p38 β - MAPK11 and its role in female cancers

Periklis Katopodis (✉ katopodisper@gmail.com)

Brunel University <https://orcid.org/0000-0002-8892-2768>

Rachel Kerslake

Brunel University College of Health and Life Sciences

Athanasios Zikopoulos

Royal Cornwall Hospital

Nefeli Eirini Beri

Karolinska Institutet

Vladimir Anikin

Royal Brompton and Harefield NHS Trust: Royal Brompton and Harefield NHS Foundation Trust

Research

Keywords: MAPK11, MAPK, female cancers, breast cancer, ovarian cancer, cervical cancer, uterine carcinosarcoma, meexress, smartapp, cbiportal, canSar, methylation, p38 β , Pan-cancer

Posted Date: November 16th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-107231/v1>

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Abstract

Background The p38MAPK family of Mitogen Activated Protein Kinases are a group of signalling molecules involved in cell growth, survival, proliferation and differentiation. The widely studied p38 α isoform is ubiquitously expressed and is implicated in a number of cancer pathologies, as are p38 γ and p38 δ . However, the mechanistic role of the isoform, p38 β , remains fairly elusive. Recent studies suggest a possible role of p38 β in both breast and endometrial cancer with research suggesting involvement in bone metastasis and cancer cell survival. Female tissue specific cancers such as breast, endometrial, uterine and ovary account for over 3,000,000 cancer related incidents annually; advancements in therapeutics and treatment however require a deeper understanding of the molecular aetiology associated with these diseases. This study provides an overview of the MAPK signalling molecule p38 β (MAPK11) in female cancers using an *in-silico* approach.

Methods A detailed gene expression and methylation analysis was performed using datasets from cBioportal, CanSar and MEXPRESS. Breast, Uterine Endometrial, Cervical, Ovarian and Uterine Carcinosarcoma TCGA cancer datasets were used and analysed.

Results Data using cBioportal and CanSAR suggest that expression of p38 β is lower in cancers: BRCA, UCEC, UCS, CESC and OV compared to normal tissue. Methylation data from SMART and MEXPRESS indicate significant probe level variation of CpG island methylation status of the gene MAPK11. Analysis of the genes' two CpG islands shows that the gene was hypermethylated in the CpG1 with increased methylation seen in BRCA, CESC and UCEC cancer data sets with a slight increase of expression recorded in cancer samples. CpG2 exhibited hypomethylation with no significant difference between samples and high levels of expression. Further analysis from MEXPRESS revealed no significance between probe methylation and altered levels of expression. In addition, no difference in the expression of BRCA oestrogen/progesterone/HER2 status was seen.

Conclusion This data provides an overview of the expression of p38 β in female tissue specific cancers, showing a decrease in expression of the gene in BRCA, UCEC, CESC, UCS and OV, increasing the understanding of p38 β MAPK expression and offering insight for future *in-vitro* investigation and therapeutic application.

Introduction

The establishment of cancer as one of the leading causes of morbidity and mortality globally is widely accepted, yet the complexity of molecular processes that contribute to the development and progression of the numerous subsets of cancer continues to plague researchers. Of the 18.1 million incidences of cancer worldwide in 2018 over 20% of cases are thought to be female reproductive tissue specific [1]. The most frequently diagnosed type of female specific cancers is breast cancer with 2,088,849 cases recorded in 2018, around only 1% of which are male [2]. Cervical cancer is the most frequently diagnosed of the gynaecological cancers, with 569,847 cases diagnosed annually followed by endometrial and

uterine with 382,069 cases; ovarian is the least common yet deadliest with 295,414 cases diagnosed globally each year and over 184,779 deaths [1].

Knowledge regarding associated risk factors such as diet, weight, heritability, and menopausal status along with global health initiatives, routine cervical screening, and breast imaging, have led to earlier detection of both cervical and breast cancer [3, 4]. However, recurrence and mortality rates are still troublesome. Gynaecological cancers such as uterine and endometrial are also often detected at early to mid-stages with treatment for female reproductive tissue cancers often involving surgical procedures such as complete or partial mastectomy (breast) or hysterectomy [5]. Ovarian cancer, however, is more frequently diagnosed at an advanced stage owing to the ambiguous nature of symptoms related to many gynaecological disorders [6]. Despite comprising the lowest number of gynaecological cases, ovarian cancer is the deadliest of gynaecological malignancies with five-year survival less than 26% for those diagnosed with advanced serous ovarian cancer [7]. Notwithstanding the continued advancements in detection and treatments of cancer many of the molecular mechanisms implicated in the development, progression and resistance related recurrence of female reproductive tissue specific cancers require further investigation [8].

Of the multitude of risk factors associated with the development of cancer, hormone dysregulation is substantial in breast, with the onset of menopause lowering the risk of breast cancer while prolonged exposure to endogenous hormones such as oestrogen as and oestrogen receptor status presenting an increased risk [9]. In addition, age, as well as genome instability and mutation are often implicated in the development and progression of cancer. Heritable mutation of the DNA repair genes BRCA1 and BRCA2 are not only significantly associated with breast cancer but are also biomarkers of ovarian and endometrial cancer [10]. Other notable genes include the Tumour Suppressor protein 53 (TP53) as well as angiogenic factors such as VEGF and TGF- β as well as signalling molecules such as the Mitogen Activated Protein Kinase (MAPK) family kinase proteins [11].

MAPKs

Mitogen activated protein kinases (MAPKs) play vital roles in signalling transduction pathways and ability to control intracellular processes such as cell survival, differentiation, proliferation and apoptosis, via the sequential phosphorylation of substrate protein Ser/Thr kinase protein cascades. The three-tiered activation structure consists of the activation of a MAPK Kinase Kinase (MAP3K) followed by the phosphorylation of a MAPK Kinase leading to the dual phosphorylation of MAPK proteins [12]. The conventional subfamilies of MAPK include: the extracellular signal regulated kinase (ERK) proteins, ERK1/2 and ERK5 along with the stress activated Jun amino-terminal kinases (JNK) as well as the stress activated p38MAPK proteins (Fig. 1) [12, 13].

p38 β

The p38MAPK family is comprised of four homologous proteins: p38 α , p38 β , p38 δ and p38 γ and is involved in the integration of biochemical signals in response to environmental stresses as well as reactive oxygen species (ROS) and inflammatory cytokines [14, 15]. The p38MAPK family has been

implicated in a number of cancer pathologies. p38 α is the most widely studied of the isoforms and is ubiquitously expressed along with p38 β , of which it shares around 75% homology, whereas p38 δ and p38 γ are differentially expressed throughout the tissues [16].

Over the last few decades, evidence implicating regulation of p38 with processes involved in cancer such as epithelial-mesenchymal transition, migration, invasion, and survival has grown. Until recently, investigation of p38 had primarily focused on the biomarker p38 α , however mounting evidence also suggests roles for p38 β and the other isoforms [17–20].

p38 β is encoded by 12 exons of the gene MAPK11 that lie on chromosome 22 at the position 22:55,263,713 – 50,270,380 (UCSC genome browser/GRCh38/hg38). It is comprised of 364 amino acids and contains a kinase domain comprised of a T-G-Y dual phosphorylation motif that enables activity [21]. p38 β is expressed in the vast majority of the organs and cell types with high expression in endothelial cells yet low in those of hematopoietic origin such as macrophages and monocytes [22]. p38 β is activated by MKK6 and expressed at a lower basal level while, p38 α is activated by MKK3/6 often leading to the past characterisation of p38 β as redundant [23]. p38 α expression is crucial for foetal development and its absence is lethal, while expression of p38 β is not [24–26]. Both p38 α and p38 β , along with the downstream MAPKs MK2/3/5, act as key regulators in gene expression as well as cell cycle progression and are activated in response to stress and many pathological processes including inflammation and cancer [27]. Unlike p38 α , p38 β modulates basal activity through self-activation via autophosphorylation [28]. While a lot of work has been done on the p38 α expression and activity, the roles of p38MAPKs ($\beta/\gamma/\delta$) remain to be elucidated.

Recent literature has presented emerging roles for p38 β in tumour progression including the ability to regulate TGF-1 β and VEGF growth factor mediated survival of endothelial cells in the absence of the proapoptotic p38 α [29].

In addition, p38 β is shown to play a significant role in the regulation of the oncogene lipocalin 2 (LCN2) a target of plakophilin 3 (PKP3). Where PKP3 expression is decreased p38 β is capable of regulating LCN2 leading to an increase in tumour invasion and metastasis [30]. In all cancers, an increasing number of key proteins or long non-coding RNAs are also starting to be associated with p38 β expression and protein-protein interaction [31–35]. The Long non-coding RNA, LINC01220 in particular, has received interest due to its roles in p38 β suppression and in endometrial cancer and as such its therapeutic potential [35].

Despite the numerous studies investigating the expression and role of p38 β in cancers such as lung, Head and Neck Squamous Cell carcinoma as well as prostate the role in female tissue specific cancers remains elusive [36, 37]. As such, this bioinformatic review will provide an overview of the role of p38 β in all cancers with a detailed focus of p38 β in female tissue specific cancers.

p38 β in female cancers

Breast cancer (BRCA)

p38MAPKs translate extracellular signals to intracellular response. Their role in cell proliferation, differentiation and response to inflammation is vital for normal cell function. They are regulators of major pathways including the ERK1/2-JNK (extracellular signal regulated-kinase, c-Jun N-Terminal Kinase) pathways which are

both associated with poor clinical outcome in breast cancer patients [38]. Despite the viability of a p38 β ^{-/-} knock out mice and the consideration of p38 α as the predominant isoform in response to cellular stresses there is increasing evidence of p38 β involvement in stress response and cancer cell biology [39, 40]. Upregulation of p38 β in breast cancer is a prime example, p38 β regulation may not have been linked to tumour growth however increased expression is associated with upregulation of monocyte chemotactic protein-1 (MCP-1) leading to osteoclast differentiation and promotion of bone metastasis in breast cancer patients [40]. Apart from the following gynaecological cancers, although rare (~ 1%), breast cancer may affect men as well. Male breast cancer is often associated with inherited mutations of BRCA1, BRCA2 and PIK3CA genes, obesity, estrogen treatments (hormonal therapies for prostate cancer) and Klinefelter syndrome [41–43].

Ovarian cancer (OV)

It has been found that Galectin-1 (Gal-1) is an indicator of poor prognosis in ovarian cancer patients where high expression of Gal-1 is observed in ovarian cancers of higher histological grade as well as advanced lymph node status [44, 45]. Activation of the MAPK JNK/p38 pathway is influenced by Gal-1 and facilitates epithelial-mesenchymal transition (EMT) making it a promising target for prevention of epithelial ovarian cancer metastasis [45]. In addition to Gal-1, overexpression of genes such as LAMC2 are also associated with increased cell proliferation, repression of cell apoptosis and increased expression of p38. Inhibition of p38 nuclear accumulation through the negative regulation of LAMC2 by miR-125a-5p is also shown to repress tumorigenesis in epithelial ovarian cancer [46].

Uterine Corpus Endometrial Carcinoma (UCEC)

Uterine Corpus Endometrial Carcinoma has not been investigated in as much detail, but a few markers have been identified that play significant roles in the progression of this type of cancer. Mutation of the PTEN gene, for example, affects cellular signalling through inhibition of MAPK pathway and is associated with histological subtype as well as the early stage characteristics of endometrial cancer. Regulation of cell proliferation - differentiation by MAPK via RAF-MEK-ERK may provide a targetable mechanism for future research [47]. Studies have shown that oestradiol is a potential activator of the MAPK pathway through estrogen (ER) and Insulin receptor (InsR) interaction. Insulin synergistically with ER activates phosphorylation of MAPK and PI3K pathways [48, 49]. Phosphorylated Akt (p-Akt), mTOR (p-mTOR) and MAPK (p-MAPK) proteins as well as lncRNAs like HEIH, are often implicated in endometrial carcinogenesis and tolerance of common antineoplastic agents such as paclitaxel [50, 51]. As such, MAPK and PI3K/Akt are promising targets of new anti-tumor agents such as emodin (rhubarb) [47].

Uterine Carcinosarcoma (UCS)

Uterine carcinosarcoma is usually classified as uterine endometrial carcinoma but is often more aggressive than UCEC. Little is known about the molecular effects that influence aggressive biphasic growth of the sarcomatous elements that account 2–5% of the uterine corpus malignancies [52, 53]. It has been shown that UCSs undergo EMT and highly express signal transducers such as TGF- β ; SMAD2/3, playing an important role in the regulation of cell growth and development [54]. There is very little evidence regarding investigation of MAPK and other signalling pathways in UCS within the literature, in light of the involvement of MAPK signalling in other female malignancies this absence presents an area for further investigation.

Cervical Squamous Cell Carcinoma (CESC)

In Cervical Squamous Cell Carcinoma, activation of p38 when driven by mediators such as osteopontin (OPN) leads to invasive progression. Phosphorylated p38 by CD44-mediated MKK3/6, high expression of OPN and furin, induction of NF- κ B and p65 are correlated with cervical cancer progression and are considered therapeutic targets [55]. Not only is p38 inhibition a target of novel anti-tumour agents, there are also reports of suppression through use of traditional herbal medicines such as Matrine, which consequently also decreases the expression of matrix metalloproteinases, MMP-2 and MMP-9 [56]. In contrast, activation of MMPs via p38/NF κ B pathway with inflammatory cytokines like interleukin 17A (IL-17A), is associated with the invasion of cervical cancer cells, making IL-17A another potential prognosis marker of CESC [57]. Despite the tumorigenic nature of p38 there is evidence of dual role status as both a tumour suppressor and protooncogene; Xanthonoids such as Alpha-mangostin for example elevate reactive oxygen species (ROS) as well as p38 and consequently damage mitochondrial integrity while instigating apoptosis within cervical cancer cells [58].

Using large-scale data sets such as TCGA, genetic analysis and potential biomarker identification is becoming increasingly accessible to researchers. *In-silico* analysis using online datasets and tools can further the understanding of alterations and mechanisms which influence expression such as the mutational status and methylation profile of genes of interest without the need of expensive and time consuming *in-vivo/in-vitro* analysis. This research seeks to use data visualization tools compiling data from TCGA for the analysis of the p38MAPK isoform p38 β in cancers of female reproductive tissue origin, presenting evidence for the further exploration of this signalling molecule in cancer cell biology for molecular understanding and potential therapeutic translation.

Results

The PanCancer analysis of MAPK11 provides an overview of expression throughout the early and advanced stages of the disease as well as the genetic alterations of MAPK11 that contribute towards changes in expression. Focusing on female tissue-specific cancers (Fig. 2a), we outline a trend where MAPK11 expression in normal tissue is higher than that of early-stage BRCA, CESC, UCEC, and UCS cancer data sets. Unlike the other female cancers, MAPK11 expression in OV is primarily shown at the advanced stage of the disease which is often the stage of diagnosis due to the ambiguity of symptom presentation (Fig. 2d). The average expression of MAPK11 in OV (0.9 RSEM ($\log_2(\text{value} + 1)$)), is relatively

low compared to the other female cancers and is mirrored in the low expression alteration profile seen in Fig. 2b where shallow and deep deletion are the most frequent type of alteration.

Gene expression and methylation

It is generally considered that DNA methylation within the CpG island region of a gene's promoter region is correlated with gene expression while DNA methylation within the gene body is also associated with chromosomal integrity [66]. To analyse the methylation status of MAPK11, 14 probes were chosen through the SMART database and studied within the female cancers: BRCA, CESC, and UCEC.

Here, we find a positive correlation of MAPK11 expression with methylation of the promoter region. Two of these CpG islands were found within the genomic region of MAPK11. The probe cg26790091 at the S-Shelf region showed lower methylation values compared to normal datasets and a positive correlation of expression and methylation was seen for all datasets with the exception of UCS ($R=-0.04$). The same pattern is observed with the N-Shore probe cg03717414, with lower methylation in all tested cancers compared to normal and a positive correlation between expression and methylation, again with exception to UCS ($R=-0.0053$). Following the genomic region of MAPK11, we found 10 locations on 2 islands with the first island having 4 methylation targets (CpG1: cg23755154, cg15036874, cg16054907, cg13577505) to present a strong positive correlation of expression-methylation for all 4 cancers (exception is probe cg15036874 in BRCA with an $R=-0.095$). Following the S-shore region, the next 6 locations located within the second island exhibit hypomethylation with a strong correlation between expression and methylation status (CpG2: cg19184963, cg08211722, cg15554007, cg00735239, cg00164898, cg00395632). Detailed results are located in Additional files 1, 2, and 3. Differences between the observed levels of expression and region-specific methylation are seen in Fig. 3 may influence the binding of transcriptional factors at the promoter region of the gene as well as the stability of the gene itself [67].

Gene expression and methylation analysis show that in BRCA, methylation at cg23755154 is significantly increased while the hypomethylated cg19184963 and cg00395632 are decreased within the tumour dataset (Additional file 1). In CESC, the dataset exhibits significant hypermethylation at cg15036874 and cg16054907 along with hypomethylation of the aggregated probes with tumour showing higher levels of methylation compared to normal tissue (Additional file 2). In UCEC, significant probe sites include the hypermethylation of cg23755154 and cg16054907 (Additional file 3). Information about the UCS and OV aggregation could not be obtained due to limitations of the SMART analysis tools (see Additional file 4).

We chose to group the methylated probes by region separating those that are located at CpG island 1 and those at CpG island 2 to analyse the separate promoter binding regions. A Spearman correlation analysis between the expression of MAPK11 and DNA methylation (M value) of MAPK11 in three of the female cancers indicates that expression is significantly positively associated with the methylation of region 1, a phenomenon that does not align with the normal paradigm of gene expression (cg23755154, cg15036874, cg16054907, cg13577505). Negative correlation however was seen with the following 6

probes that are localised to the second CpG island: cg19184963, cg08211722, cg15554007, cg00735239, cg00164898, cg00395632 (Fig. 4, see Additional file 1, 2, and 3).

Average aggregation of probes indicates that the gene is hypermethylated within the region of the first CpG island region yet hypomethylated in the second for both cancer data and normal, there is little significant difference between the levels of expression and methylation for the aggregated probes of BRCA with CESC and UCEC only exhibiting slight variation. Further analysis of the collection of probes aligning at the CpG island regions of the gene MAPK11 in wildtype and cancer data sets can be seen in Additional Fig. 5.

Complementary methylation analysis using MEXPRESS, indicates that there is no significant difference in the expression of the MAPK11 between the stages of each cancer data set studied (Fig. 5, Additional file 5). Moreover, no significant changes were observed for the BRCA oestrogen and BRCA progesterone receptor status, HER2/neu receptor, or menopause status of the cancers (data not shown here).

Methods

MEXPRESS web tool was used to integrate TCGA data for the visualisation of gene specific methylation and expression of MAPK11 in relation to genomic location and clinical data such as age, weight and receptor status [59].

DNA methylation is a reversible process consisting of the covalent binding of a methyl group to cytosine, one of four DNA bases. In humans, DNA methylation is almost exclusively restricted to the cytosines of CpG dinucleotides and plays a critical role in the regulation of gene expression. Abnormal DNA methylation patterns are found ubiquitously in all types of human cancer. The precise genomic location of DNA methylation is one of the most important regulatory factors of gene expression, and is where MEXPRESS distinguishes itself from other available tools [60].

Shiny Methylation Analysis Resource Tool (SMART) provided access to a comprehensive overview of MAPK11 DNA methylation and associated omics data, through integration of TCGA data [61, 62]. This application was used to correlate epigenetic modifications with gene expression in cancer data sets using probes specific to genomic regions of MAPK11. The following 14 probes were used in analysis of MAPK11 (Table 1).

Table 1
List of the 14 probes analysed

Probe	Chromosome	Start	End	CGIposition	CpG
cg26790091	chr22	50264031	50264032	S_Shelf	
cg03717414	chr22	50265420	50265421	N_Shore	
cg23755154	chr22	50266978	50266979	Island	CpG1
cg15036874	chr22	50267519	50267520	Island	
cg16054907	chr22	50267636	50267637	Island	
cg13577505	chr22	50267819	50267820	Island	
cg06018119	chr22	50268221	50268222	S_Shore	
cg19184963	chr22	50270210	50270211	Island	CpG2
cg08211722	chr22	50270495	50270496	Island	
cg15554007	chr22	50270507	50270508	Island	
cg00735239	chr22	50270518	50270519	Island	
cg00164898	chr22	50270698	50270699	Island	
cg00395632	chr22	50270792	50270793	Island	
cg11070772	chr22	50272060	50272061	S_Shore	

The **cBioPortal** (www.cbioportal.org/) which contained both sequencing and pathological data on 30 different cancers was used to analyze the genetic alteration of MAPK11 across different cancer types [63, 64]. The Breast Invasive Carcinoma (TCGA, PanCancer Atlas, n = 1075), Cervical Squamous Cell Carcinoma (TCGA, PanCancer Atlas, n = 297), Ovarian Serous Cystadenocarcinoma (TCGA, PanCancer Atlas, n = 585), Uterine Corpus Endometrial Carcinoma (TCGA, PanCancer Atlas, n = 529), Uterine Carcinosarcoma (TCGA, PanCancer Atlas, n = 57) datasets were selected for further analyses of MAPK11 expression and mutation status [63, 64].

canSAR. Pan-cancer analysis of the MAPK11 expression and expression in the different cancer stages of the four female cancers was conducted through canSAR (cansar.icr.ac.uk), a public, freely available, integrative translational research and drug discovery knowledge base [65]

Discussion

The MAPK signalling cascades are integral signalling mechanisms that play an active role in cellular processes including proliferation, apoptosis, differentiation, and cell development. The p38MAPK

isoforms, in particular, mediate response to external stresses, inflammatory cytokines as well as reactive oxygen species (ROS) [68–70].

Until recently, clinical evaluation of a family of key regulators, the p38MAPK isoforms have widely focused on the study and consideration of p38 α as a biomarker of cancer [71]. However, recent evaluations of p38 implicate the additional isoforms with cancer cell biology. The expression of p38 β has received growing interest for its roles in female cancers such as breast and endometrial [72].

Data generated within this study sought to explore the expression of p38 β in the female tissue-specific cancers: BRCA, CESC, OV, UCEC, and UCS, revealing down-regulated expression of the gene in each cancer data set compared to normal tissue (Fig. 2). Deep deletions within the MAPK11 gene were the most frequent type of alteration within the gene and no significant difference of expression seen between stages of the cancers studied (TCGA data regarding OV is not as extensive as the other data sets). These trends in the expression are converse to that of p38 α which is often over-expressed within cancer cells and considered to render the roles of p38 β redundant. However, recent publications suggest that p38 β is capable of self-activation through autophosphorylation and the regulation of specific pathways outlined in the introduction [28, 73].

Regulation of genes is often influenced through methylation. Using the SMART analysis tool, the methylation status of MAPK11 at specific regions was assessed. Grouped analysis of the methylation probes specific to the two CpG islands located on the MAPK11 gene was used to reveal the methylation status and expression of the gene promoter regions. Hypermethylation of the gene in the CpG1 was seen for BRCA, CESC, and UCEC with an increase in the methylation of the gene in tumour samples as well as a positive correlation with expression. This trend does not follow the general paradigm often seen with hypermethylation and gene suppression suggesting that methylation is not the only regulator of gene expression and that there are additional transcriptional and post-transcriptional factors influencing the decreased levels of p38 β expression within these cancers. The CpG2 island however displays hypomethylation of the region along with negative correlation and relatively high levels of gene expression with little difference between cancer and normal.

The differential methylation of specific regions of a gene is often associated with both expression and gene stability. Therefore, the different levels of methylation within the CpG islands of MAPK11 between normal and cancer data sets may influence the decrease in expression of MAPK11 seen in cancer tissues and warrants further investigation as a possible biomarker (Figs. 4 – 2) [67].

Additional analysis through MEXPRESS was also used to assess the correlation between the receptor status and expression of MAPK11. The oestrogen receptor alpha is thought to mediate the development of endometrial cancer and is a biomarker of breast cancer. However, no differences in expression were seen relative to oestrogen, progesterone, or HER2/neu receptor status as well as menopausal status suggesting that p38 β activation is not mediated via these pathways that are often associated with female cancers (Additional file 5) [49].

Despite the decreased level of expression, the high level of deep deletion within the gene and differences in methylation may influence post-transcriptional regulation and phosphorylation of the gene, influencing its ability to self-activate. For example, therapeutics such as emodin which target phosphorylation are shown to maintain basal levels of genes involved in the p38MAPK pathway while inducing ROS activated apoptosis of cancer cells [47, 74]

Activation of p38 β via the transcription factor Pokemon/Zbtb7 is associated with tumorigenesis and cell invasion in HepG2 cells [30]. Downstream signalling of p38 β also leads to an increase in expression of the oncogene, Lipocalin2 (LCN2), and an increase in tumour cell migration [18, 30]. Additional downstream targets include mediators of proliferation and survival such as AP-1 and mTOR which consequently are also involved in gynaecological malignancy [75, 76]. MAPK11 has shown oncogenic properties through increased regulation of the WNT inhibitor, Dickkopf WNT signalling pathway inhibitor 1 (DKK-1), a key regulator of bone metastasis [31]. Elevated levels of DKK-1 are also associated with advanced clinical stage and poor prognostic outcomes in gynaecological malignancies including ovarian cancer [77]. The upregulation of p38 β through lncRNA 1220 is also associated with endometrial cancer through the mediation of proliferation and inhibition of apoptosis. p38 β phosphorylates Myocyte Enhancer Factors (MEF) such as MEF2A and MEF2C regulators of differentiation, proliferation, apoptosis, migration as well as metabolism especially in the absence of p38 α [78]. It has been shown that it increases osteoclast differentiation and activity through upregulation of monocyte chemotactic protein-1 (MCP-1) [40, 79]. It has also been suggested that the p38MAPKS are capable of acting as both a tumour suppressor as well as an oncogene [80–82]. With the lower expression levels, its ability to regulate these vital cell functions and act as a tumour suppressor may be compromised.

Further investigation of the role in these female tissues may provide an opportunity for uncovering a dual role of MAPKp38 isoforms as both oncogenes and tumour suppressors in cancer cell biology.

Declarations

Acknowledgements

We thank Miss Heerni Halai for helping with the acquisition of some of the figures and proofreading.

Authors' contributions

PK had roles in conceptualization, methodology, data curation, funding acquisition, investigation, visualization, supervision, analyse of all data sets, formal analysis, acquiring the figures, writing-original draft, reviewing, and editing. RK had roles in investigation, writing-original draft, and writing-reviewing and editing. AZ and NB had roles in writing-reviewing. VA had roles in reviewing and funding acquisition. All authors read and approved the final manuscript.

Funding

No funding was received for this publication

Ethics approval and consent to participate

Not applicable.

Consent to publish

Not applicable.

Competing interests

The authors declare that they have no competing interests

Author details

1. Biosciences, College of Health, Medicine and Life Sciences, Brunel University London, Uxbridge, UK
2. Division of Thoracic Surgery, The Royal Brompton & Harefield NHS Foundation Trust, Harefield Hospital, UB9 6JH, London, UK
3. Obstetrics and Gynaecology, Royal Cornwall Hospitals NHS Foundation Trust, Royal Cornwall Hospital, Truro TR1 3LJ, UK
4. Department of Medicine, Karolinska Institutet, 17177 Stockholm, Sweden
5. Department of Oncology and Reconstructive Surgery, Sechenov First Moscow State Medical University, Moscow 119146, Russian Federation

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394–424.
2. Abdelwahab Yousef AJ. Male Breast Cancer: Epidemiology and Risk Factors. *Semin Oncol*. 2017;44:267–72.
3. Tsikouras P, Zervoudis S, Manav B, Tomara E, Iatrakis G, Romanidis C, et al. Cervical cancer: screening, diagnosis and staging. *J BUON*. 2016;21:320–5.
4. Massat NJ, Dibden A, Parmar D, Cuzick J, Sasieni PD, Duffy SW. Impact of Screening on Breast Cancer Mortality: The UK Program 20 Years On. *Cancer Epidemiol biomarkers Prev a Publ Am Assoc Cancer Res cosponsored by Am Soc Prev Oncol*. 2016;25:455–62.
5. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. *Lancet (London, England)*. 2005;366:491–505.
6. Doubeni CA, Doubeni AR, Myers AE. Diagnosis and Management of Ovarian Cancer. *Am Fam Physician*. 2016;93:937–44.
7. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:284–96.

8. Sonoda K. Molecular biology of gynecological cancer. *Oncol Lett.* 2016;11:16–22.
9. Rojas K, Stuckey A. Breast Cancer Epidemiology and Risk Factors. *Clin Obstet Gynecol.* 2016;59:651–72.
10. de Jonge MM, Ritterhouse LL, de Kroon CD, Vreeswijk MPG, Segal JP, Puranik R, et al. Germline BRCA-Associated Endometrial Carcinoma Is a Distinct Clinicopathologic Entity. *Clin cancer Res an Off J Am Assoc Cancer Res.* 2019;25:7517–26.
11. Ferrari G, Cook BD, Terushkin V, Pintucci G, Mignatti P. Transforming growth factor-beta 1 (TGF-beta1) induces angiogenesis through vascular endothelial growth factor (VEGF)-mediated apoptosis. *J Cell Physiol.* 2009;219:449–58.
12. Cargnello M, Roux PP. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiol Mol Biol Rev.* 2011;75:50–83. doi:10.1128/MMBR.00031-10.
13. Roux PP, Blenis J. ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions. *Microbiol Mol Biol Rev.* 2004;68:320–44. doi:10.1128/MMBR.68.2.320-344.2004.
14. Keesler GA, Bray J, Hunt J, Johnson DA, Gleason T, Yao Z, et al. Purification and activation of recombinant p38 isoforms alpha, beta, gamma, and delta. *Protein Expr Purif.* 1998;14:221–8.
15. Kim JK, Pedram A, Razandi M, Levin ER. Estrogen prevents cardiomyocyte apoptosis through inhibition of reactive oxygen species and differential regulation of p38 kinase isoforms. *J Biol Chem.* 2006;281:6760–7.
16. Bachstetter AD, Van Eldik LJ. The p38 MAP Kinase Family as Regulators of Proinflammatory Cytokine Production in Degenerative Diseases of the CNS. *Aging Dis.* 2010;1:199–211.
17. Stein B, Yang MX, Young DB, Janknecht R, Hunter T, Murray BW, et al. p38-2 , a Novel Mitogen-activated Protein Kinase with Distinct Properties *. *1997;272:19509–17.*
18. Chen Z, Liu F, Zhang N, Cao D, Liu M, Tan Y, et al. p38 β , A novel regulatory target of Pokemon in hepatic cells. *Int J Mol Sci.* 2013;14:13511–24.
19. González-Terán B, López JA, Rodríguez E, Leiva L, Martínez-Martínez S, Bernal JA, et al. p38 γ and δ promote heart hypertrophy by targeting the mTOR-inhibitory protein DEPTOR for degradation. *Nat Commun.* 2016;7:10477. doi:10.1038/ncomms10477.
20. Zur R, Garcia-Ibanez L, Nunez-Buiza A, Aparicio N, Liappas G, Escós A, et al. Combined deletion of p38 γ and p38 δ reduces skin inflammation and protects from carcinogenesis. *Oncotarget.* 2015;6:12920–35. doi:10.18632/oncotarget.4320.
21. Kumar S, McDonnell PC, Gum RJ, Hand AT, Lee JC, Young PR. Novel homologues of CSBP/p38 MAP kinase: activation, substrate specificity and sensitivity to inhibition by pyridinyl imidazoles. *Biochem Biophys Res Commun.* 1997;235:533–8.
22. Hale KK, Trollinger D, Rihanek M, Manthey CL. Differential expression and activation of p38 mitogen-activated protein kinase alpha, beta, gamma, and delta in inflammatory cell lineages. *J Immunol.* 1999;162:4246–52.

23. Martínez-Limón A, Joaquin M, Caballero M, Posas F, de Nadal E. The p38 pathway: From biology to cancer therapy. *Int J Mol Sci.* 2020;21:1–18.
24. del Barco Barrantes I, Coya JM, Maina F, Arthur JSC, Nebreda AR. Genetic analysis of specific and redundant roles for p38alpha and p38beta MAPKs during mouse development. *Proc Natl Acad Sci U S A.* 2011;108:12764–9.
25. Adams RH, Porras A, Alonso G, Jones M, Vintersten K, Panelli S, et al. Essential role of p38α MAP kinase in placental but not embryonic cardiovascular development. *Mol Cell.* 2000;6:109–16.
26. Beardmore VA, Hinton HJ, Eftychi C, Apostolaki M, Armaka M, Darragh J, et al. Generation and Characterization of p38β (MAPK11) Gene-Targeted Mice. *Mol Cell Biol.* 2005;25:10454–64.
27. Gaestel M. MAPKAP kinases - MKs - Two's company, three's a crowd. *Nat Rev Mol Cell Biol.* 2006;7:120–30.
28. Beenstock J, Ben-Yehuda S, Melamed D, Admon A, Livnah O, Ahn NG, et al. The p38β mitogen-activated protein kinase possesses an intrinsic autophosphorylation activity, generated by a short region composed of the α-G helix and MAPK insert. *J Biol Chem.* 2014;289:23546–56.
29. Ferrari G, Terushkin V, Wolff MJ, Zhang X, Valacca C, Poggio P, et al. TGF-β1 induces endothelial cell apoptosis by shifting VEGF activation of p38(MAPK) from the prosurvival p38β to proapoptotic p38α. *Mol Cancer Res.* 2012;10:605–14.
30. Basu S, Chaudhary N, Shah S, Braggs C, Sawant A, Vaz S, et al. Plakophilin3 loss leads to an increase in lipocalin2 expression, which is required for tumour formation. *Exp Cell Res.* 2018;369:251–65. doi:<https://doi.org/10.1016/j.yexcr.2018.05.026>.
31. Browne AJ, Göbel A, Thiele S, Hofbauer LC, Rauner M, Rachner TD. P38 MAPK regulates the Wnt inhibitor Dickkopf-1 in osteotropic prostate cancer cells. *Cell Death Dis.* 2016;7:1–11.
32. Yu L, Yuan X, Wang D, Barakat B, Williams ED, Hannigan GE. Selective regulation of p38β protein and signaling by integrin-linked kinase mediates bladder cancer cell migration. *Oncogene.* 2014;33:690–701.
33. Yao Z, Xu R, Yuan L, Xu M, Zhuang H, Li Y, et al. Circ_0001955 facilitates hepatocellular carcinoma (HCC) tumorigenesis by sponging miR-516a-5p to release TRAF6 and MAPK11. *Cell Death Dis.* 2019;10. doi:10.1038/s41419-019-2176-y.
34. Grossi V, Lucarelli G, Forte G, Peserico A, Matrone A, Germani A, et al. Loss of STK11 expression is an early event in prostate carcinogenesis and predicts therapeutic response to targeted therapy against MAPK/p38. *Autophagy.* 2015;11:2102–13. doi:10.1080/15548627.2015.1091910.
35. Li Y, Kong C, Wu C, Wang Y, Xu B, Liang S, et al. Knocking down of LINC01220 inhibits proliferation and induces apoptosis of endometrial carcinoma through silencing MAPK11. *Biosci Rep.* 2019;39. doi:10.1042/BSR20181794.
36. Sullivan I, Riera P, Andrés M, Altés A, Majem M, Blanco R, et al. Prognostic effect of VEGF gene variants in metastatic non-small-cell lung cancer patients. *Angiogenesis.* 2019;22:433–40.
37. Sahu V, Nigam L, Agnihotri V, Gupta A, Shekhar S, Subbarao N, et al. Diagnostic Significance of p38 Isoforms (p38α, p38β, p38γ, p38δ) in Head and Neck Squamous Cell Carcinoma: Comparative Serum

- Level Evaluation and Design of Novel Peptide Inhibitor Targeting the Same. *Cancer Res Treat.* 2019;51:313–25.
38. Mueller H, Flury N, Eppenberger-Castori S, Kueng W, David F, Eppenberger U. Potential prognostic value of mitogen-activated protein kinase activity for disease-free survival of primary breast cancer patients. *Int J cancer.* 2000;89:384–8.
39. Beardmore VA, Hinton HJ, Eftychi C, Apostolaki M, Armaka M, Darragh J, et al. Generation and characterization of p38beta (MAPK11) gene-targeted mice. *Mol Cell Biol.* 2005;25:10454–64.
40. He Z, He J, Liu Z, Xu J, Yi SF, Liu H, et al. MAPK11 in breast cancer cells enhances osteoclastogenesis and bone resorption. *Biochimie.* 2014;106:24–32.
doi:<https://doi.org/10.1016/j.biochi.2014.07.017>.
41. Robinette J, Olexo R. Breast Cancer in a 53-year-old Obese Male. *Cureus.* 2019;11:e6194–e6194.
doi:10.7759/cureus.6194.
42. Humphries MP, Jordan VC, Speirs V. Obesity and male breast cancer: provocative parallels? *BMC Med.* 2015;13:134. doi:10.1186/s12916-015-0380-x.
43. Brinton LA. Breast cancer risk among patients with Klinefelter syndrome. *Acta Paediatr.* 2011;100:814–8. doi:10.1111/j.1651-2227.2010.02131.x.
44. Zhang P, Zhang P, Shi B, Zhou M, Jiang H, Zhang H, et al. Galectin-1 overexpression promotes progression and chemoresistance to cisplatin in epithelial ovarian cancer. *Cell Death Dis.* 2014;5:e991.
45. Zhu J, Zheng Y, Zhang H, Liu Y, Sun H, Zhang P. Galectin-1 induces metastasis and epithelial-mesenchymal transition (EMT) in human ovarian cancer cells via activation of the MAPK JNK/p38 signalling pathway. *Am J Transl Res.* 2019;11:3862–78.
46. Zhang D, Guo H, Feng W, Qiu H. LAMC2 regulated by microRNA-125a-5p accelerates the progression of ovarian cancer via activating p38 MAPK signalling. *Life Sci.* 2019;232:116648.
doi:<https://doi.org/10.1016/j.lfs.2019.116648>.
47. Jiang J, Zhou N, Ying P, Zhang T, Liang R, Jiang X. Emodin promotes apoptosis of human endometrial cancer through regulating the MAPK and PI3K/ AKT pathways. *Open Life Sci.* 13:489–96. doi:<https://doi.org/10.1515/biol-2018-0058>.
48. Tian W, Teng F, Gao J, Gao C, Liu G, Zhang Y, et al. Estrogen and insulin synergistically promote endometrial cancer progression via crosstalk between their receptor signaling pathways. *Cancer Biol Med.* 2019;16:55–70.
49. Liu A, Zhang D, Yang X, Song Y. Estrogen receptor alpha activates MAPK signaling pathway to promote the development of endometrial cancer. *J Cell Biochem.* 2019;120:17593–601.
doi:10.1002/jcb.29027.
50. Kourea HP, Nikolaou M, Tzelepi V, Adonakis G, Kardamakis D, Tsapanos V, et al. Expression of phosphorylated Akt, mTOR and MAPK in type I endometrial carcinoma: clinical significance. *Anticancer Res.* 2015;35:2321–31.

51. Guo J-L, Tang T, Li J-H, Yang Y-H, Zhang L, Quan Y. LncRNA HEIH Enhances Paclitaxel-Tolerance of Endometrial Cancer Cells via Activation of MAPK Signaling Pathway. *Pathol Oncol Res.* 2020;26:1757–66.
52. Inoue H, Hashimura M, Akiya M, Chiba R, Saegusa M. Functional role of ALK-related signal cascades on modulation of epithelial-mesenchymal transition and apoptosis in uterine carcinosarcoma. *Mol Cancer.* 2017;16:1–13.
53. Chiyoda T, Tsuda H, Tanaka H, Kataoka F, Nomura H, Nishimura S, et al. Expression profiles of carcinosarcoma of the uterine corpus-are these similar to carcinoma or sarcoma? *Genes Chromosomes Cancer.* 2012;51:229–39.
54. Kim SG, Kim H-A, Jong H-S, Park J-H, Kim NK, Hong SH, et al. The endogenous ratio of Smad2 and Smad3 influences the cytostatic function of Smad3. *Mol Biol Cell.* 2005;16:4672–83.
55. Kumar V, Behera R, Lohite K, Karnik S, Kundu GC. p38 Kinase is Crucial for Osteopontin-induced Furin Expression that Supports Cervical Cancer Progression. *Cancer Res.* 2010;canres.1470.2010. doi:10.1158/0008-5472.CAN-10-1470.
56. Wu X, Zhou J, Cai D, Li M. Matrine inhibits the metastatic properties of human cervical cancer cells via downregulating the p38 signaling pathway. *Oncol Rep.* 2017;38:1312–20. doi:10.3892/or.2017.5787.
57. Feng M, Wang Y, Chen K, Bian Z, Wu J, Gao Q. IL-17A promotes the migration and invasiveness of cervical cancer cells by coordinately activating MMPs expression via the p38/NF- κ B signal pathway. *PLoS One.* 2014;9:e108502.
58. Lee C-H, Ying T-H, Chiou H-L, Hsieh S-C, Wen S-H, Chou R-H, et al. Alpha-mangostin induces apoptosis through activation of reactive oxygen species and ASK1/p38 signaling pathway in cervical cancer cells. *Oncotarget.* 2017;8:47425–39.
59. Koch A, De Meyer T, Jeschke J, Van Criekinge W. MEXPRESS: Visualizing expression, DNA methylation and clinical TCGA data. *BMC Genomics.* 2015;16:1–6. doi:10.1186/s12864-015-1847-z.
60. Koch A, Jeschke J, Van Criekinge W, Van Engeland M, De Meyer T. MEXPRESS update 2019. *Nucleic Acids Res.* 2019;47:W561–5.
61. Li Y, Ge D, Lu C. The SMART App: an interactive web application for comprehensive DNA methylation analysis and visualization. *Epigenetics Chromatin.* 2019;12:71. doi:10.1186/s13072-019-0316-3.
62. Xu W, Xu M, Wang L, Zhou W, Xiang R, Shi Y, et al. Integrative analysis of DNA methylation and gene expression identified cervical cancer-specific diagnostic biomarkers. *Signal transduction and targeted therapy.* 2019;4:55. doi:10.1038/s41392-019-0081-6.
63. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data. *Cancer Discov.* 2012;2:401 LP – 404. doi:10.1158/2159-8290.CD-12-0095.
64. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal.* 2013;6:pl1.

65. Coker EA, Mitsopoulos C, Tym JE, Komianou A, Kannas C, Di Micco P, et al. canSAR: update to the cancer translational research and drug discovery knowledgebase. *Nucleic Acids Res.* 2019;47:D917–22. doi:10.1093/nar/gky1129.
66. Milella M, Falcone I, Conciatori F, Cesta Incani U, Del Curatolo A, Inzerilli N, et al. PTEN: Multiple Functions in Human Malignant Tumors. *Front Oncol.* 2015;5:24. doi:10.3389/fonc.2015.00024.
67. Ma X, Wang Y-W, Zhang MQ, Gazdar AF. DNA methylation data analysis and its application to cancer research. *Epigenomics.* 2013;5:301–16. doi:10.2217/epi.13.26.
68. Coulthard LR, White DE, Jones DL, McDermott MF, Burchill SA. p38(MAPK): stress responses from molecular mechanisms to therapeutics. *Trends Mol Med.* 2009;15:369–79. doi:10.1016/j.molmed.2009.06.005.
69. Cowan KJ, Storey KB. Mitogen-activated protein kinases: new signaling pathways functioning in cellular responses to environmental stress. *J Exp Biol.* 2003;206:1107 LP – 1115. doi:10.1242/jeb.00220.
70. Jia Y-T, Wei W, Ma B, Xu Y, Liu W-J, Wang Y, et al. Activation of p38 MAPK by reactive oxygen species is essential in a rat model of stress-induced gastric mucosal injury. *J Immunol.* 2007;179:7808–19.
71. Mesquita FP, Moreira-Nunes CA, da Silva EL, Lima LB, Daniel JP, Zuerker WJ, et al. MAPK14 (p38 α) inhibition effects against metastatic gastric cancer cells: A potential biomarker and pharmacological target. *Toxicol In Vitro.* 2020;66:104839.
72. Li Y, Kong C, Wu C, Wang Y, Xu B, Liang S, et al. Knocking down of LINC01220 inhibits proliferation and induces apoptosis of endometrial carcinoma through silencing MAPK11. *Biosci Rep.* 2019;39.
73. Beenstock J, Melamed D, Mooshayef N, Mordechay D, Garfinkel BP, Ahn NG, et al. p38 β Mitogen-Activated Protein Kinase Modulates Its Own Basal Activity by Autophosphorylation of the Activating Residue Thr180 and the Inhibitory Residues Thr241 and Ser261. *Mol Cell Biol.* 2016;36:1540–54. doi:10.1128/MCB.01105-15.
74. Son Y, Cheong Y-K, Kim N-H, Chung H-T, Kang DG, Pae H-O. Mitogen-Activated Protein Kinases and Reactive Oxygen Species: How Can ROS Activate MAPK Pathways? *J Signal Transduct.* 2011;2011:792639. doi:10.1155/2011/792639.
75. Shaulian E, Karin M. AP-1 as a regulator of cell life and death. *Nat Cell Biol.* 2002;4:E131-6.
76. Wu X-N, Wang X-K, Wu S-Q, Lu J, Zheng M, Wang Y-H, et al. Phosphorylation of Raptor by p38 β participates in arsenite-induced mammalian target of rapamycin complex 1 (mTORC1) activation. *J Biol Chem.* 2011;286:31501–11.
77. Betella I, Turbitt WJ, Szul T, Wu B, Martinez A, Katre A, et al. Wnt signaling modulator DKK1 as an immunotherapeutic target in ovarian cancer. *Gynecol Oncol.* 2020;157:765–74.
78. Pon JR, Marra MA. MEF2 transcription factors: developmental regulators and emerging cancer genes. *Oncotarget.* 2016;7:2297–312.
79. He J, Liu Z, Zheng Y, Qian J, Li H, Lu Y, et al. p38 MAPK in myeloma cells regulates osteoclast and osteoblast activity and induces bone destruction. *Cancer Res.* 2012;72:6393–402. doi:10.1158/0008-5472.CAN-12-2664.

80. Loesch M, Chen G. The p38 MAPK stress pathway as a tumor suppressor or more? *Front Biosci.* 2008;13:3581–93. doi:10.2741/2951.
81. Bulavin D V, Fornace AJJ. p38 MAP kinase's emerging role as a tumor suppressor. *Adv Cancer Res.* 2004;92:95–118.
82. Kennedy NJ, Cellurale C, Davis RJ. A Radical Role for p38 MAPK in Tumor Initiation. *Cancer Cell.* 2007;11:101–3.

Figures

Figure 1

a MAPK11 protein association network acquired by StringDB; b MAPK signalling pathways showing the initiation of JNK and p38 following external stimulation from UV and Reactive Oxygen Species (yellow) as well as CKs and growth factors (red). The p38 isoforms (green) are phosphorylated via MKK3/6 and MKK4 (grey) in response to ROS and environmental stress consequently increasing activation of downstream targets involved in processes such as cell migration, survival and differentiation, proliferation and apoptosis. UV: Ultraviolet radiation; ROS: Reactive Oxygen Species; GFs: Growth Factors; CKs: Cytokines; MEKK3,4: MAP3K3, MAP3K4; TAO: Serine/threonine-protein kinase Tao; ASK: Apoptosis signal-regulating kinase, MAP3K5 ; MLK1-3: Mitogen-Activated Protein Kinase Kinase Kinase 9-11; MKK4: Mitogen-Activated Protein Kinase Kinase 4 ; STAT1/3: Signal Transducer And Activator Of Transcription 1/3 ; ATF1,2: Activating Transcription Factor 1,2 ; cMYC: MYC Proto-Oncogene; ELK1: ETS Transcription Factor ELK1.

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Figure 2

a PanCancer expression analyses of MAPK11 from canSAR database. A higher expression is seen in normal (blue) samples from female data sets: BRCA, OV, UCEC, and UCS compared with early (yellow) and advanced stage (pink) samples, with OV exhibiting the lowest level of expression in the advanced stage compared to all cancer data sets; b PanCancer data analysis using cBioPortal provides an overview of the landscape of MAPK11 genetic alterations across the range of TCGA data sets. OV, UCEC exhibit the

highest level of alteration within the cancer types with deep deletion presenting as the most prevalent throughout the data sets. Of the female-specific cancers: BRCA, OV, CESC, UCEC, each exhibit varying levels of amplification specific alterations as well as high levels of deep deletion; c Deep deletions in BRCA 7/1084, CESC: 4/297, OV: 28/585, UCEC: 22/529 and UCS: 1/57. OV and the UCEC patients with deep deletions of MAPK11 are the biggest populations compared to all other cancers; d MAPK11 expression in female tissues: BRCA, CESC, UCEC, and UCS, indicating higher expression in normal tissue compared to downregulation in cancer data sets across all four cancer stages.

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Figure 3

a Genomic information of the gene MAPK11. The segment plot showing the detailed information of genomic locations of CpGs of MAPK11, highlighting CpG island, shelves, and shores. The name and the type of each transcript are given. The coverage of the CpG islands is displayed as the red region. 14 probes are included in this genomic location with 10 of them to lie on the two island regions (CpG1 and CpG2); b Red bars on chromosome 22 indicate hypermethylated regions. MAPK11 gene can be found in the right end of the chromosome at the cytogenetic band 22q13.33 (green box).

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Figure 5

MEXPRESS view of the TCGA data for MAPK11 in breast invasive carcinoma. The samples are ordered by MAPK11 expression, revealing that the expression in the different stages is not significantly altered. Probes have been coloured differently depending on the genomic region they target. The detailed analysis for all cancers analysed can be found in Additional file 5.

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