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PRECLINICAL STUDY

Transcriptomic analyses identify association between mitotic kinases, PDZ-binding kinase and BUB1, and clinical outcome in breast cancer

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Abstract Protein kinases are important components in oncogenic transformation of breast cancer. Evaluation of upregulated genes that codify for protein kinases could be used as biomarkers to predict clinical outcome. Gene expression and functional analyses using public datasets were performed to identify differential gene expression and functions in basal-like tumors compared with normal breast tissue. Overall survival (OS) associated with upregulated genes was explored using the KM Plotter online tool. The prognostic influence of these genes in luminal tumors and systemically untreated patients was also assessed. Of the 426 transcripts identified in basal-like tumors, 11 genes that coded for components of protein kinases were upregulated with more than a fourfold change. Regulation of cell cycle was an enriched function containing 10 of these 11 identified genes. Among them, expression of four genes, BUB1β, CDC28, NIMA, and PDZ binding kinase, were all associated with improved OS when using at least one probe in the basal-like subtype. Two genes, BUB1β and PDZ binding kinase, showed consistent association with improved OS irrespective of the gene probe used for the analysis. No association was observed for these genes with relapse-free survival. In contrast, both BUB1β and PDZ binding kinase showed worse OS in luminal tumors and in a cohort of systemically untreated patients. BUB1β and PDZ binding kinase are associated with improved OS in basal-like tumors and worse OS in luminal and untreated patients. The association with a better outcome in basal-like tumors could be due to a more favorable response to chemotherapy.

Keywords Mitotic kinases · Breast cancer · BUB1 · PDZ binding kinase

Introduction

Triple negative breast cancer (TNBC) represents around 15 % of all tumors and are mainly included in the basal-like gene profiling subgroup [1]. Due to the absence of druggable molecular targets, TNBC is treated typically with cytotoxic chemotherapy [2]. The predominant mechanism of action of these anti-cancer drugs is direct DNA damage or interference with the process of mitosis [2]. Predictive markers for cytotoxic chemotherapy benefit are not available and as such, cytotoxic chemotherapy cannot be tailored. Identification of such biomarkers is therefore highly desirable.

Protein kinases play a central role in many different biological functions including proliferation, cell survival, or migration, among others [3, 4]. Proteins with kinase activity have been considered as oncogenic targets and

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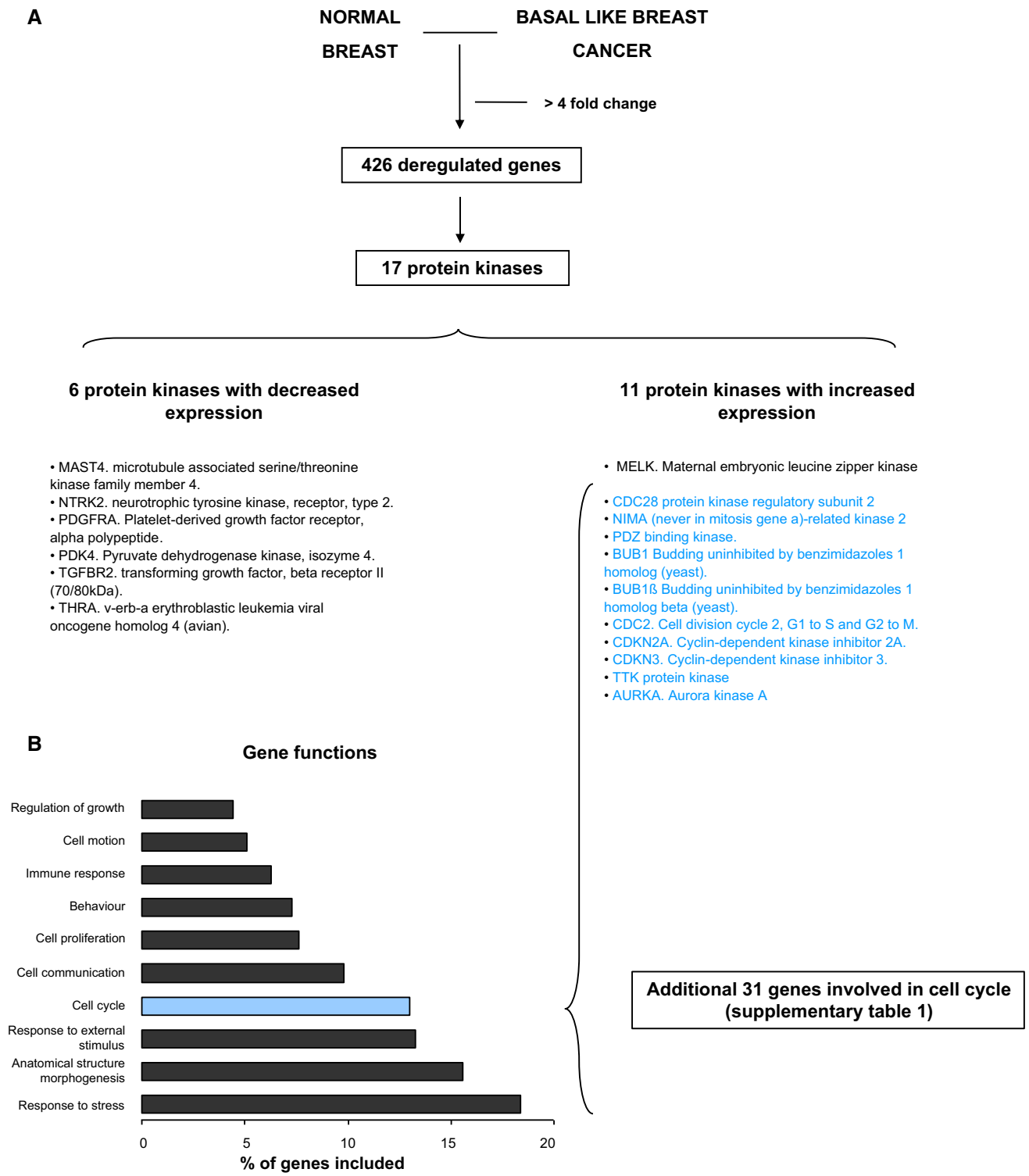

Fig. 1 In silico transcriptomic analyses of basal-like tumors compared with normal breast, and gene-set enrichment analyses. **a** Selection of upregulated genes that encodes for protein kinases with a fold change >4. **b** Pathway analyses. Ten out of the 11 upregulated genes are included in cell cycle regulation function

have been used as biomarkers to select targeted agents [3–5]. In addition, protein kinases have been implicated in mechanisms of resistance [5]. In TNBC, certain kinases are important components in oncogenic transformation [6–8] and are the target of novel agents in preclinical and clinical evaluation [9–12].

Table 1 Affymetrix probe set, gene names, fold changed, and *p* value of the identified genes

Probe set	Gene name	Fold change	ANOVA (*p* value)
204825_at	MELK maternal embryonic leucine zipper kinase	36.17	5.01E−09
204170_s_at	CDC28 protein kinase regulatory subunit 2	9.54	1.97E−09
204641_at	NIMA (never in mitosis gene a)-related kinase 2	18.24	0.000011
219148_at	PDZ binding kinase	12.07	4.34E−07
209642_at	BUB1 budding uninhibited by benzimidazoles 1 homolog (yeast)	11.78	1.51E−08
203755_at	BUB1β budding uninhibited by benzimidazoles 1 homolog beta (yeast)	6.42	2.94E−08
203213_at	CDK1 cell division cycle 2, G1 to S and G2 to M	17.95	5.02E−08
207039_at	CDKN2A cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	13.71	0.000588
1555758_a_at	CDKN3 cyclin-dependent kinase inhibitor 3	9.79	0.000049
204822_at	TTK protein kinase	11.91	5.37E−10
204092_s_at	AURKA aurora kinase A; aurora kinase A pseudogene 1 // serine/threonine kinase 6	7.45	1.35E−10
225613_at	MAST4 microtubule associated serine/threonine kinase family member 4	−5.4	4.21E−07
221796_at	NTRK2 neurotrophic tyrosine kinase, receptor, type 2	−15.46	0.000027
203131_at	PDGFRA platelet-derived growth factor receptor, alpha polypeptide	−4.01	0.057906
225207_at	PDK4 pyruvate dehydrogenase kinase, isozyme 4	−10.17	0.000001
208944_at	TGFBR2 transforming growth factor, beta receptor II (70/80 kDa)	−4	2.67E−07
214053_at	THRA v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	−6.02	0.000624

Among the altered functions identified in this tumor type, proliferation is a key characteristic. Most TNBC express elevated levels of the proliferation marker Ki67 and morphologically exhibit high histological features, indicating an accelerated and continuous cell division [13]. Several protein kinases are implicated in the development of TNBC, including those that participate in the formation of the mitotic spindle during cell cycle, like polo-like kinases, Mps1/TTKs, or aurora kinases, among others; and indeed, agents targeting some of these proteins have shown preclinical activity in this breast cancer subtype [10–12].

In this article, by using an in silico approach, we identify relevant pathways and upregulated genes linked with clinical outcome in basal-like tumors. Particularly, BUB1β and PDZ binding kinase are upregulated genes involved in mitosis that are associated with better overall survival (OS) probably as they identify those tumors that respond better to chemotherapy. By contrast, expression of BUB1β and PDZ binding kinase are linked with worse outcome in luminal tumors and untreated patients.

Materials and methods

Transcriptomic and gene-set enrichment analyses

We used a public dataset (GEO DataSet accession number: GDS2250 [14]) of mRNA level data from normal breast tissue and basal-like breast tumors to identify deregulated genes. Affymetrix CEL files were downloaded and analyzed with dChip software (Dana Farber Cancer Institute, Boston, MA).

Genes with different expression values from the normal breast and basal-like breast cancer groups were obtained. Specifically, we used a fourfold change difference cutoff between both groups to identify clearly upregulated genes. We used the affymetrix software for evaluation of the volcano plot.

The list of genes was analyzed using gene-set enrichment analyses (DAVID Bioinformatics Resources 6.7) in order to identify functions of these genes. We used an adjusted *p* value <0.05 to select the enriched gene sets.

Outcome analyses

The KM Plotter Online Tool was used to analyze the relationship between the gene expression and patient clinical outcome in breast cancer (http://www.kmplot.com); this public database allowed us to investigate OS and relapse-free survival (RFS) [15, 16]. Information for OS were obtained from 594 patients, and RFS from 1593 patients. A cohort of systemically untreated patients including 1005 patients were also used for the analyses. Analysis was carried out as follows. First, the association between the gene of interest and outcome was explored after selection of the specific probe utilized initially. Analysis was then repeated using all probes available in the online software tool for each individual gene. Finally, in order to get insights into the association of BUB1β and PDZ binding kinase with clinical outcome, we evaluated the influence of their

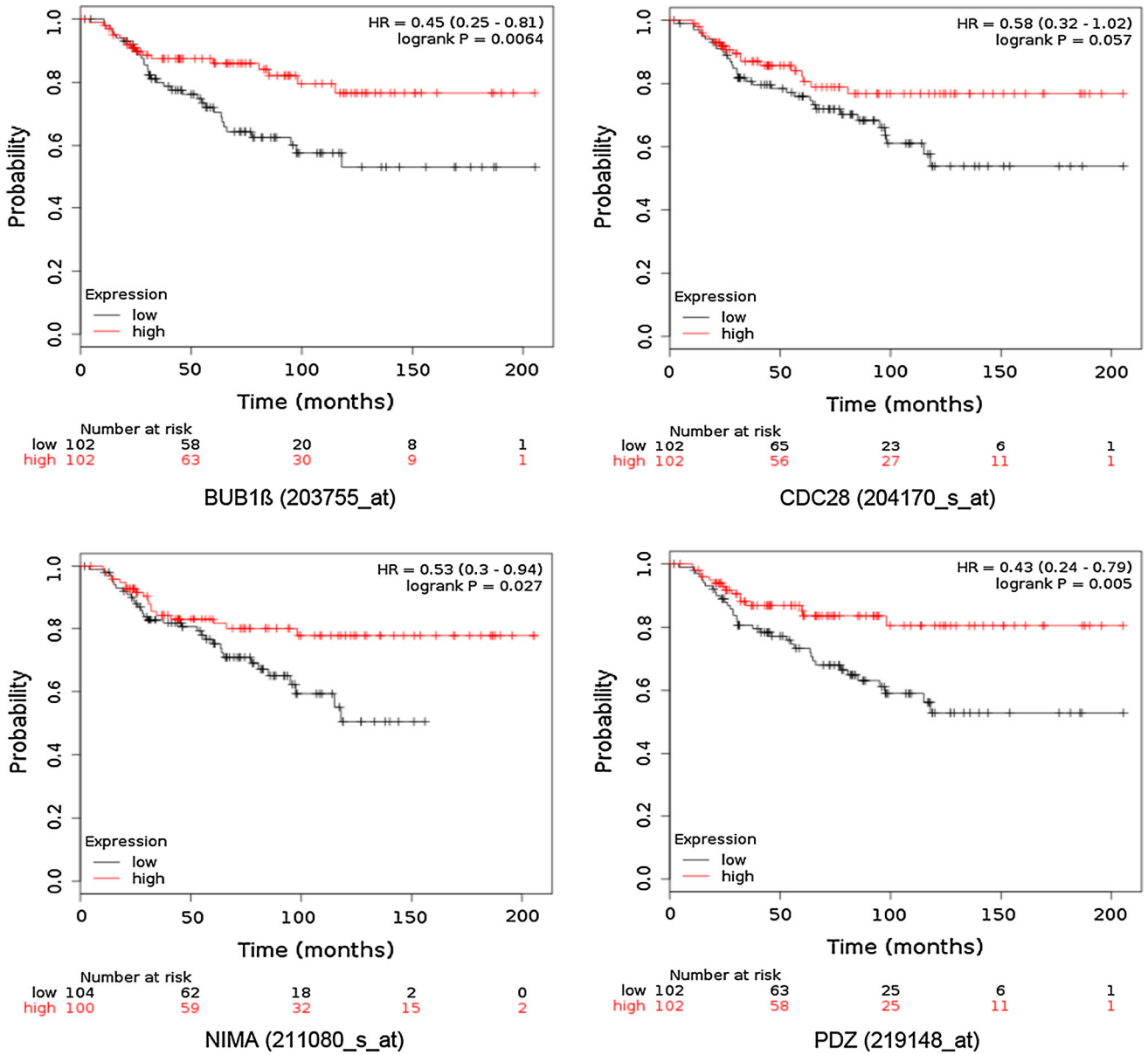

Fig. 2 Association of BUB1β, CDC28, NIMA, and PDZ binding kinase mRNA expression with overall survival in basal-like tumors

expression on OS in luminal tumors and systemically untreated patients.

Definitions of breast cancer subgroups reported in the online tool are as follows: triple negative (ER−/HER2−), luminal A (ESR1+/HER2−/MKI67-low), luminal B (ESR1+/HER2−/MKI67-high or ESR1+/HER2+), and basal-like (ESR1−/HER2−) breast cancers [15, 16]. In addition, the application permits to perform the analyses by using the immunohistochemical information of ER/PR and HER2 [15, 16].

All the analyses were performed independently by two authors (JPP and LDG) and reviewed by a third author (VSC). No discrepancies were observed.

Results

Transcriptomic analyses identify upregulated kinases involved in cell cycle progression

Our initial search identified 426 transcripts with a fold change greater than four between basal-like tumors (18 samples) and epithelial cells (7 samples). Of these, 17 genes coded for protein kinases; 11 of them being upregulated (Fig. 1a). Table 1 shows the Affimetrix probe sets, the gene names, and the fold change identified including *p* value. Volcano plot is showed in Supplementary Fig. 1.

Table 2 Description of the identified genes with their biological functions

Probe set	Gene name	Gene symbol	Function
204170_s_at	CDC28 protein kinase regulatory subunit 2	CDC28, CKS2	Binds to the catalytic subunit of the cyclin-dependent kinases and is essential for their biological function
211080_s_at	NIMA (never in mitosis gene a)-related kinase 2	NEK2, NEK2A, NLK1	Protein kinase which is involved in the control of centrosome separation and bipolar spindle formation in mitotic cells and chromatin condensation in meiotic cells. Regulates centrosome separation (essential for the formation of bipolar spindles and high-fidelity chromosome separation) by phosphorylating centrosomal proteins such as CROCC, CEP250, and NINL, resulting in their displacement from the centrosomes. Regulates kinetochore microtubule attachment stability in mitosis via phosphorylation of NDC80. Involved in regulation of mitotic checkpoint protein complex via phosphorylation of CDC20 and MAD2L1. Plays an active role in chromatin condensation during the first meiotic division through phosphorylation of HMGA2. Phosphorylates: PPP1CC; SGOL1; NECAB3; and NPM1. Essential for localization of MAD2L1 to kinetochore and MAPK1 and NPM1 to the centrosome. Isoform1 phosphorylates and activates NEK11 in G1/S-arrested cells. Isoform2, which is not present in the nucleolus, does not
219148_at	PDZ binding kinase	CT84, PBK, TOPK	Phosphorylates MAP kinase p38. Seems to be active only in mitosis. May also play a role in the activation of lymphoid cells. When phosphorylated, forms a complex with TP53, leading to TP53 destabilization and attenuation of G2/M checkpoint during doxorubicin-induced DNA damage
203755_at	Budding uninhibited by benzimidazoles 1 homolog beta	BUB1B, BUBR1, MAD3L, SSK1	Essential component of the mitotic checkpoint. Required for normal mitosis progression. The mitotic checkpoint delays anaphase until all chromosomes are properly attached to the mitotic spindle. One of its checkpoint functions is to inhibit the activity of the anaphase-promoting complex/cyclosome (APC/C) by blocking the binding of CDC20 to APC/C, independently of its kinase activity. The other is to monitor kinetochore activities that depend on the kinetochore motor CENPE. Required for kinetochore localization of CENPE. Negatively regulates PLK1 activity in interphase cells and suppresses centrosome amplification. Also implicated in triggering apoptosis in polyploid cells that exit aberrantly from mitotic arrest

Two of the identified genes, aurora kinase A and TTK ,codify for druggable proteins.

Gene-set enrichment analyses performed to identify biological functions and pathways showed that 10 of the 11 upregulated genes (91 %) participated in the regulation of cell cycle progression. Among genes not directly related to protein kinases, an additional 31 genes were associated with this function (see Fig. 1b). Supplementary Table 1 describes all genes included in the cell cycle and proliferation function as provided by DAVID Bioinformatics Resources 6.7.

Association of selected transcripts with outcome in basal-like tumors

Among the 11 upregulated genes, 4 were associated with outcome. Expression of BUB1β, CDC28, NIMA, and PDZ binding kinase were linked with improved OS (Fig. 2). These differences were statistically significant except for CDC28 which showed a non-significant association with improved outcome. Table 2 describes the functions of the evaluated genes. Repeating the analysis using all probes available for each gene confirmed the association between PDZ binding kinase and BUB1β and improved OS. The combined analyses of BUB1β and PDZ binding kinase were associated with better OS in both immunohistochemical-based subgroups (triple negative tumors), and those molecular-based subgroups (basal-like tumors) (see Supplementary Fig. 2A and B, respectively). Of note, BUB1β and PDZ were also upregulated in a subgroup of non-basal tumors from the same database (GEO DataSet accession number: GDS2250) (20 samples) as shown in Supplementary Fig. 3.

Prognostic influence of BUB1 and PDZ binding kinase in luminal tumors and systemically untreated patients

Expression of PDZ binding kinase was associated with poor OS in luminal A and luminal B tumors. BUB1β was associated with poor outcome in luminal A tumors, but in

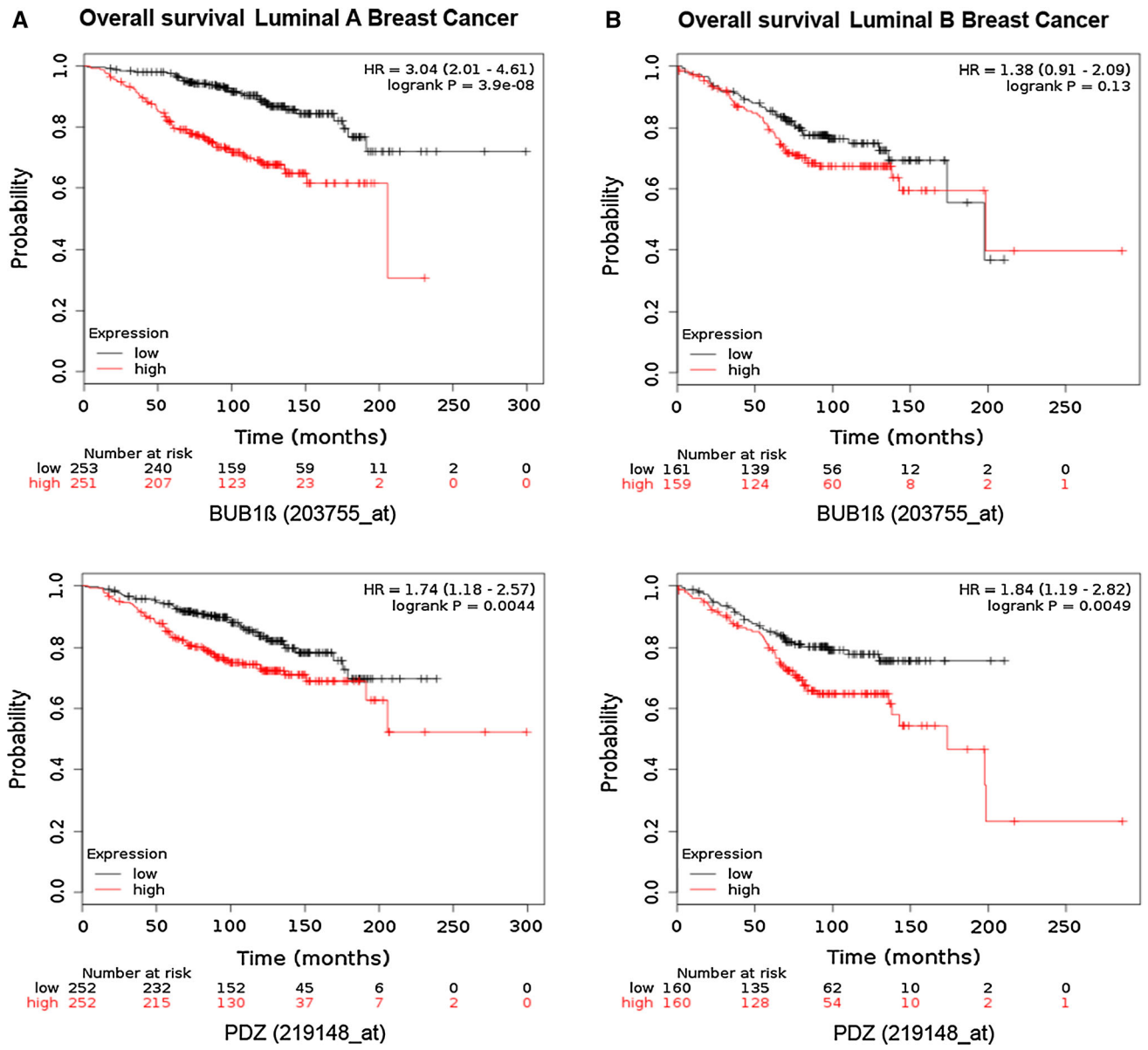

Fig. 3 Association of BUB1β and PDZ binding kinase mRNA expression with OS in luminal A and B tumors (**a** and **b**, respectively)

luminal B tumors, there was a non-significant association (see Fig. 3).

Similarly, expression of BUB1β and PDZ binding kinase was associated with worse OS in a cohort of systemically untreated breast cancer patients (Fig. 4).

Association with outcome of other cell cycle genes in basal-like tumors

Finally, we evaluated the association with outcome of all the 31 genes included in the cell cycle function as described in Supplementary Table 1, observing some of them linked with worse outcome (Supplementary Table 2).

Discussion

TNBC is one of the most devastating diseases as no current therapies exist beyond cytotoxic chemotherapy [2]. In this context, the identification of targets and biomarkers of response to a given treatment, including chemotherapy, is a main goal. As protein kinases have been implicated in the oncogenesis of breast cancer and are potentially druggable, we decided to evaluate the expression and prognostic relevance of this family of proteins in TNBC. A relevant finding of our study has been the identification of a substantial number of deregulated kinases which participate in cell proliferation/cell cycle regulation. This is especially

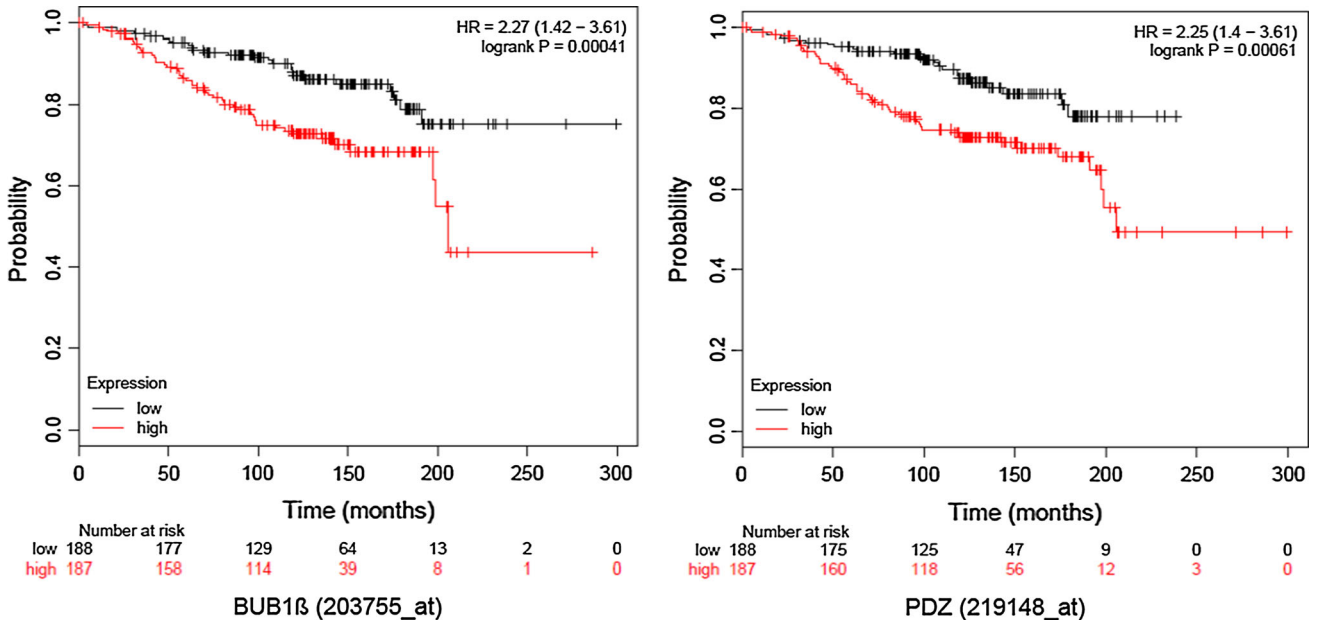

Fig. 4 Association of BUB1β and PDZ binding kinase mRNA expression with overall survival in a cohort of systemically untreated patients

interesting since it is well known that chemotherapy drugs acting on DNA/cell duplication are particularly efficient in this subtype of breast cancer.

Our study identified that BUB1β and PDZ binding kinase have a consistent association with improved OS irrespective of the gene probe used for analysis in basal-like tumors. In contrast, both BUB1β and PDZ showed worse OS in luminal tumors and in a cohort of systemically untreated patients.

The BUB1 family of genes codes for serine/threonine protein kinases that phosphorylate members of the mitotic checkpoint complex including Mad1, Mad2, BubR1, CENP-E, and PLK1 among others, and activates the spindle checkpoint [17–19]. BUB1 accumulates during G2/M and drops after mitosis [18]. PDZ binding kinase, also known as PBK, SPK, CT84, TOPK, HEL164, and Nori-3, is a serine/threonine protein kinase related to the dual-specific mitogen-activated protein kinase kinase (MAPKK) family [20]. It has been described in highly proliferative processes like the spermatogenesis and in some tumors such as lymphomas [21, 22].

Of the four genes identified as potentially prognostic, all are involved in the mitotic process. However, only BUB1β and PDZ binding kinase were associated with outcome for all the probe sets used. BUB1 and PDZ binding kinase are important in the formation of the mitotic spindle and could potentially be considered as surrogate markers of tumors where cells are highly dividing, including luminal B and triple negative tumors [17]. However, it is unclear if the expression of these genes are a better marker of proliferation compared with others, although, in our analyses, these genes provided stronger prognostication than Ki67 (data not shown).

The fact that many of these genes are linked with mitosis suggest that agents targeting kinases involved in this process could have a potential for therapeutic activity. This is the case with the remarkable preclinical activity identified for Mps1/TTK, and polo-like kinase inhibitors in triple negative breast cancer [10, 11].

The reasons for the differential prognostic value of BUB1 and PDZ binding kinase in basal and luminal tumors is unclear. One possible explanation is that as in TNBC the majority of patients are treated with chemotherapy, the improved prognosis may relate to a better response to chemotherapy. It is known that chemotherapy is more active in patients with tumors that express elevated levels of the Ki67 marker or have a high histological grade, both indicative of tumors that are highly proliferative [1].

Our study has limitations. This is an in silico evaluation of upregulated genes linked with clinical outcome in breast tumors. The fact that this is the first time that these kinases are described as upregulated and associated with outcome in different types of breast cancer warrants validation in clinical studies. The potential interaction of estrogen receptor signaling with genes coding for cell cycle and mitosis has not been explored. The analyses of outcome using the KM plotter tool have also boundaries, as it uses the median sample for dividing the samples into high- and low-expression groups. The determination of the exact cutoff value for each transcript could provide a more robust result. Finally, other proteins can be linked with outcome as some of those described in Supplementary Table 2.

We describe a set of genes in basal-like tumors that encode for mitotic checkpoint kinases and that are associated with better OS. The same genes are linked with worse outcome in luminal tumors and systemically untreated patients. The potential of these genes to predict response to chemotherapy in basal-like tumors and outcome in luminal tumors warrants further evaluation.

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Compliance with ethical standards

Conflict of interest Bostjan Seruga receives advisory honorarium from Astellas, Sanofi and Janssen. There is no conflict of interest to declare for the rest of the authors.

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