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Network analysis revealed aurora kinase dysregulation in five gynecological types of cancer

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Abstract. Gene markers are crucial for cancer prognosis and treatment. Previous studies have placed greater emphasis on individual diagnostic genes, thereby ignoring systemic-level attributes across diseases. Female-specific cells namely, breast, endometrium, cervical, ovarian and vulvar cells are highly susceptible to cancer. To date, a limited number of molecular studies have been performed that evaluate common biological processes across gynecological types of cancer. Differentially expressed genes in breast, cervical, endometrial, vulvar and ovarian cancer were utilized to construct protein-protein interaction networks, and to identify a common module across the five cancer types. A single common module with 8 nodes and 26 edges was mined among the five cancer systems. In total, four hub genes were present across the five cancer gene sets. Genes in the common module were enriched for the common pathways and associated diseases. The aurora kinase pathway was revealed to be conserved across the five cancer types surveyed. The present study, therefore, revealed that the aurora kinase pathway has a crucial function in the pathogenesis of the five aforementioned gynecological types of cancer through cross-tumor conservation.

Introduction

Gynecological cancer constitutes >10% of cancer cases in the female population globally (1). Major gynecological types of cancer, including cervical, endometrial, ovarian and vulvar cancer, are a cause of concern in females. Breast cancer accounts for ~23% of all cancer cases among females (2). Diagnosis at advanced stages leads to increased morbidity and mortality, in contrast to an early diagnosis, which increases the chance of a cure and has correspondingly improved survival rates. Diagnostic factors, including age, histology, race, histological grade and stage at diagnosis, along with clinical phenotypes and the degree of causal association of human papillomavirus (HPV) infection (3), and the disease mechanisms of the five aforementioned cancer types appear to be distinct and precise (1). Extensive efforts have been made over recent decades to identify diagnostic genes and develop mechanisms for recognizing cancer in individuals (1). However, a previous study looking to identify prognostic genes has highlighted individual diagnostic genes and their potential function, without scrutinizing the properties and behavior of these diagnostic genes at the systemic level (4).

Studies regarding expression profiles and mutation rates have been conducted to identify common features among various cancer types, although few studies have identified common molecular mechanisms across diverse types of cancer (1,5,6). Certain studies employing novel profiling techniques integrated with existing bioinformatics methods have revealed systemic-level properties emphasizing on networks that instigate the interconnection of genes, proteins and metabolites whose dynamic interactions generate a corresponding function (7) in various types of cancer (5,6,8-11). Previously, one study identified four transcriptional modules associated with the cell cycle and apoptosis in cervical, endometrial and vulvar cancer (1).

System-level attributes may be better understood by utilizing biological networks. Protein-protein interaction (PPI) networks are the most commonly used biological networks for exploiting information on protein interactions. Utilizing expression profiles of the five gynecological types of cancer (cervical, ovarian, vulvar, breast and endometrial), the present study constructed PPI networks for each cancer type, focusing on two main questions regarding these five disease systems. First: Are there genes that are commonly expressed across the five disease systems? Second: Do these commonly expressed genes share similar network properties (including inclusion in hub genes and enrichment in modules) across the five disease systems? The present comparative study revealed common mechanisms and pathways associated with the five gynecological types of cancer.

Materials and methods

Expression datasets. Gene expression datasets for five gynecological types of cancer, breast, cervical, endometrial, vulvar and ovarian cancer, were retrieved from the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) (12) for the

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mining of differentially expressed genes (DEGs) in the disease systems for comparison with normal systems. The expression dataset GSE63678 (1) incorporated 5 samples of normal cervical cells and 5 of cervical cancer cells, 5 of normal endometrial cells and 7 of endometrial cancer cells and 7 of vulvar cancer cells and 6 of normal vulvar cells. The dataset GSE57297 (13) included 7 samples of normal and 25 samples of breast cancer cells. The ovarian cancer dataset GSE26712 (14) included 10 samples of normal and 185 samples of ovarian cancer cells.

Analyses of differential expression. Differential expression analyses of the datasets of different cancer types were performed using the Limma (Linear Models for Microarray Data) package (15) in R (16). Pre-processing and normalization were performed to remove noise from the datasets. Adjusted P-values <0.05 and |fold change| >2 were taken into account for the identification of DEGs. The P-value was adjusted using the Benjamini-Hochberg method (17) to minimize errors due to multiple hypothesis testing. Overlapping DEGs among the five gynecological types of cancer were selected for further study.

PPI network construction. DEGs of the five cancer types were individually mapped to PPI networks, considering a medium confidence in the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) version 10.0 (18) database, with *Homo sapiens* as the source species. Interaction data from high-throughput experiments, genomic contexts, previous knowledge and conserved co-expression are extensively integrated by STRING. The PPI networks were constructed and visualized in Cytoscape (19) version 3.2.

Common module and hubs extraction. The PPI networks for the five gynecological types of cancer were scrutinized for the presence of common sub-network, module and hub genes. A common sub-network was identified by comparing the nodes and edges among the five PPI networks. The common sub-network was further investigated to identify a common high-modularity cluster among the five PPI networks using the Molecular Complex Detection (MCODE) (20) plug-in for Cytoscape. Node score ≥0.2, k-core=2, degree ≥2 and maximum depth=100 were used as the cut-off criteria for the extraction of common modules. Hub genes were selected from the PPI networks with a connectivity degree of >25, and overlapping hubs among the five cancer networks were identified.

Enrichment analyses. Pathway and disease enrichment analyses for the common module genes and common hubs shared between the five gynecological types of cancer were performed using the Web-based Gene Set Analysis Toolkit (21). The cutoff criteria of P<0.05 and number of genes >2 were used for enrichment. Hyper-geometric distribution was utilized for enrichment analyses.

Results

DEGs identification. P<0.05 and |fold change| >2 were used as the demarcating parameters for the identification of DEGs in the five disease systems. A total of 3,521 DEGs for breast cancer, 1,086 DEGs for cervical cancer, 478 DEGs for endometrial cancer, 2,028 DEGs for ovarian cancer and 728 DEGs for vulvar cancer were identified, all compared with normal samples. The mined DEGs included upregulated and downregulated DEGs. Next, overlapping DEGs among the five cancer disease systems were identified (Fig. 1). A total of 10 DEGs, namely, cyclin B2 (CCNB2), ubiquitin-conjugating enzyme E2C (UBE2C), topoisomerase (DNA) II-α (TOP2A), centromere protein F (CENPF), baculoviral IAP repeat containing 5 (BIRC5), aurora kinase A (AURKA), discs, large (*Drosophila*) homolog-associated protein 5 (DLGAP5), transforming growth factor-β receptor III (TGFBR3), Krüppel-like factor 11 (KLF11) and kinesin family member 20A (KIF20A), were found to be differentially expressed in all five gynecological types of cancer. In total, 29 DEGs were revealed to overlap among cervical, endometrial, breast and ovarian cancer.

PPI network construction. Extracted DEGs from the five cancer datasets were mapped to create PPI networks by utilizing gene-coding protein interaction information. PPI networks for cervical cancer, breast cancer, endometrial cancer, ovarian cancer and vulvar cancer were formed with 689 nodes (4,505 edges), 364 nodes (1,494 edges), 155 nodes (1,005 edges), 733 nodes (5,721 edges) and 542 nodes (1,772 edges), respectively where each node represents a protein and the edge between the nodes represents the interaction between the proteins. These PPI networks were visualized in Cytoscape for further analysis.

Common module and hubs. Overlapping nodes and edges among the five PPI networks were identified to construct a common sub-network among the five gynecological types of cancer. A common module with 8 nodes (MCODE score=7.429; with 26 edges) was extracted from the common sub-network by MCODE. The common modules of the five cancer networks included 8/10 overlapping DEGs: CCNB2, UBE2C, TOP2A, CENPF, BIRC5, AURKA, DLGAP5 and KIF20A (Fig. 2). Additionally, the PPI networks for the five gynecological types of cancer were analyzed for the identification of hub genes exhibiting connectivity degrees of >25 (Table I). In total, 4 common hub genes (TOP2A, BIRC5, AURKA and CCNB2) were mined from the five gynecological types of cancer.

Enrichment analyses. Pathway enrichment analyses of the common module genes (Fig. 3A) revealed their association with the cell cycle, mitotic and aurora kinase signaling pathways. Overall, 7 genes from the common module were found to be associated with the cell cycle and mitotic pathways. There were 4 genes, KIF20A, UBE2C, BIRC5 and CENPF, enriched in the mitotic phase-associated pathways. KIF20A, BIRC5, AURKA and DLGAP5 were involved in multiple pathways, including the aurora kinase signaling pathway and the polo-like kinase signaling event in the cell cycle. Moreover, 3/4 common hub genes (TOP2A, BIRC5 and AURKA) were revealed to have a function in the aurora kinase signaling pathway. The genes of the common module were enriched in certain conditions, including cancer, viral infection and adenocarcinoma (Fig. 3B).

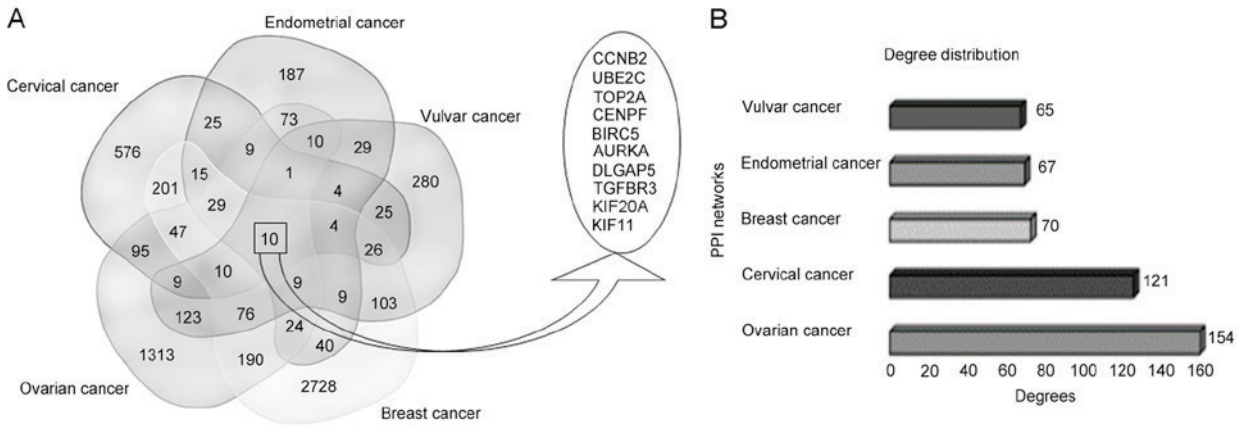

Figure 1. (A) Venn diagram representing the 10 common differently expressed genes among the five female-specific cancer types. (B) Degree distribution of the five cancer PPI networks. Number adjacent to the horizontal represents the maximum degree of the nodes (proteins) in the PPI network. PPI, protein-protein interaction; CCNB2, cyclin 2; UBE2C, ubiquitin-conjugating enzyme E2 C; TOP2A, DNA topoisomerase II-α; CENPF, centromere protein F; BIRC5, baculoviral IAP repeat containing 5; AURKA, aurora kinase A; DLGAP5, DLG associated protein 5; TGFBR3, transforming growth factor-β receptor 3; KIF20A, kinesin family member 20A; KIF11, kinesin family member 11.

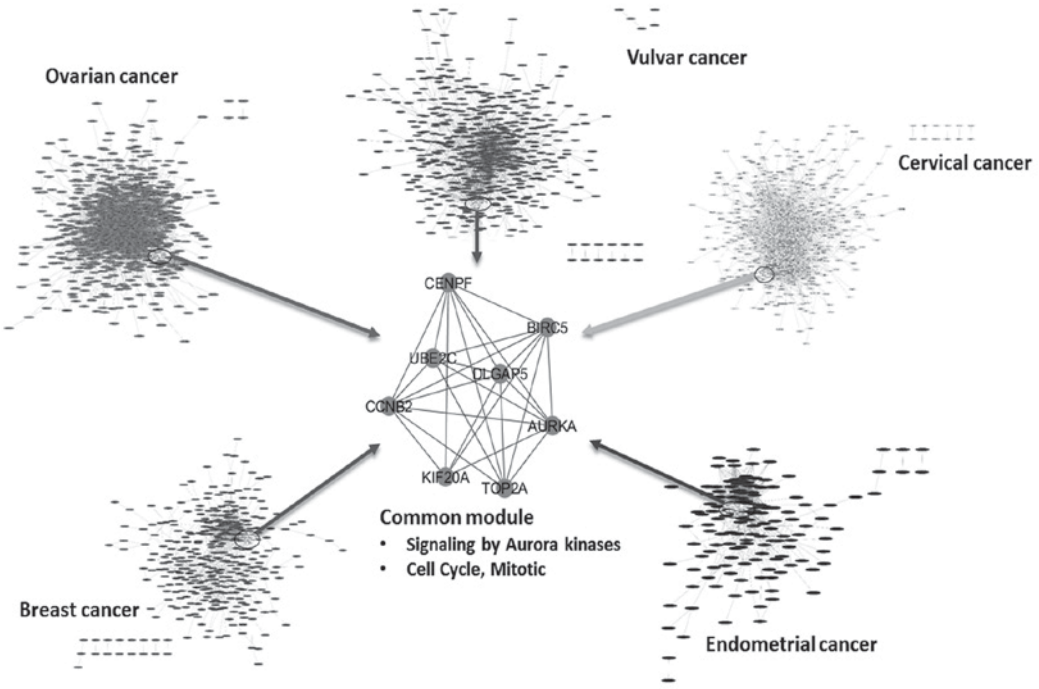

Figure 2. Common modules among the five female-specific cancer types. (A) Pathways enriched; (B) diseases enriched. PLK1, polo-like kinase 1; FOXM1, forkhead box M1.

Discussion

In the present study, overlapping modules and DEGs among five gynecological types of cancer (breast, cervical, endometrial, vulvar and ovarian cancer) were mined to identify common pathways, which may indicate a common method of tumorigenesis. An integrative approach utilizing differential expression and network analyses was employed for this purpose. It has been hypothesized that cervical, endometrial and vulvar cancer may share common molecular and biochemical features, and the resulting pathways present during cancer development in these three cancer types could shed light on disease development and embryogenesis aspects (1). The present study involved the construction of PPI networks for the five gynecological types of cancer from the gene-encoded protein interaction information, which are differentially expressed at the malignant stage compared with normal tissues. There were 10 DEGs found to be overlapping among the five cancer systems, with 4 DEGs identified as common hubs of the five PPI networks. The PPI networks were investigated to identify overlapping nodes and edges, and to reveal a common sub-network shared by all five female-specific cancer types. There were 4 genes (AURKA, KIF20A, DLGAP5 and BIRC5) involved in aurora kinase signaling pathway activation. Aurora kinase activity peaks during the G_2 phase to mitotic phase transition in the cell cycle. KIF20A, UBE2C, BIRC5

Table I. Hub genes of five female-specific cancer PPI networks.

Cancer type	Hub genes
Ovarian cancer	AKT1, GAPDH, CDK1, JUN, TOP2A, CCNB1, RAC1, FOS, ACTB, AURKA, HSPA5, ACTA2, BIRC5, CCNB2, CCNA2, CDC20, MMP2, TBP, SMARCA4, ERBB2, MAD2L1, YWHAZ, VEGFA, CDKN2A, TGFB1, BUB1, CDK16, IL8, MCM3, BUB1B, ACTG2, YWHAE, H2AFX, GNB2L1, ISG15, ENO1, TUBA1B, COL1A1, RHOB, TUBA4A, APOE, RACGAP1, MYBL2, TUBB4B, BUB3, RRM2, THBS1, TUBA1C, EIF4G1, PRKDC, HSPB1, MCM7, UBE2C, JUND, COL1A2, TUBB3, NCBP2, SERPINE1, CCNA1, TUBB, KIF2C, PRC1, CCT5, RPL23, TYMS, CALR, HSPD1, CCNE1, PSMB2, PSMB3, TXN, PKM, MYH9, RAD23A, RPL27A, RAD21, SDHC, NEK2, HNRNPC, RPL38, RPL37A, CCT2, HMGB1, FOXM1, OAS1, MMP14, RALA, CALM1, YWHAH, CDCA8, VWF, SDC1, MCL1, ACTN1, PSMC2, SMC4, SNRPE, KIF20A, RBBP4, SNRPF, RPS7, MCM4, KIF4A, SNRPB, OAS3, ACTN4, CFL1, MMP7, CENPF, OASL, ASF1A, RPL36, SMARCB1, BAK1, HSPH1, CTGF, MRPL13, JUNB, COL18A1, SPTAN1, HSPG2, PTBP1, PLK2, RANGAP1, MCM2, ATF3, HSF1, MELK, PPP1CA, SNRPD2, POLR2K, P4HB, COL4A1, SF3A2, ASF1B, PABPN1, DLGAP5, SNCA, CEBPB, PDIA4, PAK2, CLU, PRKCD, COL4A2, ARF1, NUSAP1, POLR2J, RPL36A, SMARCC1, UBA1, RAB8A, COX6A1, POLR2I, TSC2, CEP55, PRPF4
Cervical cancer	CDK1, TOP2A, PCNA, CDK2, CCNB1, BUB1, MAD2L1, BIRC5, CCNB2, MCM5, AURKA, CDC6, MCM3, CHEK1, MCM4, CENPA, MCM7, KIF11, BUB1B, MCM2, RAD51, NDC80, BRCA1, ESR1, ATR, XPO1, STAT1, RFC4, CDKN2A, KIF2C, NUF2, KIF23, CDC25A, BUB3, PRC1, CENPF, RRM2, RBBP4, MMP9, MCM6, TYMS, SMC4, IL8, RFC3, CCNE1, PIK3CA, KIF20A, FEN1, SMC2, RECQL, KNTC1, TOPBP1, KIF4A, NEK2, MSH2, PRKDC, MCM8, CDC7, CDC25C, WEE1, STAG1, CASC5, RACGAP1, CCNE2, EGR1, ZWILCH, CENPI, MCM10, KIF18A, RFC5, NCAPG, NUP107, ACTA2, MSH6, E2F3, NDE1, PDS5B, DLGAP5, CDC25B, GMPS, WDHD1, NUSAP1, PLK4, FOXM1, ISG15, RBL1, ECT2, CKS2, CENPN, CENPQ, CENPK, TTK, ZWINT, ITGB1, AHCTF1, DSN1, CEP55, ANLN, UBE2C, BARD1, GEN1, DDX58, COL1A1, SGOL2, POLE2, MELK, TRIP13, APOE, DNA2, ASPM, CKS1B, GINS1, EZH2, MMP1, FANCD2, DBF4, ESCO2, PRIM1, YWHAH
Endometrial cancer	CDK1, TOP2A, CCNB1, CDC20, CCNB2, AURKA, BIRC5, MAD2L1, CCNA2, KIF11, BUB1B, PRC1, CENPE, KIF23, KIF4A, KIF2C, CENPA, CDC6, DLGAP5, CENPF, NEK2, ESPL1, KIF20A, RACGAP1, NUSAP1, RRM2, UBE2C, MELK, CEP55, NCAPG
Breast cancer	CDK1, TOP2A, PLK1, CCNB2, AURKA, BUB1, BIRC5, CENPA, MMP9, BUB1B, AGT, NDC80, PRC1, CENPE, KIF2C, CDC42, KIF4A, NUF2, CDCA8, ESR1, KIF20A, STAT1, CENPF, DLGAP5, NUSAP1, ANLN
Vulvar cancer	BCL2, VEGFA, NOTCH1, FYN, AR, STAT1, CREB1, PIK3R1, MMP9, KIT, IL8, TOP2A, ACACB, IGF1, VWF, MET, BIRC5, MMP1, FOXO3, GATA3, DCN, YWHAZ, CCNB2, AURKA, IL1B

and CENPF were enriched in the mitotic phase-associated pathways, thus assisting in the dysregulation of the aurora kinase pathway. AURKA, TOP2A, KIF20A, CCNB2, UBE2C, BIRC5 and CENPF were enriched in the dysregulation of the cell cycle and mitotic pathways, which in turn could affect the normal function of the aurora kinase signaling pathways. In total, 7/8 genes from the common module were involved in the dysregulation of the aurora kinase signaling pathway.

The aurora kinase family is comprised of 3 serine-threonine protein kinases: Aurora kinase A, aurora kinase B and aurora kinase C, and the aurora kinase A protein is encoded by the AURKA gene. This family of proteins are regulators of cell division (22). Since the aurora kinase pathway is involved in chromatin duplication, mitotic entry, centromere maturation, chromatin condensation, spindle assembly and bipolar spindle formation (Fig. 4A) (23), overexpression or dysregulation of the associated pathways may lead to an increased rate of cell division and then to tumorigenesis.

Overexpression of aurora kinase has been reported in breast, liver, pancreatic, bladder, thyroid and gastrointestinal cancer types (24). AURKA overexpression has been proposed to be associated with aneuploidy in breast cancer (25). Polymorphisms in the AURKA gene have been shown to increase the risk of primary breast cancer (26). Studies have revealed that the increased expression of AURKA is associated with laryngeal, nasopharyngeal and breast cancer metastasis (27-30). AURKA has been demonstrated to be accountable for the phosphorylation of Breast Cancer 1, Early Onset (BRCA1) (31). Tanaka *et al* (32) investigated the immunohistochemical analysis of invasive ductal adenocarcinomas of the breast, that revealed the overexpression of aurora kinases in a majority of cases. Miyoshi *et al* (33) investigated the correlation of aurora kinase A mRNA expression with numerous clinic pathological factors and CIN in breast cancer. Nadler *et al* (34) investigated the correlation of a population of patients with a decreased survival rate based on aurora kinase A expression,

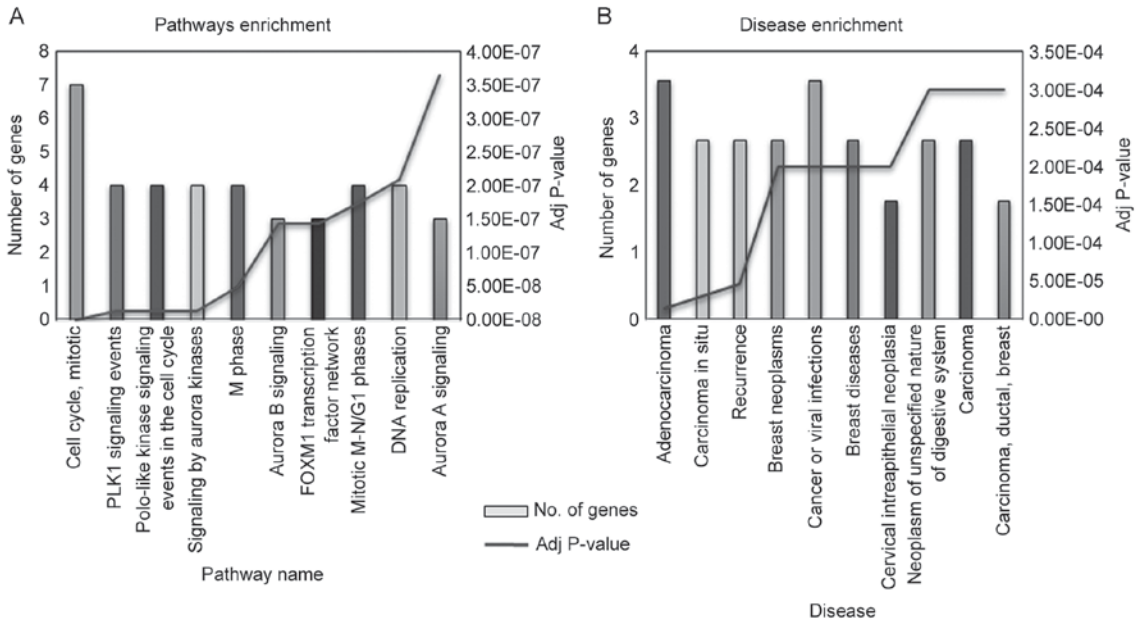

Figure 3. (A) Common pathway enrichment and (B) disease enrichment analyses of the common module genes by considering the number of genes and adjusted P-values. MAD2, mitotic arrest deficient 2 like 1; MCAK, kinesin family member 2C; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; RalA, RAS like proto-oncogene A; BRCA1, breast cancer type 1 susceptibility protein; BUBR1, mitotic checkpoint serine/threonine-protein kinase BUB1-β; AURKA, aurora kinase A.

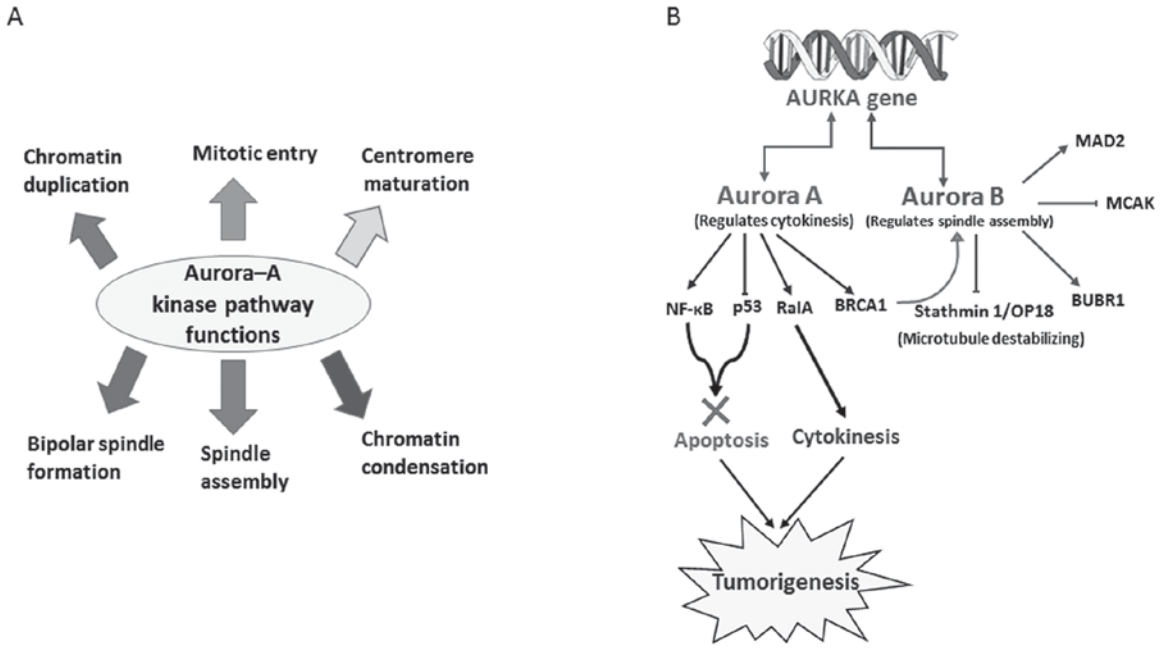

Figure 4. (A) Aurora kinase A and aurora kinase B interact with oncogenes to initiate tumorigenesis. (B) Function of the AURKA pathway. CENPF, centromere protein F; BIRC5, baculoviral IAP repeat containing 5; UBE2C, ubiquitin-conjugating enzyme E2 C; DLGAP5, DLG associated protein 5; CCNB2, cyclin 2; AURKA, aurora kinase A; KIF20A, kinesin family member 20A; TOP2A, DNA topoisomerase II-α.

whereas aurora kinase B does not interfere with the survival of patients. Thus, aurora kinase A was proposed to be a preferred drug target in breast cancer. Studies have indicated that aurora kinase A and aurora kinase B are significantly overexpressed in carcinoma and in cervical intraepithelial neoplasia 3 (CIN3), compared with in the normal cervix (35). A previous study found that the overexpression of aurora kinase A is crucial for survival of HPV-transformed cervical cancer cells (36). Overexpression of aurora kinase A is observed in 83% of human epithelial ovarian carcinoma cases (37). It has been proposed that AURKA regulates cell migration and adhesion in epithelial ovarian cancer (38). Human chromosome 20q13.2, which contains AURKA, is usually amplified in ovarian cancer (39). Furthermore, Aurora kinase A has been revealed to be associated with Federation Internationale de Gynecologie et d'Obstetrique stage, tumor grade and survival (37). AURKA and AURKB

are overexpressed in endometrial cancer, in comparison with normal proliferative tissues, as determined by Kurai *et al* (40). Moreno-Bueno *et al* (41) revealed the presence of high AURKA expression levels in type-II adenocarcinoma via the microarray analysis of endometrial cancer tissue. Few studies are available that highlight the potential mechanisms for vulvar cancer (42). It has been revealed to originate from two distinct pathways: HPV-dependent and HPV-independent (43).

KIF20A belongs to the kinesin superfamily, which is involved in essential cellular functions including migration, mitosis and intracellular transport though interaction with microtubules (44). KIF20A has been proposed to be a potential immunotherapeutic target for cancer (45) and is often overexpressed in breast cancer, lung cancer, pancreatic cancer, gastric cancer, bladder cancer, melanoma and other malignancies. (46-48). KIF20A small interfering RNA (siRNA), along with six other siRNAs, has been reported to kill HeLa cervical cancer cells (49). Another study revealed KIF20A to be a hub of the gene co-expression network of endometrial cancer (50).

BIRC5 is a member of the inhibitor of apoptosis family, which is involved in mitosis and protection against apoptotic cell death (51). Signaling networks required for tumor maintenance are expected to be compromised by disabling BIRC5 and survivin, thereby enhancing its utility as a cancer drug target (52). Genomic copy number variations in BIRC5 have been proposed to be involved in the progression of breast cancer (53). Furthermore, BIRC5 expression may result in breast tumor proliferation by promoting genetic instability (54). BIRC5 has been reported to be overexpressed in cervical cancer (55). Overexpression of BIRC5 promotes cervical cancer progression and metastasis (55). BIRC5 has been reported to be overexpressed in various human malignancies, including ovarian cancer (56) and endometrial cancer (57). Human telomerase reverse transcriptase is an enzyme that enables cells to divide indefinitely and overcome replicative senescence (58); this enzyme has been reported to be upregulated in vulvar intraepithelial neoplasia, with the emergence of resistance to apoptosis and cellular longevity via survivin activation (58).

Silencing of DLGAP suppresses tumorigenicity and inhibits cellular proliferation by inducing cell cycle arrest at the G_2/M phase (59). DLGAP5 has been proposed to be a target of the neurogenic locus notch homolog protein 3 signaling pathway (59), which is associated with embryogenesis and breast cancer tumorigenesis (60). DLAGP5 is reportedly a member of the cervical cancer interaction network (61), and has been revealed to be overexpressed in ovarian carcinoma compared with in normal ovarian epithelium (59). DLGAP5 is overexpressed in endometrial cancer tissues, in comparison with normal endometrial tissues (62).

Overexpression of aurora kinases not only dysregulates the cell cycle but also facilitates interactions with several cancer-associated proteins, including tumor protein p53, nuclear factor κ-light-chain enhancer of activated B cells (NF-κB), v-Myc, Ras and pathways including the mitogen-activated protein kinase/extracellular-related kinase and phosphoinositide-3 kinase/protein kinase B signaling pathways (Fig. 4B) (63,64). In the present study, the overexpression of these oncogenes was also observed. Aurora kinase A is essential for cytokinesis as it activates NF-κB, an anti-apoptotic gene that is involved in growth regulation of cells, the overexpression of which leads to cancer (65). Additionally, p53 induces apoptosis; the overexpression of aurora kinase A phosphorylates p53 and inhibits its function. (22). Aurora kinase A may phosphorylate RalA, thus influencing Ras signaling and leading to tumorigenesis (66). Myc was also overexpressed in the present analysis. Myc is a quintessential oncogene, which is overexpressed in cancer cells and functions as an angiogenic switch (67). Myc has been revealed to be present in number of cancer types, including colorectal, prostate and breast cancer (68). Aurora kinase B overexpression leads to chromosomal segregation error and abnormal cytokinesis, potentially causing carcinogenesis (63).

Aurora kinase A has been revealed to have a vital function in increasing chemotherapy resistance, cell exhibiting stem-cell-like properties and mesenchymal phenotypes (69). Thus, the inhibition of aurora kinase A has demonstrated an increased sensitivity and decreased proliferation of breast cancer to chemotherapy and hormonal treatments (70). The aurora kinase B inhibitor ZM447439 has already been proven to suppress the growth of cervical cancer cells, thus enhancing chemosensitivity (71). A previous study has confirmed the potential utility of the aurora kinase A inhibitor alisertib, when used in combination with taxanes, as a therapeutic strategy for ovarian cancer (72). To verify the clinical significance of AURKA in improving the therapy of endometrial cancer, a combination treatment utilizing AURKA inhibitors and paclitaxel is proposed (73).

DEGs identified from the microarray analysis of the five gynecological types of cancerous cell sample were utilized for the construction of PPI networks in the present study. Identification and analysis of the common hub genes and modules suggested the presence of the aurora kinase pathway in all five of the gynecological types of cancer. Aurora kinases are a potentially promising area of research, as they are overexpressed in five gynecological types of cancer and are key regulators of cell division, as well as acting together with a number of oncogenes. The findings of the present study may be utilized for the development of exhaustive models of carcinogenesis, which may lead to the development of novel therapeutic approaches that target mechanisms frequently altered across various cancer types. However, further experimental validations are required to confirm these findings.

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