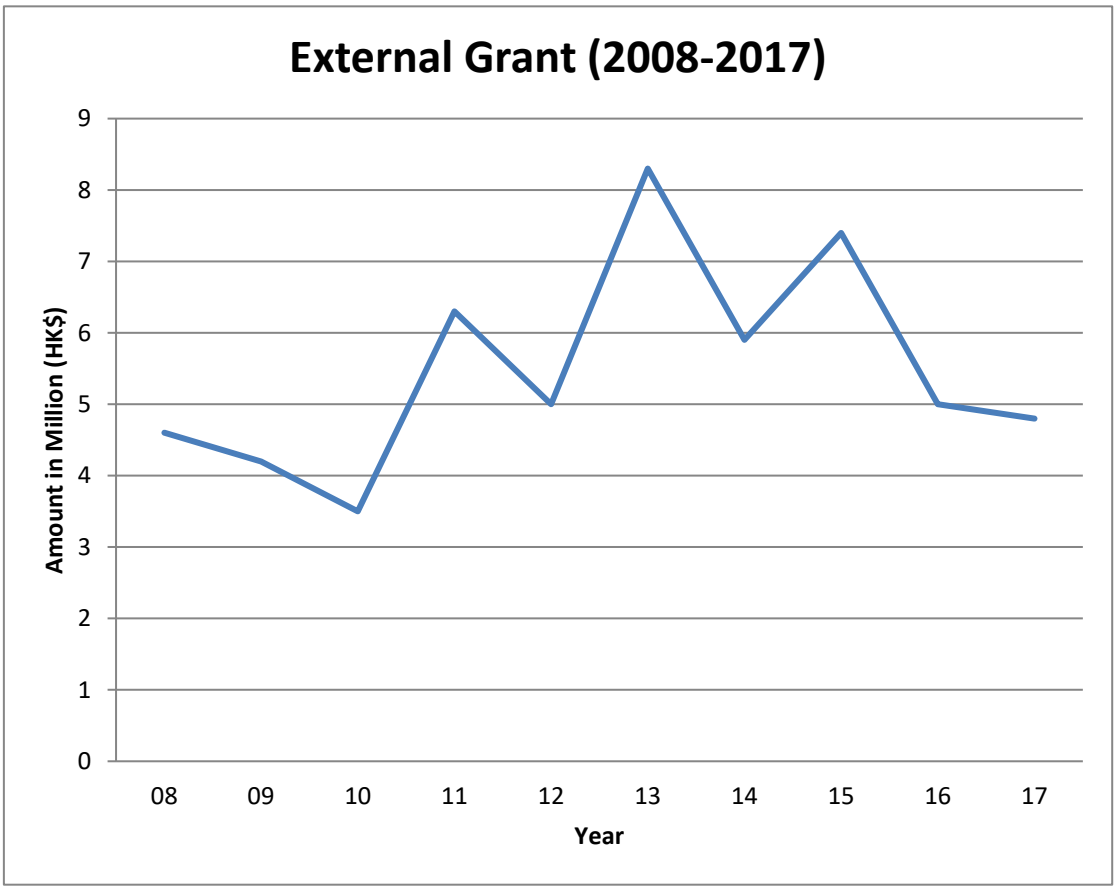
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Gynaecological Oncology

Staff: Prof. H.Y.S. Ngan, Dr. K.K.L. Chan, Dr. K.Y. Tse, Dr M.M.Y. Chu, Dr. S.F. Ngu, Dr. S.S. Liu, Dr. D.W. Chan, Dr. T.H.Y Leung, Dr. Mingo M.H. Yung and Dr. M.K.Y. Siu

Part I - Basic cancer research

1. Tumour protein markers in blood

Tumour cells usually have abnormal gene expressions; and many tumour-specific gene products can be detected in the blood. Therefore, tumour protein markers are widely used as a tool for the diagnostic, prognostic and follow-up tests of various human cancers. Tumour protein marker assays are usually performed using radio-immunoassay or non-radioactive immunoassay such as micro-particle enzyme immunoassay. Clinical evaluation of tumour protein markers in various gynaecological cancers is being carried out in our department. Furthermore, in addition to the conventional approach, we are trying to use the latest proteomics and miRNA array technologies to identify new cancer-specific biomarkers which may be useful as diagnostic and/or prognostic indicators of human cancers. The followings are current studies on tumour markers in various gynaecological malignancies:

A. Serum human chorionic gonadotrophin (hCG) monitoring the gestational trophoblastic diseases;

B. Serum CA125 and HE4 monitoring the carcinomas of the ovary;

C. Serum squamous cell carcinoma antigen (SCC) monitoring the squamous cell carcinomas of the cervix;

D. Serum or plasma miRNAs used as a non-invasive diagnostic approach in monitoring ovarian cancers and cervical cancer.

2. Human papillomavirus and cervical precancerous lesions and carcinomas

Cervical cancer is the second most common cancer in women worldwide. In developing countries, it is the commonest female cancer, contributing to about 80% of all new cases. Molecular and epidemiologic studies have shown that a persistent infection with high-risk human papillomavirus (HPV) is the most important risk factor for both cervical cancer and its precancerous lesions. Recently, we studied and compared the prevalence of HPV infection in

women residing in Hong Kong (HK) and Guangzhou (GZ) and identified the potential risk factors for acquisition of HPV infection in both regions. The overall HPV prevalence was 6.2% and 10% in HK and GZ women with normal cytology, respectively (Figure 1). Women in GZ had significantly higher HPV infection ($p<0.001$) compared to women in HK. The patterns of the age-specific HPV prevalence were also different between the two study cohorts. In HK cohort, women at the age of 20-29 years old had the highest prevalence and a second peak was observed in the age of ≥60 years old. In the GZ cohort, the highest HPV prevalence was also observed in 20-29 years old but declined as the age increased and a second peak was not seen. HPV16 and HPV52 were the most common high-risk types found in the HK and GZ cohorts, respectively. Age was the most consistently observed independent risk factor for HPV infection in the HK cohort, while the number of sexual partners had association in the GZ cohort.

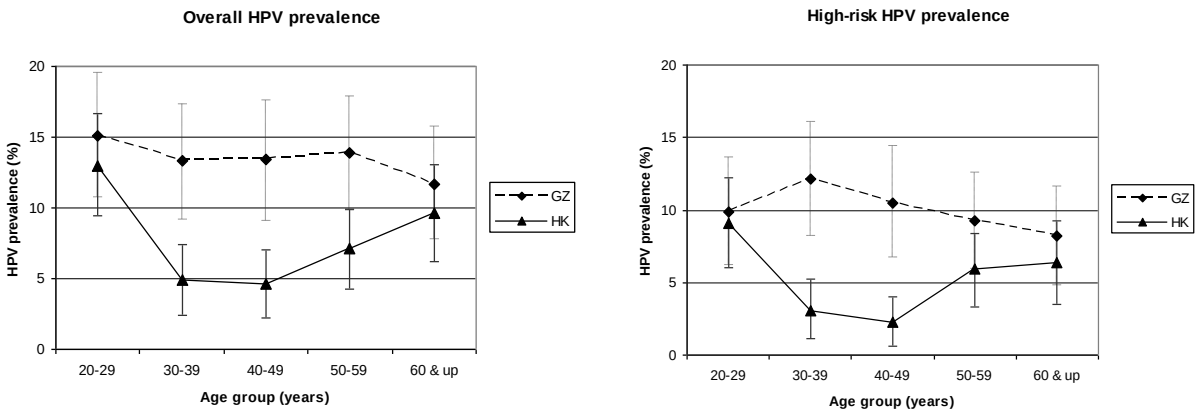

Fig. 1 Comparison of the age-specific overall and high-risk HPV prevalence in five age-groups in the HK and GZ cohorts. (A) Overall HPV prevalence: significant difference in the overall HPV prevalence between the two cohorts in age-groups of 30-39, 40-49 and 50-59 ($p<0.001$, $p<0.001$ and $p=0.007$, respectively, z test). (B) High-risk HPV prevalence: significant difference in the high-risk HPV prevalence between the two cohorts in age-groups of 30-39 and 40-49 ($p<0.001$ and $p<0.001$, respectively, z test). The error bar indicates 95% confidence interval.

As HPV is the causative agent of cervical cancer, a randomized controlled trial has been carried out in our research team to compare concomitant HPV-cytology testing with conventional cytology testing for the detection of precancerous cervical lesion in primary cervical cancer screening in Hong Kong. A total of 12000 women attending cervical cancer screening will be recruited from community in the study. The effect of HPV testing or HPV-cytology co-testing as a primary screening strategy will be evaluated.

3. Tumour suppressor genes and oncogenes

The cDNA array technology and comparative genomic hybridization (CGH) have been used for genome-wide analysis of differential gene expressions in various cancer conditions and large-scale chromosomal abnormalities, respectively. By studying the gene expression profile with cDNA apoptotic array, the p73 gene was found over-expressed in radiosensitive cervical cancers when compared with radio-resistant ones. Over-expression of exogenous p73alpha by transfection in the radio-resistant cells resulted in a significant increase of cellular sensitivity to radiation. Enhanced radio-sensitivity in p73alpha-transfected cells was attributed by increase of cellular apoptosis. Recently, we investigated the role of p73 in ovarian cancer cells in response to chemotherapeutic agent. We observed that TAp73α enhanced cellular sensitivity to cisplatin in ovarian cancer cells via the induction of cell apoptosis and such TAp73 function was irrespective of p53 status. We demonstrated a novel molecular mechanism for TAp73α-mediated cell apoptosis. TAp73α acted as an activator of the c-jun N-terminal kinase (JNK) signaling pathway by up-regulating the expression of its target gene, growth arrest and DNA-damage-inducible protein GADD45α, and subsequently activating mitogen-activated protein kinase kinase-4 (MKK4). Inhibition of JNK activity by a specific inhibitor or small interfering RNA (siRNA) significantly abrogated TAp73-mediated apoptosis induced by cisplatin. Our study suggested that this TAp73-dependent and p53-independent cellular response would play an important role in DNA damage response in ovarian cancer cells, as p53 function was defective in most of these cancer cells.

In studying the molecular pathways that p73 participates in the cervical cancer carcinogenesis, we found that the differential expression of TAp73 and DNp73 is related to the radio-sensitivity in cervical cancer. However, the detail mechanisms on how p73 contributes to the resistance of the treatment remain largely unclear. p73 has been suggested to play a role in an alternative p53-independent apoptotic pathway in ovarian cancer. p73 mainly exists in two forms: the N-terminal transactivation domain containing form (TAp73) and the dominant negative isoforms lacking the transactivation domain (DNp73). TAp73 exhibits growth inhibitory, tumor suppressive and pro-apoptotic functions whereas DNp73 form complexes with TAp73 and p53 which abolishes the tumor suppressor functions of TAp73 and p53. Several studies suggested the expression of TAp73 enhanced cisplatin induced apoptosis by up-regulating downstream genes such as p21 and Bax in ovarian cancer. Evidence from our previous observations have demonstrated the radio-sensitivity of cervical cancer is associated with the expression of TAp73 and DNp73 and implicated that p73 might play an important role in controlling cellular radio-sensitivity. We also showed the interaction of TAp73 with Breast Cancer Associated gene 3 (BCA3) enhanced the sensitivity of cervical cancer cells in response

to irradiation and documented its importance in the treatment of cervical cancer. Therefore, it is speculated that interaction of p73 with other signaling proteins might contribute to its function in response to cancer treatment. To further investigate the molecular mechanisms of p73, we have identified C35, also known as MIEN1, as a potential protein partner of p73 by yeast-2-hybrid screening using HeLa cDNA library. C35 is a novel protein which plays an important role in cancer progression and metastasis. Although the functional roles of C35 are implicated in cancers, the detailed mechanisms remain largely unclear. We are investigating the impact of the interaction between DNp73 and C35 in carcinogenesis and the underlying mechanisms in contributing to the chemo-resistance of cancer cells in ovarian cancer. To further investigate the molecular mechanisms of p73, we identified C35, also known as MIEN1, as a potential protein partner of p73 by yeast-2-hybrid screening using HeLa cDNA library. C35 is a novel protein which plays an important role in cancer progression and metastasis. We found that C35 is highly expressed in ovarian cancer cells and tumor tissues. C35 potentiated the functions of DNp73 in tumor progression and chemo-resistance by activating AKT and nuclear NFκB p65. This study is the first to illustrate a possible mechanism by which DNp73 and C35 contribute to the chemo-resistance of ovarian cancer cells. Further studies of the functional importance of the C35–DNp73 interaction will be essential to gain better insight into the roles of these proteins in ovarian cancer.

Using CGH, we have found that the gene coding for the catalytic alpha-1 subunit of the AMP-activated protein kinase (AMPK-α1) was amplified and over-expressed in cervical cancer (Figure 2). The AMPK is a stress responsive protein kinase. The over-expression of AMPK may enhance survival of cervical cancer cells under adverse conditions. Thus, the relationship between AMPK over-expression and cancer development is being investigated.

In addition to the above, aberrant gene expressions of cancer-related genes are being investigated in various gynaecological cancers. Forkhead box M1 (FOXM1) is a member of the Forkhead box family, with a conserved wing helix DNA-binding domain. It is critically involved in embryogenesis and organ development. Alternative splicing of FOXM1 generates three variants; FOXM1A contains alternative exons Va and VIIa, FOXM1C contains Va, and FOXM1B contains none of these exons. Both FOXM1B and FOXM1C are transcriptionally active, whereas FOXM1A is transcriptionally inactive, due to an insertion of exon VIIa in the transactivation domain (TBD). Emerging evidence has documented that aberrant upregulation of FOXM1 is frequently observed in various human cancers. Our previous studies revealed that FOXM1 overexpression is frequently found in the tumour development of cervical cancer (Figure 3).

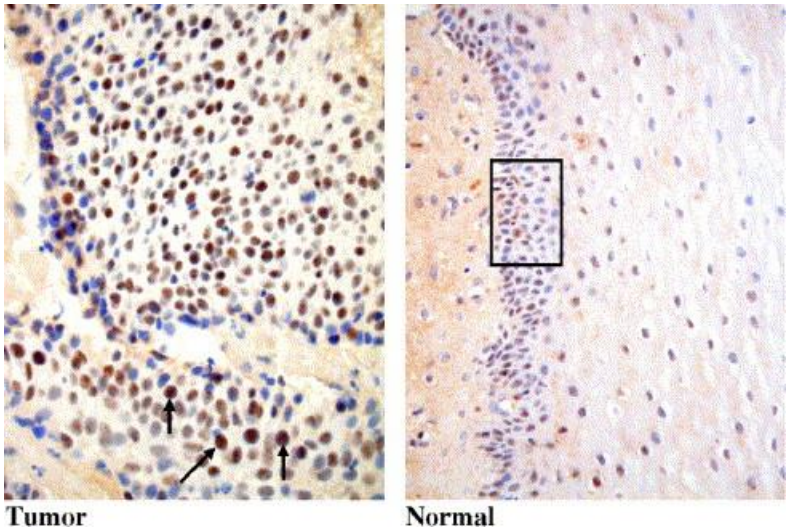

Fig. 2 Immunohistochemical staining of AMPK-α1 protein. An antibody against AMPK-α1 was used to detect the expression of AMPK-α1 in tumor and normal cervical tissues embedded in paraffin. Immunoreactivity for AMPK-α1 was predominantly found in the nuclei of the cells as indicated by the arrows. Immunoreactivity was found in most tumor cells; while in normal epithelium, staining was found mainly in the basal cells as indicated by the rectangular box. The intensity of staining is much stronger in the tumor than in the normal tissue.

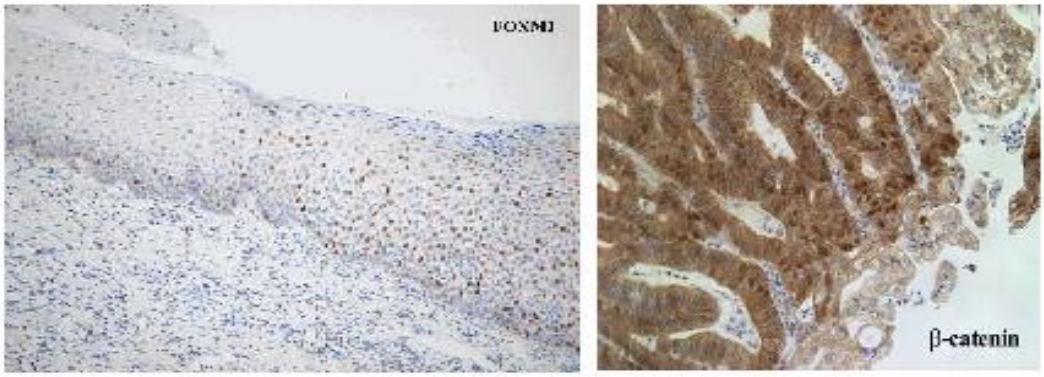

Fig. 3 Immunohistochemical analysis of FOXM1 expression in cervical carcinoma, and β-catenin expression in endometrial carcinoma.

According The Cancer Genome Atlas (TCGA), activated FOXM1 is significantly associated with the majority of high-grade serous ovarian cancers, which is the most common and deadly subtype of epithelial ovarian cancer (EOC). FOXM1 exhibits potent oncogenic properties in promoting cell proliferation in human cancer cells, and acts as a major activator of cancer metastasis through enhancing the epithelial-mesenchymal transition (EMT), invasion, cell migration and angiogenesis. Given that FOXM1 acts as a crucial master regulator of tumorigenesis and metastasis in human cancers, it is of interest to understand the underlying molecular mechanism of FOXM1 in the transcriptional regulation of the diverse signaling pathways in each step of tumorigenesis. The identification of downstream targets of FOXM1 will provide reliable

biomarkers and better therapeutic targets for the tailored treatment of ovarian cancers. Indeed, we have recently identified that that DLX1 acts as a FOXM1 downstream target, exerting pro-metastatic function in ovarian cancers. Both FOXM1 isoforms (FOXM1B or FOXM1C) could transcriptionally upregulate DLX1 through two conserved binding sites, located at +61 to +69bp downstream (TFBS1) and -675 to -667bp upstream (TFBS2) of the DLX1 promoter, respectively. This regulation was further accentuated by the significant correlation between the nuclear expression of FOXM1 and DLX1 in high-grade serous ovarian cancers (Figure 4). Functionally, the ectopic expression of DLX1 promoted ovarian cancer cell growth, cell migration/invasion and intraperitoneal dissemination of ovarian cancer in mice, whereas small interfering RNA-mediated DLX1 knockdown in FOXM1-overexpressing ovarian cancer cells abrogated these oncogenic capacities. In contrast, depletion of FOXM1 by shRNA only partially attenuated tumor growth and exerted almost no effect on cell migration/invasion and the intraperitoneal dissemination of DLX1-overexpressing ovarian cancer cells. Furthermore, the mechanistic studies showed that DLX1 positively modulates TGF-β signaling by upregulating PAI-1 and JUNB through direct interaction with SMAD4 in the nucleus upon TGF-β1 induction. Taken together, these data strongly suggest that DLX1 plays a pivotal role in FOXM1 signaling to promote cancer aggressiveness through intensifying TGF-β/SMAD4 signaling in high-grade serous ovarian cancer cells (Figure 5).

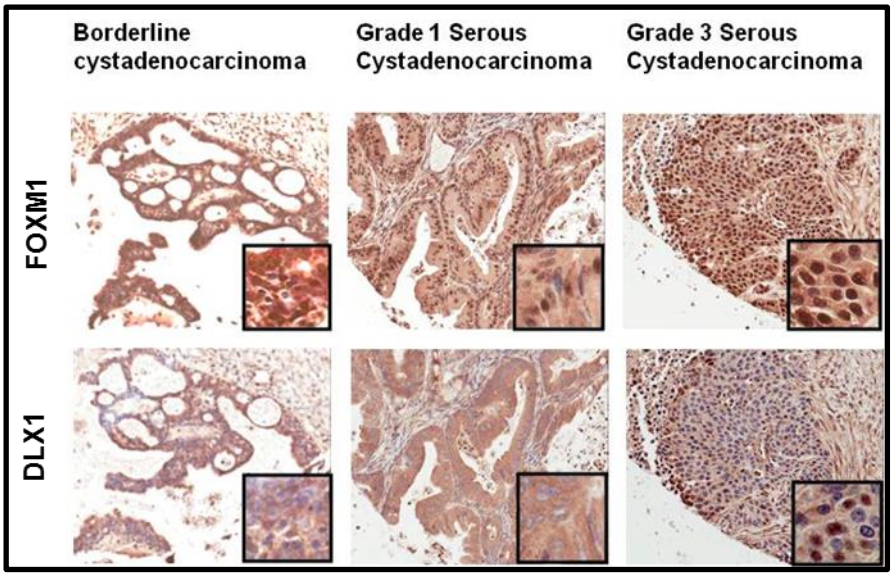

Fig. 4 Representative photos showing the immunohistochemical images of FOXM1 and DLX1 staining on the ovarian cancer tissue array. Both FOXM1 and DLX1 expression were progressively increased from borderline cystadenocarcinoma to Grade 3 serous cystadenocarcinoma. (Magnification x100).

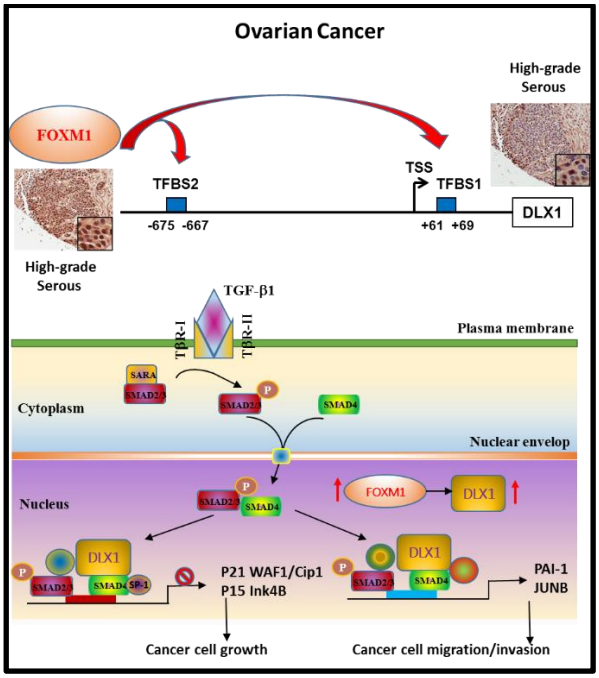

Fig. 5 Graphical summary of the role of DLX1 in high grade serous ovarian cancer.

4. Oestrogen receptor subtypes in ovarian cancer

Ovarian cancer expresses hormone receptors and is hormone sensitive. However, the use of hormonal therapy is not well established in the treatment of ovarian cancer. This may be hindered by the lack of good evidence in its effectiveness from earlier studies on the use of Tamoxifen, an anti-estrogen, where little attention was paid to the response with respect to the tumor receptor status. Furthermore, a new estrogen receptor subtype has been discovered (ERβ).

At mRNA level, we demonstrated similar ERα mRNA expression in normal ovarian tissues and cancer tissues whilst loss of ERβ mRNA expression in cancer tissues compared with normal tissues. Moreover, ERs mRNA expressions seemed to be different for different histologic types. A high ERβ expression was also significantly associated with a longer disease free survival as well as overall survival. At protein level, we found that aberrant ERα, ERβ1, ERβ2 and ERβ5 expressions contribute to ovarian tumorigenesis (Figure 6). Since tamoxifen binds to both ERα and ERβ1 which appear bear opposing oncogenic roles, the histotypes-specific expression pattern of ERs found in the present study indicates that personalized ovarian cancer treatment for women based on their ERs expression status using selective estrogen receptor modulators may improve response rate. This study also suggests nuclear ERβ5 to be a potential prognostic marker and therapeutic molecular target in ovarian cancer. Functionally, we found that ERβ5 overexpression promoted ovarian cancer cell migration, invasion and proliferation via activation of FAK whereas ERβ2 induced cell migration and invasion.

Our findings of in vitro and in vivo SERM treatment suggest that targeting specific ER subtypes after determining the relative ER subtypes may enhance the response to hormonal treatment in women with ovarian cancer. We found that blockage of ERα by ERα antagonist (MPP) or stimulation of ERβ1 by ERβ agonist (DPN) in ERα+ or ERβ1+ ovarian cancer cells inhibited cell proliferation, implicating the opposing roles of ERα and ERβ. Synergistic effect was achieved when using ERα antagonist and ERβ agonist together in ERα+ERβ1+ cells.

Hormonal treatment offers a very good option for women because of its low toxicity profile. Selective ERβ agonist has already been developed for clinical use and has been tested in phase 2 clinical trial for treatment of menopausal symptoms and rheumatoid arthritis. Our preclinical results on ER subtypes selective modulations and their mechanisms of action in ovarian cancer can potentially translate to selective, personalized ovarian cancer treatment for patients with different ERs status to obtain better clinical response with minimal side effects.

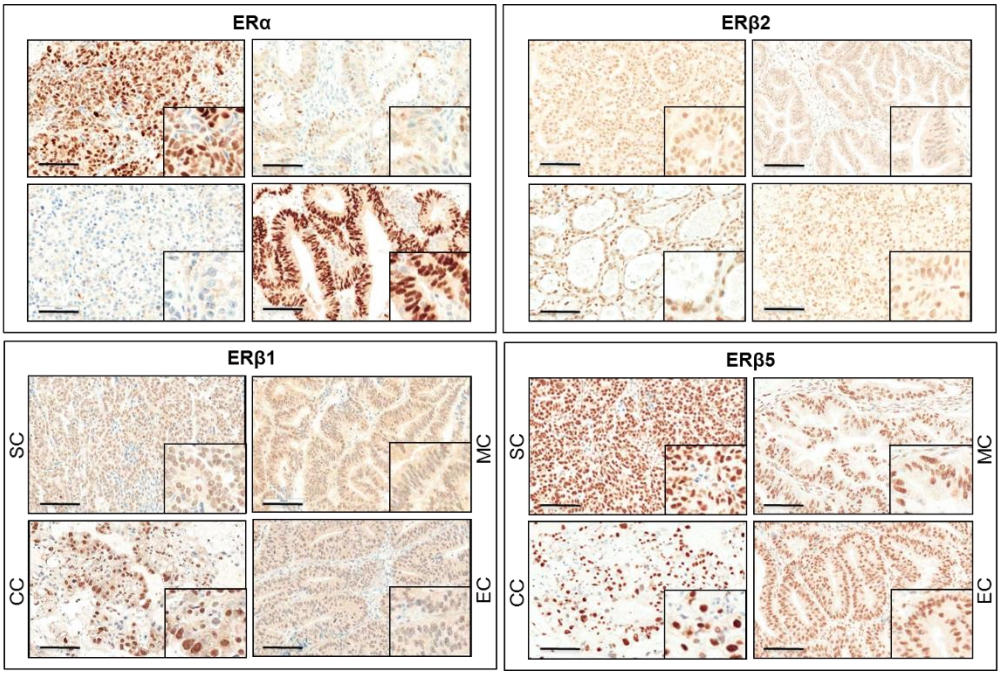

Fig. 6 Immunohistochemical staining of ER α, ER β1, ER β2 and ER β5 in serous (SC), mucinous (MC), endometrial (EC) and clear cell (CC) carcinomas. Scale bar=100μm. Insets highlight regions with higher magnification.

5. <u>Delineation of the underlying molecular mechanisms in promoting metastatic progression of ovarian cancer</u>

Unlike in other human cancers, transcoelomic metastasis is the most common route of cancer spread in ovarian cancer. Clinical evidence indicates that ovarian cancer with peritoneal

metastases is usually accompanied with poor prognosis. Within the peritoneal cavity, the omentum is one of the most preferential tissues for metastatic ovarian cancer seeding. However, this organ is rarely studied, and the underlying molecular mechanism for the interaction between the omental microenvironment and metastatic ovarian cancer cells in tumor colonization remains obscure. Emerging evidence has suggested that chemokines play an active role in reprogramming the tumor microenvironment and promoting cancer cell dissemination. For example, omental adipocytes secrete numerous growth factors and hormones, such as IL-6, IL-8, MCP-1, TIMP-1 and adiponectin, to promote tumor growth and cancer cell aggressiveness in various human cancers, suggesting the importance of chemokine-induced oncogenic alteration of the tumor microenvironment in promoting omental metastasis. In addition to the effects of the tumor microenvironment, malignant cells intrinsically alter their behaviors and qualities to adapt to microenvironmental reprogramming during tumor development and progression. It is hypothesized that metastatic cancer cells escaping from primary tumor sites acquire genetic and epigenetic alterations to resist stresses and traverse boundaries. This hypothesis implies that metastatic cancer cells are considered more aggressive than primary tumor cells due to their gain of tumorigenic capacities. Numerous studies have documented that nuclear factor-kappa B (NFκB) deregulation is favorably associated with cancer progression via its promotion of cancer cell proliferation and metastatic capacity. Indeed, our previous report showed that aberrant phosphorylation of transforming growth factor (TGF)-β-activating kinase 1 (TAK1) at serine 412 is critically involved in the activation of NFκB signaling and is associated with ovarian cancer cell aggressiveness. These findings suggest that TAK1/NFκB signaling plays a vital role in ovarian cancer metastasis. Our current findings showed that GRO-α and IL-8 are predominately upregulated in OCM derived from either normal or cancerous omenta and are associated with increased ovarian cancer aggressiveness. Both chemokines can activate TAK1/NFκB signaling via the CXCR2 receptor. Intriguingly, TAK1/NFκB signaling activity was higher in metastatic ovarian cancer cells; this higher activity makes them more susceptible to OCM-induced tumor aggressiveness. Treatment of ovarian cancer cells with GRO-α and IL-8 neutralizing antibodies or depletion of CXCR2 by shRNA gene knockdown, CRISPR/Cas9 gene knockout, or CXCR2 inhibitor SB225002 treatment significantly attenuated TAK1/NFκB signaling and decreased *in vitro* and *in vivo* oncogenic and metastatic potential, suggesting CXCR2 plays a key role in the GRO-α and IL-8-governed metastatic spreading of ovarian cancer cells in the intraperitoneal cavity (Figure 7). Taken together, our study highlights the significance of GRO-α and IL-8 as the key chemokines in the peritoneal tumor microenvironment and suggests the utility of targeting their receptor CXCR2 as a potential target-based therapy for peritoneal metastases of ovarian cancer (Figure 8).

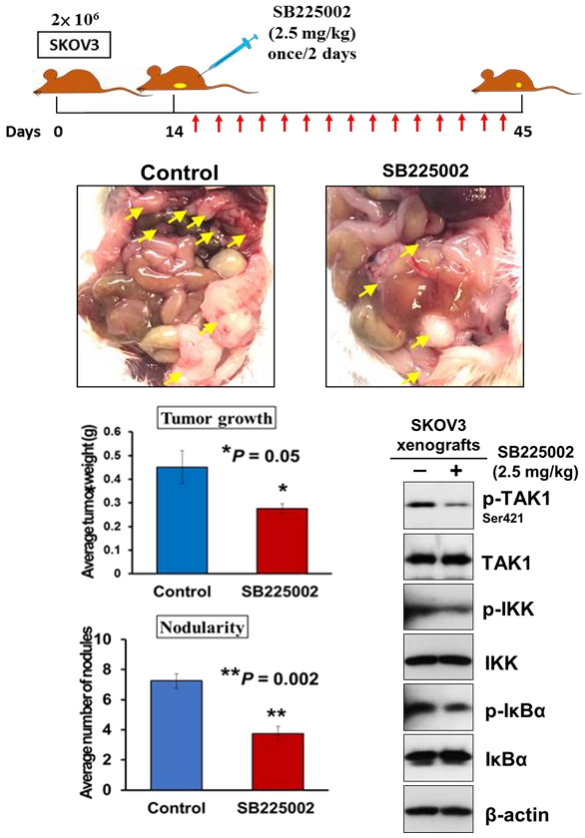

Fig. 7 A tumor xenograft mouse model showed that injection of CXCR2 blocker SB225002 could significantly inhibit ovarian cancer cell dissemination in intraperitoneal cavity of mouse (by tumor weight and nodularity). Western blot analysis on tumor tissues confirmed that SB225002 could suppress TAK1/NFkB signaling activity of ovarian cancer cells.

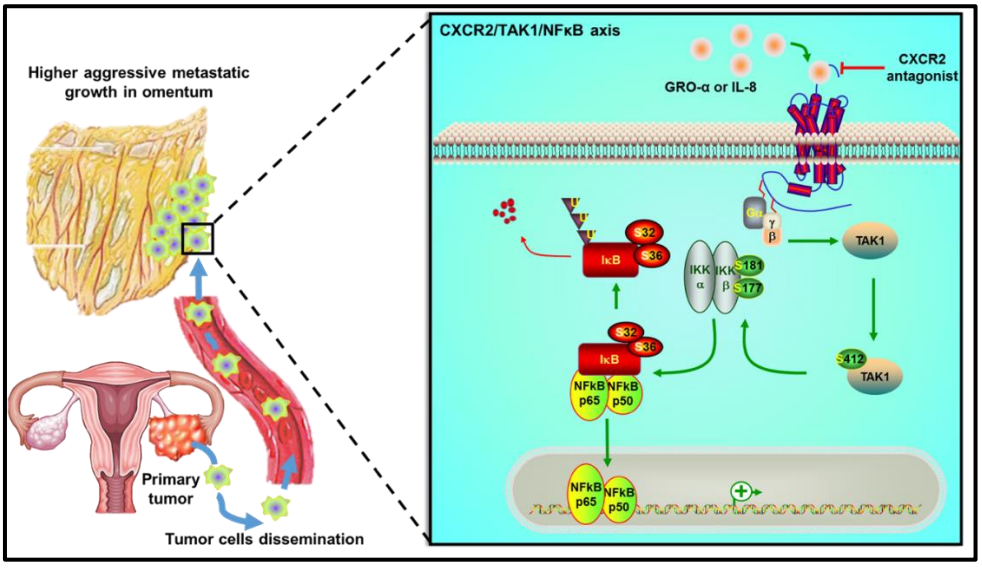

Fig. 8 A schematic diagram illustrates CXCR2/TAK1/NFκB as the proposed molecular mechanism by which CXC chemokines GRO-α and IL-8 aggravates ovarian cancer aggressiveness.

6. Targeting cancer cell metabolism in the treatment of ovarian cancer

Ovarian cancer is a lethal disease because it is usually asymptomatic until the late stage of development. Conventional cisplatin treatment is hindered by the development of chemo-resistance in ovarian cancer cells. Thus, new treatment to reduce its mortality is urgently needed. Targeting cancer cell metabolism is a hot and novel strategy to fight over human cancers. AMP-activated protein kinase (AMPK) is an energy-sensor governing energy homeostasis in eukaryotic cells. Mounting evidences have documented that increased AMPK activity inhibits cell growth and induces apoptosis in many human cancer cells. We have previously reported that the use of AICAR, A23187 and Metformin (pharmaceutical AMPK activators), as well as bitter melon extract (BME) (natural AMPK activator) could inhibit cell proliferation through suppression of mTOR signaling activity (Figure 9). Moreover, we also found that co-treatment of Metformin and LY294002 (AKT inhibitor) could synergistically suppress ovarian cancer cell growth and even sensitize ovarian cancer cells to cisplatin-induced cell apoptosis. Further investigations will focus on the effects of these AMPK activators in tumor microenvironment, other co-factors in regulating AMPK activity and the cross-talk of AMPK and Wnt/β-catenin signaling pathways. In additional, we are also interested in exploring natural AMPK activators to be used as supplement in enhancing cytotoxicity of current chemo drugs. Given that BME has effect on AMPK activation, we are investigating the bioactive components in BME which has such capacity. Their functional effects and molecular mechanism will be studied.

On the other aspect, cancer cells take up more glucose than normal tissue and prefer to undergo aerobic glycolysis, a phenomenon known as the Warburg effect. It is still unclear if glycolysis-related genes may affect ovarian cancer progression and clinical outcome. Moreover, mounting evidence has suggested that higher intake of dietary lipids, systemic lipid metabolism malfunction, and abnormal levels of serum lipid are associated with ovarian cancer development and metastatic progression. Aberrant upregulation of some lipid metabolic enzymes are usually found in ovarian cancer. This is particularly found in peritoneal metastases of ovarian cancer. Therefore, we will characterize the expression, genetic alteration, functional roles and signaling pathways of glycolysis- or lipid metabolism-related genes in ovarian cancer can explore their possible interactive roles in tumorigenesis, metastasis and chemoresistance of ovarian cancer; and to evaluate their potential impacts on the development of targeted anticancer therapies.

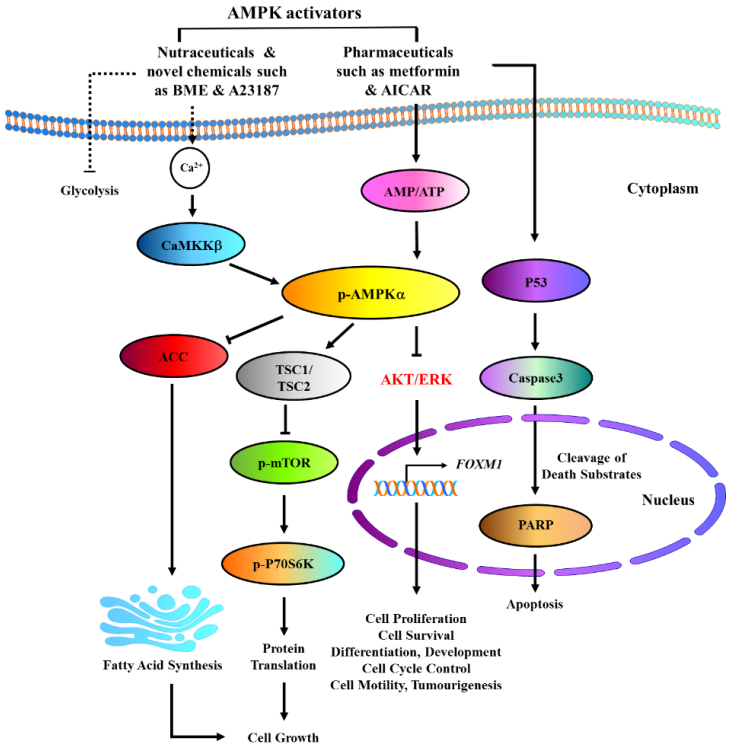

Fig. 9 Proposed mechanisms summarizing pharmaceutical and natural AMPK activators mediated cell growth inhibition and apoptosis in ovarian cancer.

7. Functional characterization of key drivers associated with ovarian cancer metastasis

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy worldwide. This disease is generally called the "silent killer" because there are no symptoms and thus, the majority of patients are found in advanced stages accompanied by extensive metastasis. Most deaths from this cancer are attributed to metastatic progression. Therefore, understanding the molecular mechanisms of related metastases may assist in the development of "targeted" oncologic therapies to improve the cure rate of this disease. The cancer metastasis is determined by the priming of metastatic niche and the intrinsic properties of cancer cells to adapt the micro-environmental stresses. However, the associated molecular mechanisms remain unclear. Using miRCURY™ LNA Array profiling in combination with a series of biochemical and functional analyses, we have recently found some miRNAs are aberrantly upregulated and are associated with anoikis resistance, which is a fundamental feature of metastatic cancer cells, allowing for their survival during metastatic cancer progression. Further studies revealed that these miRNAs not only play a key role in altering cancer cell plasticity against anoikis but also be able to reprogram stroma to be a pre-metastatic niche facilitating the ovarian cancer metastatic colonization. Therefore, further investigations are needed to characterize the significance and molecular mechanism of these miRNAs in ovarian cancer metastasis.

8. Identification of putative miRNAs involved in ovarian cancer oncogenesis

MicroRNAs (miRNAs) are a class of ~22 nucleotide noncoding RNAs that regulate gene expression by post-transcriptionally silencing large number of target messenger RNA (mRNA). The silencing mechanism of miRNAs relies on the presence of a relatively short sequence motif found in multiple mRNA transcripts. The combinatorial targeting effects allow highly complex network programming in cells. Thus, alterations of miRNA expression can lead to crucial impact on the proteome and cellular functions. Emerging evidence suggests that the deregulation of miRNAs expressions were involved in the initiation, progression, and metastasis of human cancers. Many miRNAs are expressed in a tissue-specific manner and may act as oncogenes tumor suppressor genes, depending on whether they are overexpressed or under expressed in cancer cells as compared with normal tissue counterparts. The understanding of functional consequences of altered patterns of miRNAs in human cancers is just the beginning and is the hottest topic in cancer field. Recent studies on miRNAs are mainly focus on the functions of distinct miRNAs in the regulation of cell survival, apoptosis, cell migration and metastasis. However, there is lack of reports on the expression patterns of miRNAs associated with chemoresistance in ovarian cancer. Resistance to chemotherapy is a major cause of treatment failure in human cancers. Cisplatin is one of the most potent anti-tumor agents commonly used in ovarian cancer. However, the major limitation of using this drug is the acquisition of resistance to initially responsive tumors. There are two possibilities leading to chemoresistance in human cancers; it may be inherent in a subpopulation of heterogeneous cancer cells or be acquired as a cellular response to drug exposure. In this study, we will mainly focus on analyzing the molecular mechanisms in the development of acquired chemoresistance in human ovarian cancer cells. The identification specific or signatures of miRNA involving in tumorigenicity and chemoresistance of human ovarian cancer cells is the novel approach to investigate the mechanism. We will apply miRNA expression profiling from commercial miRNA expression arrays to analysis 2 pairs of ovarian cancer cell lines; cisplatin-sensitive (OV2008 and A2780s) and cisplatin-resistant (C13* and A2780cp) ovarian cancer cell lines (Figure 10). In addition, we will investigate and characterize the roles of putative miRNAs screened from miRNA expression profiling in tumorigenicity and metastasis of ovarian cancers.

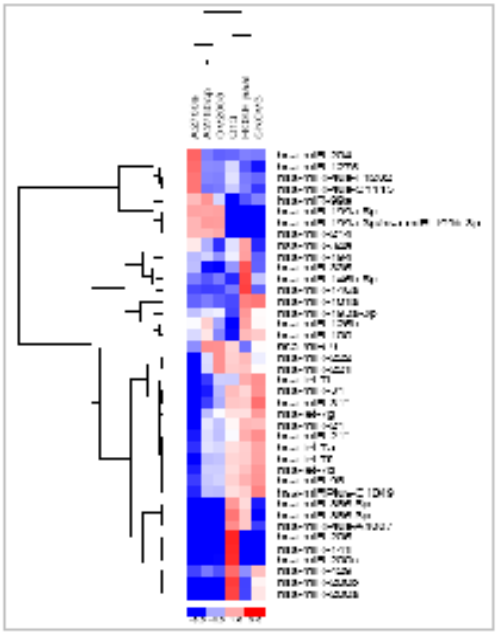

Fig. 10 The heat map diagram shows the result of the two-way hierarchical clustering of miRNAs and samples.

9. Characterization and identification of cancer stem cells in cervical cancer

Cancer stem cells (CSCs) have been suggested as a subpopulation of cells residing in tumors that possess the ability to initiate tumor cell growth and contribute to resistance of the treatment. Recent studies reported that CSCs exist in various types of solid tumor. However, the identity and character of CSCs in cervical cancer have not yet been investigated. The relationship and the significance of cervical CSCs in radiotherapy also remain largely unclear. Therefore, understanding the characteristics of CSCs may help to develop targeted cancer therapeutics aiming to eradicate all the CSCs. We established primary cervical cancer cell lines with the resected tumor tissues from cervical cancer patients. Spheroid formation assay indicated that the existence of CSCs in the primary cervical cancer tissues. Spheroid cells and attached cells of the primary cancer cell lines were cultured. Microarray analysis was performed to study the expression profiles of the spheroid and attached cells. Gene expression profiling revealed that CD55 was upregulated in primary cervical cancer sphere cells. Flow cytometric analysis detected abundant CD55(+) populations among a panel of HPV-positive cervical cancer cell lines, while only few CD55(+) cells were found in HPV-negative cervical cancer and normal cervical epithelial cell lines. The isolated CD55(+) sub-population from the C33A cell line exhibited significant sphere-forming ability and enhanced tumorigenicity, cell migration and radio-resistance. In contrast, the suppression of CD55 in HPV-positive Caski cells inhibited tumorigenicity both in vitro and in vivo and sensitized cells to irradiation treatment. In addition, ectopic expression of HPV-E6 in HPV-negative cervical cancer cells dramatically enriched the CD55(+) sub-population. CRISPR/Cas9 knockout of the CD55 gene in an HPV-E6-overexpressing stable clone abolished the tumorigenic properties exerted by HPV-E6. Taken

together, our data suggest that HPV-E6 protein expression enriches the CD55(+) population, which contributes to tumorigenicity and radio-resistance in cervical cancer cells. Targeting CD55 via CRISPR/Cas9 may represent a novel avenue for developing new strategies and effective therapies for the treatment of cervical cancer. In addition, we are now investigating the significance of other differentially expressed genes in the identification and isolation of CSCs in cervical cancer.

The followings are on-going projects

A. The study of radiosensitivity and aberrant gene expression in cervical cancer
B. The study of chemosensitivity and aberrant gene expression in ovarian cancer
C. The study of apoptotic genes in gynaecological cancer
E HPV prevalence and HPV testing
F. Epidemiology of cervical cancer and cervical screening
G. Epigenetic modification of HPV viral genes
H. The study of miRNAs in cervical pre-cancerous lesions and cancer
I. Serum biomarker detection in gynaecological cancers
J. The study of genetic aberrations in vulvar cancer
K. Role of estrogen receptor in ovarian cancer
L. The role of lipid metabolism in peritoneal metastases of ovarian cancer.
M. Functional characterization of putative miRNAs in chemoresistance and metastasis of ovarian cancers.
N. The significance of chemokines and TAK1/NFkB signaling cascade in regulating omental metastasis of ovarian cancer
O. Functional study of natural AMPK activators in anti-cancer and anti-chemoresistance.
P. Investigation of key signalings in crosstalk of ovarian metastatic cancer cells and tumour microenvironment.

Research opportunities for Master of Philosophy and Doctor of Philosophy are opened in the new projects to be started as follow:

A. The study of candidate oncogenes and tumour suppressor genes and search of new genetic alterations in cervical cancer in Hong Kong Chinese
B. Genome-wide analysis of gene expression and aberrations of chromosomes
C. Hypermethylation of tumour suppressor genes in gynaecological cancers
D. Determination of HPV typing and integration site in host genome in cervical cancers
E. Functional analysis of newly identified cancer-related genes and their roles in cell signalling pathways.

F. Functional characterization of putative miRNAs associated with chemoresistance, metastasis and oncogenesis in ovarian cancers.
G. Study of the interactions between metastatic ovarian cancer cells and tumour microenvironment
H. Identification and characterization of cancer stem cells of cervical cancer

Part II - Clinical cancer research

The Department of Obstetrics and Gynaecology is very active in carrying out various clinical research projects in gynaecological oncology.

On-going studies include:

1. Gestational Trophoblastic Neoplasia
    a. Treatment strategies and outcomes
2. Cervical Cancer
    a. Human Papillomavirus (HPV) test in cervical screening
    b. HPV 16 in adenocarcinoma
    c. Multimodality treatment for advanced disease
3. Ovarian cancer
    a. Quality of life studies in patients with recurrent ovarian cancer
    b. Multi-gene mutation-drug matching for recurrent ovarian cancer
    c. Genetic mutation in ovarian cancer
4. Others:
    a. Lynch syndrome in endometrial cancer
    b. Vault stripping for vaginal pre-malignant conditions
    c. Sentinel lymph node biopsies for cervical and endometrial cancer
    d. Robotic surgery for cervical and endometrial cancer
    e. Follow up assessments in patients after treatment for gynaecological cancers
    f. Uterus sarcoma
    g. Combined electroacupuncture and auricular acupuncture for postoperative pain after abdominal surgery for gynecological Diseases

Reproductive Medicine

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The Reproductive Medicine Division is recognised by the Royal College of Obstetricians and Gynaecologists and Hong Kong College of Obstetricians and Gynaecologists for subspecialty training in Reproductive Medicine. It provides a tertiary referral service in reproductive medicine in Hong Kong. The Division is actively collaborating with a number of centres in Mainland China and other countries on various aspects of reproductive medicine. There are 12 basic scientists within the division to provide support for basic scientific research.

1. Fertility Regulation

Ulipristal in Emergency Contraception - Research carried out in the area of emergency contraception (EC) has aimed at finding agents that are more effective and less restrictive in timing of use after unprotected sexual intercourse (UPSI). In the 1990s, our Department pioneered the use of levonorgestrel in EC, which is now the standard preparation used worldwide for EC as adopted by the World Health Organization. In the past few years, ulipristal acetate (UPA), a selective progestogen receptor modulator, has been introduced for EC. We recently completed the first clinical trial in Asia to assess the efficacy of UPA in EC, and compared its effectiveness when administered before and after ovulation. We have also conducted a series of laboratory studies on the post-ovulatory actions of UPA on human sperm and oviductal functions, as well as on embryo-endometrial attachment.

In collaboration with the General Gynaecology Division, we are also conducting clinical and laboratory studies on the use of UPA for treatment of uterine fibroids and endometriosis.

2. Studies on endometrial receptivity

We have studied extensively on factors influencing endometrial receptivity by means of ultrasound indices as well as by an in-vitro trophoblastic spheroid – endometrial cell co-culture model. We conducted a series of studies on the adverse effect of high circulating level of estradiol and progesterone on endometrial receptivity. Recently, we have been studying the effect of clinical interventions (e.g. endometrial scratching, herbal medication) and pathological conditions (e.g. endometrial polyp), as well as various endocrine disrupting

chemicals, on endometrial receptivity. We have also pioneered on an in-vitro co-culture model using endometrial stem cell spheroids as the embryo surrogate to study endometrial receptivity. We are applying this model to work on prognostic prediction of assisted reproduction treatment outcomes and on the pathophysiology of repeated implantation failure.

3. Clinical studies in assisted reproduction

We are active in conducting randomised controlled clinical trials to explore methods to improve the success of assisted reproduction treatment. We have studied the role of acupuncture, endometrial scratching, dehydroepiandrosterone (DHEA), oxytocin antagonist, elective embryo freezing, hyaluronic acid-enriched transfer medium and various luteal phase support protocols on the outcome of IVF-embryo transfer and/or frozen-thawed embryo transfer cycles. Some of these trials are conducted in collaboration with other centres in China or overseas. For instance, we contributed to a multi-centred randomised controlled trial on the use of oral dydrogesterone versus vaginal progesterone for luteal phase support (LOTUS-II study). We also participated in a multi-centred observational study comparing ovarian response to corifollitropin-alfa, a long-acting recombinant FSH preparation, between two different ethnic groups. We have started a randomised clinical trial on the use of letrozole as an adjunct in ovarian stimulation for in vitro fertilisation cycles in women with good ovarian reserve.

We were also conducting an observational study comparing the severity of nausea and vomiting in women who conceived from the fresh in vitro fertilisation cycle versus those from unstimulated frozen-thawed embryo transfer cycles.

4. Psycho-social aspects of assisted reproduction

It is well-known that women with infertility problems are under a lot of stress and anxiety. This is especially true for whom undergoing assisted reproduction treatment. With the help and support from the Department of Social Work and Social Administration, University of Hong Kong, group psycho-social counseling sessions are regularly offered to our patients undergoing IVF. We have joint research studies on the psychosocial profile of our patients undergoing fertility treatment, including clinical trials on psychosocial interventions to reduce stress and anxiety in this setting.

6. Reproductive endocrinology

Anti-Mullerian hormone (AMH) is a glycoprotein hormone which in the adult female is solely produced by the granulosa cells of preantral and small antral follicles, and has been

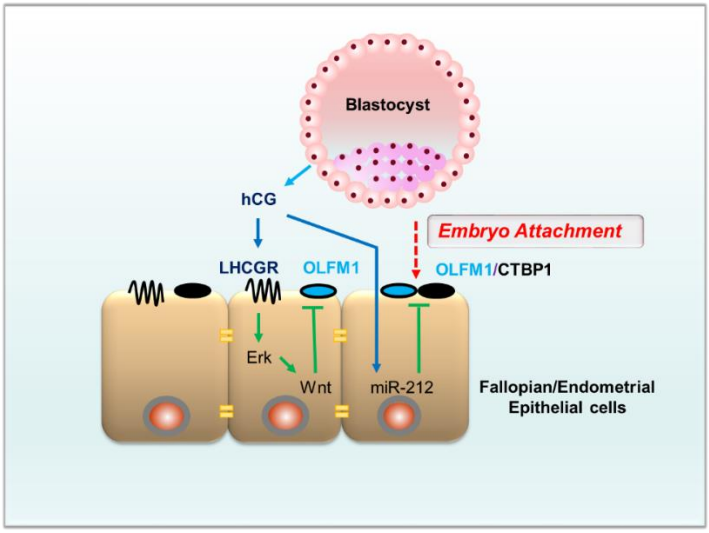
proposed to regulate folliculogenesis. Because of this exclusive source of production in the adult female, and that its production is stable throughout the menstrual cycle with clinically insignificant intra- and inter-cycle variation, AMH is a potentially useful marker of ovarian function. We have been working on the clinical utility of AMH measurement in reproductive medicine, including its use in the differential diagnosis of anovulatory disorders, its correlation with endocrine and metabolic profile in women with polycystic ovary syndrome, and its role in management of patients undergoing assisted reproduction treatment. We have also been actively evaluating the new automated platforms for AMH measurement. Establishment of an age-specific normogram of AMH measured on one of the new automated platforms in the Chinese population has been started. A randomised controlled trial comparing the use of serum AMH level and antral follicle count in determining the gonadotrophin dosage in in-vitro fertilisation treatment has been performed.

We are also conducting a longitudinal study to evaluate the endocrine and metabolic profile of women with polycystic ovary syndrome in Hong Kong, and to explore the factors predicting long-term cardiovascular and metabolic morbidity in this disease group. An observational study comparing the effect of letrozole and clomiphene treatment on the hormone profile of women with polycystic ovary syndrome is also underway.

7. Reproductive biology

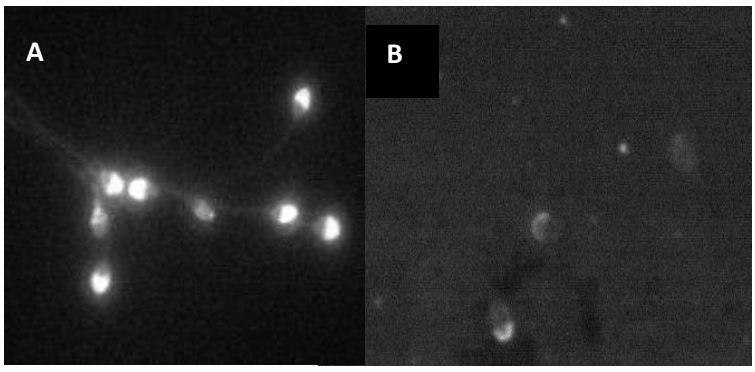
We have a strong team of reproductive scientists in the research laboratory, and our current main research interests are in the following areas:

Interaction of sperm and embryo with the female reproductive tract - In the past two decades, our team has been studying the interaction of gametes/ embryos with the female reproductive tract by means of co-culture techniques. Our work has shown that: (1) human oviductal cells produce embryotrophic factors that improve the development of human and mouse embryos; (2) preimplantation embryos influence the mRNA expression of the oviduct; (3) the oviductal cells maintain the motility of human spermatozoa *in vitro*, which would otherwise decrease rapidly in culture; and (4) human spermatozoa bind to the oviductal cells and change their protein secretion. We have ongoing studies on the mechanism of these interactions.



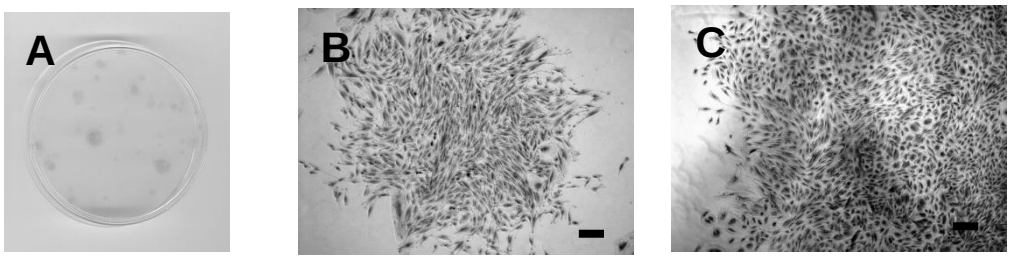
MicroRNAs in reproduction - In recent years, we also started to work on the role of microRNAs in early embryonic development and implantation. MicroRNAs are small non-coding RNAs. They do not code for proteins but suppress their production. They are important in a number of developmental processes. Recently, microRNAs have been reported to be involved in reproduction. We have shown that sperm-borne microRNA-34c is important for the first cleavage division of mouse embryos, and the microRNA let-7a is important in modulating the implantation potential of mouse blastocysts. Research opportunities are open for studying the role of microRNAs in early embryo development.

Glycodelin and reproduction - We discovered two isoforms of glycodelin, namely glycodelin-F and glycodelin-C, and have extensively studied their diverse functions in reproduction including sperm function, fertilisation and trophoblastic function. Recently, we have extended our study on the actions of glycodelin on trophoblast cells and immune cells. These studies are likely to enhance our understanding on the regulation of fertilization and placentation in human.



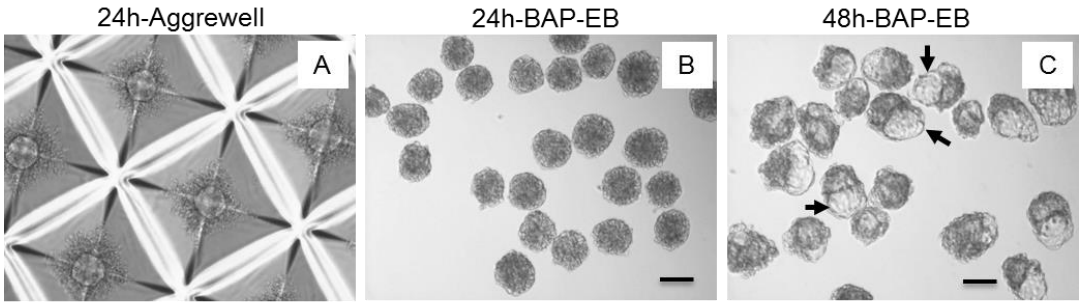
Immunofluorescence staining of human spermatozoa. (**A**) Spermatozoa incubated with 1ug/ml glycodelin-F at 37°C in an atmosphere of 5% CO_2 in air for 3 hr. (**B**) Spermatozoa incubated with 1ug/ml glycodelin-A at 37°C in an atmosphere of 5% CO_2 in air for 3 hr.

Endometrial stem cells - Study on endometrial stem cells is another new interest of our group. The human endometrium has remarkable regenerative capacity during the female reproductive years. The endometrium regenerates from the lower *basalis* layer, which persists after each menstruation and gives rise to the new upper *functionalis* containing mature endometrial and epithelial stromal cells. Since the endometrium is one of the few tissues that sheds and undergoes cyclical re-growth, the presence of somatic stem cells has long been speculated. We contributed to the first finding of human endometrial epithelial and stromal stem/progenitor cells using a functional approach (clonogenic assay), and are now continuing with the characterisation endometrial stem cells and investigating for its involvement in the development of endometriosis.



(A) A representative culture dish displaying the distribution of endometriotic colonies and variation of colony size after 21 days of culture. (B) A typical small colony of endometriotic stromal cells, (C) a typical large colony.

Embryonic stem cell and Endometrial receptivity – We established a protocol to differentiate human trophoblastic-like cells from embryonic stem cell and generate spheroid (BAP-EB, blastocyst surrogate) that able to differentially attach to receptive, but not non-receptive human primary endometrial epithelial cells. We are now further to study the mechanism of the differentiation process and explore the application of this co-culture system in clinical setting.



Endocrine disrupting chemicals (EDCs) on female fertility – EDCs are exogenous chemical(s) that interferes with any aspect of hormone action in our bodies. We have been collaborating with the Hong Kong Baptist University to study the association of EDCs in serum and follicular fluid of patients who visited our IVF clinic with their fertility potential. Particularly the effect of different bisphenol substitutes on embryo implantation using in vitro and in vivo models.

Adrenomedullin in oviductal physiology and pathophysiology - We have been collaborating with the Departments of Anatomy and Physiology (now the School of Biomedical Sciences) in studying the role of adrenomedullin in human oviductal function, and its possible pathophysiological role in tubal ectopic pregnancy. We are now studying the interaction of oviductal adrenomedullin and inflammatory activities in the pathogenesis of tubal ectopic pregnancy.

Regulation of AMH production from ovarian granulosa cells - We are studying the regulation of AMH production from ovarian granulosa cells by various hormonal factors and adipocytokines, and its implication in the pathogenesis of polycystic ovary syndrome.

Maternal Fetal Medicine

Staff: Dr. M.H.Y. Tang, Dr. C.P. Lee, Dr. A.P.W. Hui, Dr. A.S.Y. Kan, Dr. N.W.M. Shek, Dr. T.K.T. Li, Dr. C.W.S. Lai, Dr. K.W. Cheung, Dr. M.T.Y. Seto, Dr. H.H.Y. Cheng, Dr. V.W.Y Ng, Dr. K.Y.K. Chan, Dr B.H.Y. Chung

1. <u>The accuracy of self-screening of Group B Streptococcus in the local population in Hong Kong</u>

Group B Streptococcus (GBS) is a leading infectious cause of neonatal morbidity and mortality with vertical transmission being implicated in early onset GBS infection in the newborn. Studies have shown that patient-collected swabs are at least as sensitive as those taken by physicians. We have carried out a study to compare the accuracy of self-taken swabs and physician taken swabs for GBS screening in the local population and to look at the acceptability of patient regarding GBS screening and the local prevalence of GBS. 422 patients were being recruited. The prevalence of GBS was 19.7% (83/422). Sensitivities of self-screening and screening by healthcare workers were 61.4% (51/83) and 97.6% (81/83) respectively ($p<0.05$). Women who used vaginal pessaries and non-Chinese had a higher positive concordance rate with healthcare workers ($p<0.05$). Neonatal outcome of GBS positive mother between the concordant and discordant group were similar. Cultural difference needs to be considered when implementing self-screening in different population provided that the sensitivity of self-screening of GBS in Hong Kong was lower than that of the healthcare workers.

2. <u>A multi-center prospective study on the evaluation of paternal, maternal and obstetric factors leading to the hepatitis B immunization failure in Hong Kong</u>

Globally, hepatitis B virus (HBV) infection is the most common form of chronic hepatitis. HBV infection can be acquired through vertical or horizontal transmission. The chance of chronic infection depends on the age of exposure and the risk is highest during perinatal period. HBV vaccination and hepatitis B immunoglobulin (HBIG) are introduced into the national immunisation programme in various countries and dramatically decrease the incidence of HBV infection, cirrhosis and hepatocellular carcinoma. This great success however does not result in complete eradication of HBV disease because of in-utero infection and immunoprophylaxis failure. The aim of the study is to find out the possible paternal, maternal and obstetric factors leading to immunoprophylaxis failure, and the prevalence of immunoprophyaxis failure in Hong Kong. Data from 641 women was available for final analysis. All infants had routine HBV

vaccination. There were 7 cases of IF (1.1%, 7/641). Positive HBeAg and HBV DNA ≥8log10 copies/mL (≥17,000,000 IU/mL) at 28-30 weeks were significant predictors of IF (4.5% (95% CI 1.83-9.08%) versus 0% (95% CI 0-0.76%), and 5.8% (95% CI 2.36-11.56%) versus 0% (95% CI 0-0.71%), respectively, p-value <0.0001).

3. Array comparative genomic hybridization in prenatal diagnosis

The use of chromosomal microarray technology in prenatal diagnosis has been confirmed to increase the diagnostic yield than conventional cytogenetics in various studies. The knowledge and acceptance of aCGH in prenatal diagnosis was studied by questionnaire survey and showed that aCGH is perceived as a better test by both doctors and patients. Counselling support or training, and better understanding and communication of uncertain clinical significance are necessary to provide improved doctor-patient experience. A prospective demonstration study was completed which showed aCGH can be routinely used post rapid aneuploidy QF-PCR testing to replace about two-thirds of the cytogenetic study, with acceptable counselling workload. It is cost saving whilst maximizing the number of diagnoses achieved for invasive prenatal diagnosis. It is recommended to implement aCGH post rapid aneuploidy exclusion be the standard of practice in the prenatal diagnostic setting.

4. Identifying the Genetic Causes for Prenatally Diagnosed Structural Congenital Anomalies (SCAs) by Whole-Exome Sequencing

Whole-exome sequencing (WES) has become an invaluable tool for genetic diagnosis in paediatrics; however, it has not been widely adopted in the prenatal setting. This study evaluated the use of WES in prenatal genetic diagnosis in foetuses with structural congenital anomalies (SCAs) detected on prenatal ultrasound. Thirty-three families with fetal SCAs on prenatal ultrasonography and normal chromosomal microarray results were recruited. WES identified pathogenic mutations in 9.1% of fetuses. Databases for fetal genotype-phenotype correlations and standardized guidelines for variant interpretation in prenatal diagnosis need to be established to facilitate the use of WES for routine testing in prenatal diagnosis.

5. A prospective double-blind randomized controlled trial comparing the use of carbetocin versus oxytocin in prevention of postpartum haemorrhage in Caesarean section of multiple pregnancies

Postpartum haemorrhage (PPH) is one of the leading causes of maternal mortality and morbidity in obstetrics. Previous studies had shown a decrease in need for therapeutic uterotonics in Caesarean sections for singletons with use of carbetocin over oxytocin. As there are not much data available on use of carbetocin on twin pregnancies, we have carried out a study comparing the use of carbetocin versus oxytocin in prevention of postpartum haemorrhage in Caesarean section of multiple pregnancies. We plan to recruit 120 patients into this double-blinded randomized controlled trial, with 60 patients in each arm. The primary outcome is the difference in the need for uterine massage between the two groups. So far 120 patients were recruited with outcome available. An abstract of the interim analysis was available and published, while the full paper will be expected by end of 2018.

6. Prognosis Asia Study – A multicentre, prospective, double-blind, non-interventional study validating the short-term prediction of preeclampsia / eclampsia / HELLP syndrome in pregnant Asian women with suspected preeclampsia

Preeclampsia and Eclampsia cause significant maternal and fetal morbidity and mortality. Both over and under treatment may occur in patients suspecting to have hypertension and/or proteinuria. The correct prediction of preeclampsia is a highly unmet medical need. The assay of serum markers may help to provide short term predication of preeclampsia and guiding subsequent management. A previous study in Europe supports its usefulness. Our centre participated as one of the studied site and this has been completed in July 2016.

7. Expanded carrier screening in Hong Kong

Genetic carrier screening has evolved from targeted or ethnic based approach to more recent commercial offering of expanded screening using a non-targeted pan-ethnic approach. Whether the latter approach should replace the conventional targeted approach remains a controversy. We conducted a questionnaire survey to healthcare providers and patients to understand their knowledge, attitude and acceptance of expanded carrier screening and to assess the preferred mode of information giving in offering the tests. Unpublished data of our pilot study carried out in the Hong Kong showed that thirteen patients out of one hundred or 50 couples were screened positive for recessive genetic disorders such as cystic fibrosis, propionic academia, Wilson's disease, hyperphenyalaninemia and citrullinemia. No couple have positive results for the same disease but this is likely to be limited by the small sample size. Results from the research shall fill the gap of our current knowledge and facilitating future research on cost-effectiveness of this non-targeted pan-ethnic approach of genetic carrier

screening in the local setting. Patient acceptance for the test is under investigation for antenatal and subfertility patients.

8. A questionnaire survey on women's knowledge and view on contraception in the immediate postpartum period

Provision of postpartum long-acting reversible contraception (PPLARC) in the form of IUCD or contraceptive implants has been advocated in recent years. A Cochrane review has been published in 2015 confirming the safety of postpartum IUCD use. Previous studies among Caucasian populations show that women's acceptability towards effective contraception in the form of LARC is also increasing throughout the decade. Although Hong Kong embraces its cultural diversity, Southern Chinese made up the majority of the population. The traditional Chinese belief in 'postnatal confinement' and taboo towards discussion on sex both can affect opinion towards contraception. We aim to conduct a self-administered survey asking women their views on postnatal contraception. The results of this survey wound provide guidance for to prevent unintended pregnancies and improve contraception counselling targeted at our local population.

9. Assessment of Obstructive Sleep Apnea and Correlation with Maternal-Fetal Outcomes in Adult Pregnant Ladies Presenting with Cardiac-related Symptoms – A Prospective Case-Control Study

Obstructive sleep apnea (OSA) has been found to be an important risk factor for developing hypertension and coronary artery disease in non-pregnant adults. It was also reported that obstructive sleep apnea was associated with increased risk for developing pregnancy complications, including pre-eclampsia, cardiomyopathy, pulmonary embolism and in-hospital mortality. Polysomnography is the gold standard for diagnosing OSA. Home assessment improves flexibility and reduced the need to resort to formal polysomnography. In this joint study with department of Cardiology, we would utilize a novel ring-type home-based home monitoring and assessment device for the purpose of recording blood oxygenation and apnea-hypopnea index during sleep within the subject's usual sleep environment. We could correlate maternal and fetal outcomes with the clinical data collected by the home-based device throughout the course of pregnancy. Sixty subjects will be recruited.

10. Validation of T-cell receptor excision circles (TRECs) test

Severe combined immunodeficiency (SCID) is characterized by severe impairment in T cell development, with variable impairment of B cell functions. It often presents as recurrent severe infections, chronic diarrhea and failure to thrive since early childhood. T-cell receptor excision circles (TRECs) is currently employed in some countries as newborn screening for SCID, so there can be an earlier workup for suspected cases. Nevertheless, this test has not yet been implemented in Hong Kong. Through this joint study with department of Pathology, we plan to validate the TREC real time polymerase chain reaction (PCR) kit. 200 samples of newborn cord blood will be obtained. TREC will be run on each of these specimens to compare with the reference values from kit standards. Reference value for newborn TREC will be set up using these data.

11. Expression of adrenomedullin and its receptor in the first trimester placental cells from pregnancies diagnosed to have preeclampsia at delivery

The growth of the fetus in the mother's womb depends on an optimal development of the placenta, which is principally made up of trophoblasts. One of the main functions of the trophoblast is to anchor the placenta and the fetus onto the endometrium of the uterus. In the anchorage process, the trophoblast cells invade into the uterine endometrium and undergo endovascular differentiation. Dysregulation of trophoblast invasion and differentiation is associated with various pregnancy complications, including gestational trophoblastic diseases, intrauterine growth restriction and preeclampsia, leading to significant maternal and fetal complications. We know that a molecule known as adrenomedullin can affect trophoblast invasion and differentiation. This study is to investigate how adrenomedullin affects the trophoblast invasion/differentiation and its possible implication in preeclampsia, which is a pregnancy complication associated with decrease in trophoblast invasion/differentiation. The outcome of this project will give a better understanding on the regulation of early placentation in human, and may give indication as to whether adrenomedullin and/or its receptor level in trophoblast can be used as test for early prediction of PE.

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Ngan H.Y.S., Cancer Prevention in the Most Populous Country in the World, 2017 IFCPC World Congress for Cervical Pathology and Colposcopy, Orlando, Florida, USA, 4-7 April 2017.

Ngan H.Y.S., Complications of Robotic Surgery, 3rd Asian Congress of Robotic and Endoscopic Surgery, Taipei, Taiwan, 24-6 November 2017.

Ngan H.Y.S., Detection and management of CIN in AOGIN countries, Asia-Oceania Research Organisation in Genital Infection and Neoplasia ("AOGIN") 2016 Congress - Science, prevention, diagnosis and therapy on HPV related cancers, Tokyo, Japan, 18-19 October 2017.

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Prizes and awards

Lee C.L., Doris Zimmern HKU-Cambridge Hughes Hall Fellowship, The University of Hong Kong. 2017.

Lee C.L., University of Hong Kong-China Medical Board Grants, The University of Hong Kong. 2017.

Vijayan M., Global Health Travel Award, Keystone symposia /Melinda and Bill Gates Foundation. 2017.