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BIOMEDICAL SCIENCES

Phosphokinases related to drug resistance in two cohorts from the cancer genome atlas (TCGA): uterine carcinoma and testicular cancer

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Abstract: We aimed to find new therapeutic targets related to Cancer Stem Cell alterations in recurrent patients from two TCGA cohorts: Testicular Germ Cell Tumor (TGCT) and Uterine Corpus Endometrial Carcinoma (UCEC). Raw sequencing data were downloaded from the TCGA database. Datasets containing RNA expression and Methylation files were directly downloaded from cBioportal. Variant Call Format files (VCFs) were downloaded from the GDC portal. Gene enrichment analysis was performed using GSEA (Gene Set Enrichment Analysis) software. Transcriptome profiling, coexpression co-occurrence, networks, and survival analyses were performed using cBioportal tools, while mutational analysis of patients was processed using UNIX scripts. We found that cancer stem cell transcription factors were highly expressed in Testicular Germ Cell Tumor (TGCT) and Uterine Corpus Endometrial Carcinoma (UCEC) cohorts, compared to the other 29 cancer cohorts in TCGA. Patients presented a poorer diagnosis when the genes (POU5F1, NANOG, SOX2, SALL4, ABCB1, ABCC1, and ABCG2) were altered. In UCEC cohorts, recurrent patients showed the ABCG2 potentially phosphorylated by the PIM1 kinase. In the TGCT cohort, genes ABCB1 and ABCG2 only appeared in the phosphonetwork in recurrent patients potentially phosphorylated by the same kinase, PIM1, but also by PRKACA. Our data indicate that PRKACA and PIM1 may modulate POU5F1 phosphorylation.

Key words: TGCT, UCEC, PIM1, PRKACA, ABC Transporters, recurrence.

INTRODUCTION

Among all cancer aspects, drug resistance is the primary cause of chemotherapy failure, often associated with cancer stem cells (CSCs) (Abdullah & Chow 2013, Zhao 2016, Li et al. 2021). Therefore, identifying alterations only belonging to patients with resistant tumors is a crucial way to overcome this issue. Resistant tumors show alterations in CSCs-related molecules, often related to changes in gene expression profiles leading to altered protein levels or structural changes altering many cellular pathways. Once the cause of such alterations is revealed, we will get closer to wiping out cancer stem cells from the tumor bulk, making the tumor more likely to be eliminated with regular chemotherapy (Li et al. 2021).

For this goal, targeting specific alterations found only in cancer stem cells may help fight drug resistance without harming healthy cells. Clinically, targeting CSCs can improve the patient's survival rate, sparing them from metastasis and recurrence and preventing tumors from developing in a chronic and incurable state (Carnero et al. 2016).

Several types of cancer have been related to stem cell transcription factors, such as POU5F1, SOX2, NANOG, and, currently, SALL4 (Tanimura et al. 2013). These molecules are commonly

associated with pluripotency, renewal, and homeostasis in healthy tissues. On the other hand, in cancer, they are related to many tumoral processes, such as metastasis, tumor maintenance, and drug resistance (Cabrera et al. 2015, Zhang et al. 2015).

Bioinformatic research is becoming a meaningful approach to finding new treatments, which have improved mainly in the last decade, alongside the creation and development of cancer databases (Lincoln 2015). Among the databases created until now, TCGA (The Cancer Genome Atlas) seems to be the most impactful, gathering datasets from several cancer cohorts and a helpful data analysis portal (Tomczak et al. 2015). We aimed to find new therapeutic targets related to Cancer Stem Cell alterations in recurrent patients from two TCGA cohorts: Testicular Germ Cell Tumor (TGCT) and Uterine Corpus Endometrial Carcinoma (UCEC).

MATERIALS AND METHODS

TCGA Data download and preparation for analyses

Approval for access to TCGA case sequence and clinical data was obtained from the National Center for Biotechnology Information Genotypes and Phenotypes Database (NCBI dbGaP) for data access to TCGA-controlled data files. VCF files from Testicular Germ Cell Tumors (TGCT) and UCEC (Uterine Corpus Endometrial Carcinoma) cohorts were downloaded from the GDC portal (https://portal.gdc.cancer.gov/) and processed to extract single gene SNV data. All mutations were compared to the reference base from the 1,000 genomes project (Abdullah & Chow 2010).

Clinical data

Patients were split into two groups by clinical data. Disease-free and recurred/progressed patients, extracted from the clinical attribute disease-free status. This way, TGCT patients were split into two groups, disease-free (98 patients, 98 samples) and recurred/progressed (34 patients, 38 samples), while UCEC was separate in 398 disease-free patients and 109 recurred/progressed. (Figure 1)

Gene Enrichment Analysis

Levels of gene expression from TGCT and UCEC samples were analyzed using Gene Set Enrichment Analysis (GSEA) with 1000 permutations, version 2.2.4 (Subramanian et al. 2005).

Cbioportal analysis

Transcriptome profiling, coexpression co-occurrence, networks, and survival analyses were performed using cBIOPORTAL (http://www.cbioportal.org) (Plotly Technologies 2015, Gao et al. 2013, Cerami et al. 2012).

Graphics and representations

Graphics were generated directly from cBIORPORTAL, which uses Plotly to plot figures (https://plot.ly/) (Gao et al. 2013, Cerami et al. 2012).

Statistical analyses

ANOVA with Tukey Poshoc Test (95% confidence) was used to compare transcriptome analyses between groups. The Fisher Exact test was used in co-occurrence/mutual exclusivity analysis, assuming Log odds ratio > 0: Association towards co-occurrence and Log odds ratio ≤ 0: Association towards mutual exclusivity. Significant association when p-Value < 0.05.

RESULTS AND DISCUSSION

Among all 30 TCGA cancer tissues, Testicular Cancer (TGCT) has shown the highest mRNA expression when analyzing the gene

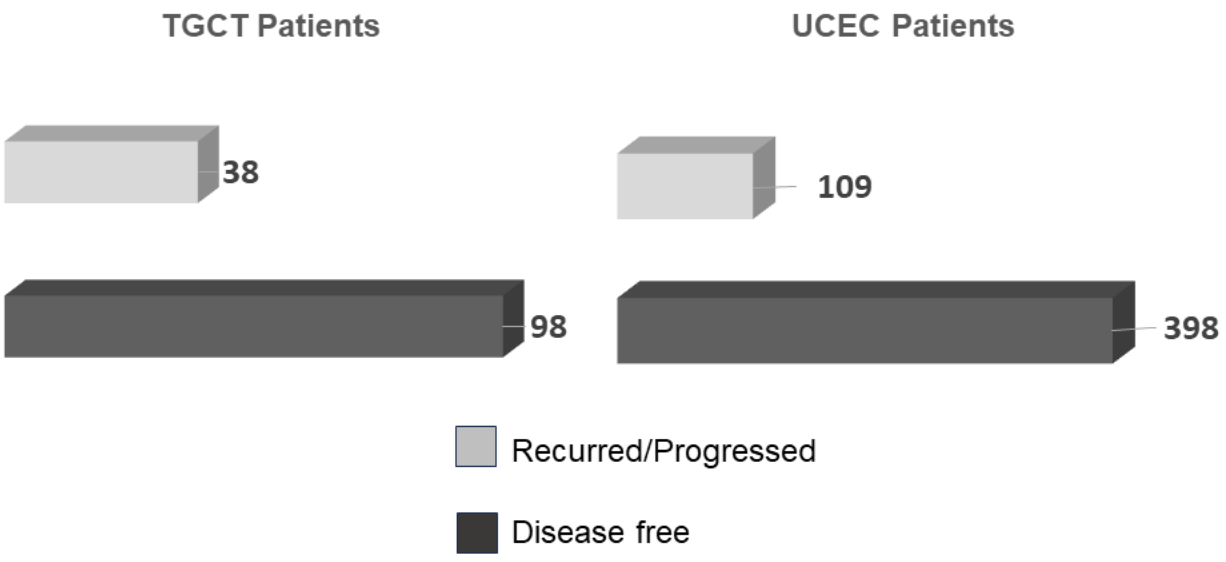


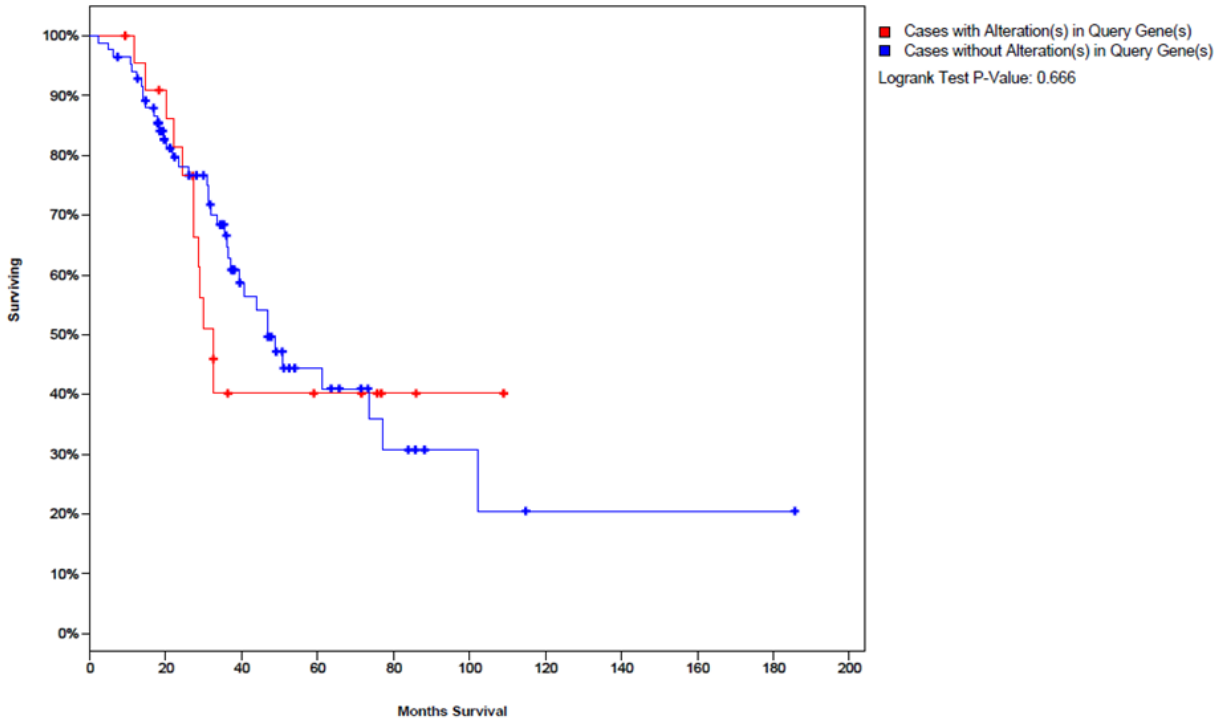
Figure 1. TCGT and UCEC Cohorts sorted by Disease Free Status.

POU5F1(Supplementary Material - Figure S1c), followed by NANOG (Figure S1a) and SALL4 (Figure S1d). SOX2 (Figure S1b) is also among the highly expressed transcription factors in testicular cancer, only lower than Glioma (Figure S1b). Likewise, Uterine Corpus Endometrial Carcinoma also showed a high expression of POU5F1, NANOG, SOX2, and SALL4 within the same cohorts.

Moreover, the ABC transporter genes (ABCB1, ABCG2, and ABCC1) also elevated gene expression within the same cancer types, including TGCT and UCEC. This pattern is associated with drug resistance and recurrence since the stem, as mentioned earlier, cell transcription factors regulate ABC transporters, also upregulated. Moreover, the high amount of estrogen, related to the genesis of endometrial tumors, matches the elevation of ABCG2 since this gene has an estrogen response element (Ee et al. 2004, Chang et al. 2017).

Chemotherapy treatment options for resistant TGCT/UCEC patients are often related to less than 50% of cure rates; thereby, innovative research is crucial (Kondagunta et al. 2005, Lorch et al. 2007, Morice et al. 2016). In this scenario, we have analyzed the impact of alterations in the stem cell transcription factors and ABC transporters used herein to assess the survival rate of the TGCT patients from TCGA. The survival analysis has shown that patients with alterations in this subset of genes had a poor diagnosis compared to patients without alteration in such genes. Moreover, TGCT recurred patients with alterations in the selected genes had an overall survival time of 5.62 months, much lower than the 20.47 found in patients without such alterations (Figure 2). Similarly, UCEC recurred patients had an overall survival time of 32.5 months, also lower than the 47 months found in patients without those alterations. (Figure 3) Alterations in the same genes but within disease-free patients from both cohorts showed no differences in survival time (Figure 3).

These findings reinforce studies on the POU5F1, NANOG, and SOX2 stem cell transcription factors due to their well-known relationship with stemness and drug resistance. Another transcription factor, SALL4, is a novel marker related to the same issue. We then separated



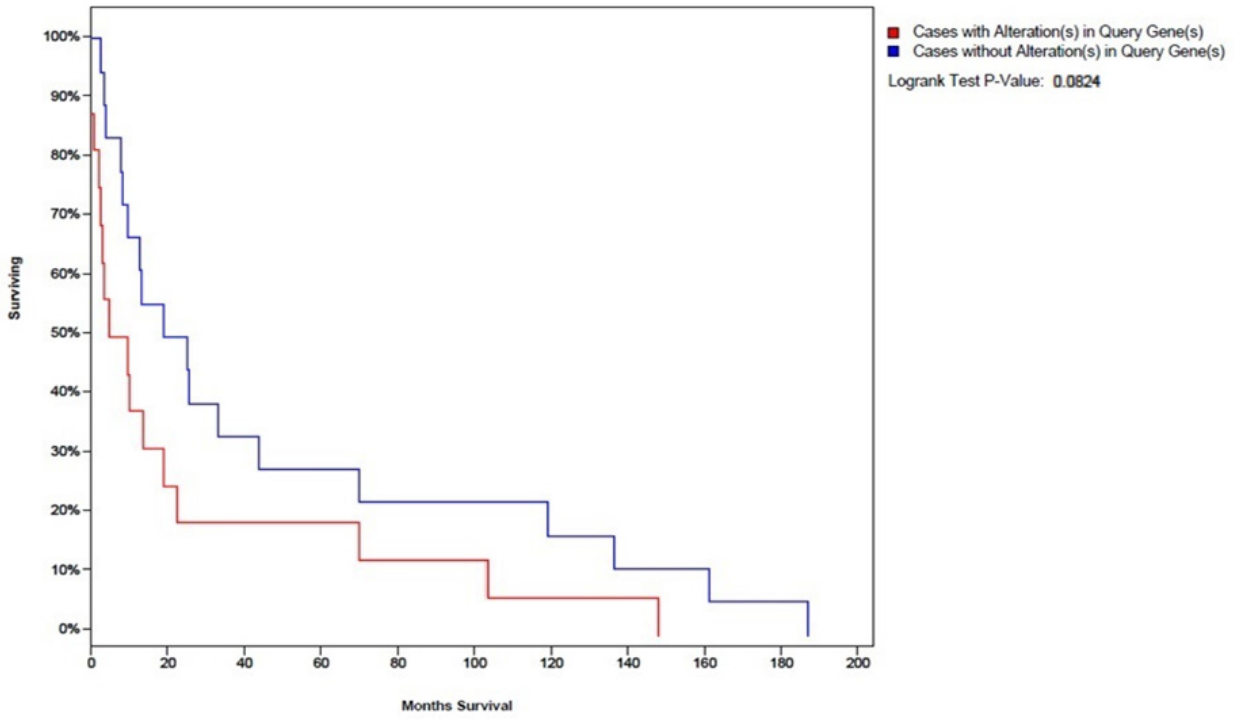
	#Total cases	#Cases relapses	Median months disease free
Cases with Alteration(s) in Query Gene(s)	23	12	32.49
Cases without Alteration(s) in Query Gene(s)	84	38	46.91

Figure 2. Survival rate of recurred patients with alterations in the studied genes, TGCT patients survival rate.

TGCT and UCEC patients into two clinical groups (disease-free - DF and recurred/progressed - REC) to find answers about recurrence. Our first aim was to analyze the co-expression of the target genes to understand their relationship to recurrence better. NANOG has shown a higher correlation with POU5F1 in REC patients (0.65 DF and 0.78 REC), followed by its isoform POU5F1B (0.62 DF and 0.80 REC), which may illustrate that SALL4 also has shown the exact correlation between disease-free and recurred/progressed patients (0.44 DF, and 0.67 REC) reinforcing its association with recurrence.

In this scenario, it seemed crucial to analyze the mRNA expression of these genes in Testicular Cancer. When comparing the seven genes (ABCB1, ABCG2, ABCC1, POU5F1, SOX2, NANOG, and SALL4), POU5F1 presented the highest levels of expression, NANOG had an expression level more incredible than the other genes, except for POU5F1. No differences were found from differential gene expression levels when comparing DF and REC groups within the seven target genes. In addition, analyzing methylation patterns on the target genes revealed the exact hypomethylation profile in the same groups. Therefore, gene expression and methylation analysis have not answered how TGCT and UCEC patients develop resistance.

We then compared the gene expression of microRNAs available in the UCEC and TGCT cohorts (MIR22HG MIR1-1HG MIR99AHG MIR600HG MIR9-3HG MIR4697HG MIR4435-2HG MIR31HG MIR205HG MIR924HG MIR503HG MIR155HG



	#Total cases	#Cases relapses	Median months disease free
Cases with Alteration(s) in Query Gene(s)	16	16	5.62
Cases without Alteration(s) in Query Gene(s)	18	18	20.47

Figure 3. Survival rate of recurred patients with alterations in the studied genes, UCEC patients survival rate.

MIR17HG MIR100HG). The microRNAs MIR4435-2HG and MIR100HG presented the highest gene expression levels in both cohorts. MIR100HG even showed a higher level of gene expression in REC patients from TGCT compared to DF ones. These two microRNAs may contribute to this disease onset by triggering oncogenes (Ke et al. 2017, Deng et al. 2016) and to recurrence in TGCT patients. A study on the immortalized cell lineage (Hela) of cervical cancer origin shows that MIR4435-2HG may be related to the progression of the cell cycle, acting as a non-coding oncogene (Nötzold et al. 2017).

Those findings lead us to study other alterations, such as mutation. We analyzed the global mutation rate via cBIOPORTAL and SNVs (Single Nucleotide Variants) accumulated at a single position at the target genes through VCFinder. POU5F1 presented a global mutation rate of 0.6% in TGCT patients and 3% in UCEC, while SNV analysis revealed 2.6% and 3.2 % for TGCT and UCEC, respectively. The same analysis revealed that SALL4 presented a 0.6% global mutation rate and three SNVs with 2% TGCT, 13% mutational rate, and 15% SNVs in UCEC. SOX2 showed a mutation rate of 0%. Ultimately, NANOG presented a 1.3% and 5.3% mutation rate in TGCT, with a 3% mutation rate and 4.5% SNV frequency in UCEC. In the comparison between DF and REC, no detected mutation was exclusive to any group. Thus, we assumed that the relationship of these transcription factors to recurrence may be related to post-translational modifications such as, for example, phosphorylation.

Patient sequencing data are used to generate phosphorylation networks, identifying the phosphorylation sites and the associated kinases. Moreover, these analyses involve copy number variation (CNV), protein Z score, and mRNA expression. Thus, networks are generated considering the presence or absence of phosphorylation sites on DNA, copy number variation, protein quantification, and altered gene expression related to the effects of phosphorylation. Besides that, the tool uses literature data to determine interactions between the molecules that make up the phosphorylation network. Finally, genes are ranked to show the potential to present interactions by control of phosphorylation in the group of patients analyzed. This tool revealed that only REC patients showed phosphorylation potential for ABCG2 and ABCB1 in TGCT and only for ABCG2 in UCEC. These interactions between ABCG2 and uterine cancer stand out once this pump related to drug resistance has an estrogen response element, which is often elevated in this type of cancer and requires phosphorylation to make homodimers, which such protein requires to become functional. (Taylor et al. 2017, Xie et al. 2008).

Moreover, ABCG2 showed potential interaction with PIM1, a serine/threonine kinase that can phosphorylate L-threonine or L-serine residues found at phosphorylation sites on ABCG2 and POU5F1. The relationship between PIM1 and ABCG2 is well known. The phosphorylation of this kinase on the respective efflux pump produces a multimerization and, thereby, increases chemoresistance (Xie et al. 2008, Yuan et al. 2022). In a recent article from the same research group, it has been reported that, in prostate tumor cell lines, POU5F1 is directly related to the acquisition of resistance to chemotherapy (Linn et al. 2010). In addition, a study with transgenic mice overexpressing PIM1 in the male reproductive organs showed a direct relationship of PIM1 with cancer stem cell markers such as POU5F1 (Jiménez-García et al. 2016). Other studies corroborate, which affirm that PIM1 when phosphorylating POU5F1, increases its activity (Xie & Bayakhmetov 2016, Brumbaugh et al. 2012). Taking into consideration that POU5F1 has its function modulated mainly by phosphorylation, it seems plausible to hypothesize that PIM1 may have a pivotal role in the acquisition of resistance through its direct and simultaneous action on the POU5F1 transcription factor and ABCG2 extrusion pump.

Figure 4 shows that, besides PIM1, another kinase has the potential to phosphorylate POU5F1: PRKACA. This enzyme is the main effector of cAMP signaling in all tissues and is part of the family of AGC kinases. PRKACA represents a catalytic subunit of a larger complex, which controls when and where other proteins are phosphorylated. The relationship between PRKACA and resistance has only been demonstrated in breast cancer (Moody et al. 2015, Saidy et al. 2021). In this work, the authors have identified that overexpression of this kinase leads to resistance to chemotherapeutics such as Trastuzumab and Lapatinib. Additionally, they identified PIM1 as a new mediator of resistance to anti-HER2 therapy. According to the authors, the joint action of PRKACA and PIM1 may reestablish anti-apoptotic signaling.

These results for breast cancer corroborate with the results obtained in the present study for testicular cancer. Figure 4 shows, for the first time, a direct and simultaneous relationship of these two kinases on one of the significant cancer stem cell markers (POU5F1) in the recurrent patient group only. Thus, we hypothesize that these two molecules are directly involved in the acquisition of resistance and relapse of testicular cancer since the hyperphosphorylation of POU5F1 may lead to a transcriptional increase of the genes

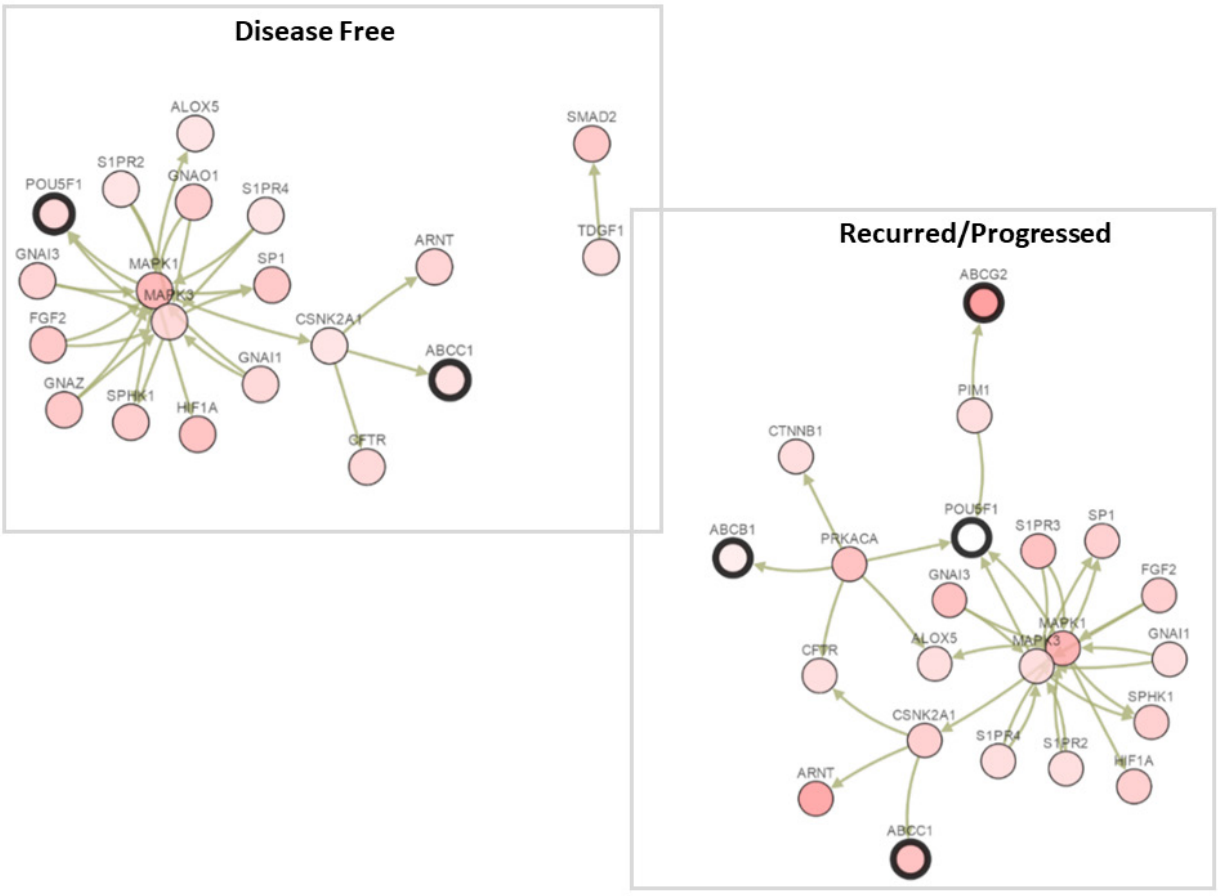


Figure 4. Phosphorylation Network comparing the most related genes in DF and REC groups.

coding for extrusion pumps like ABCB1 and ABCG2. Moreover, when comparing the networks generated for the two groups analyzed, it is clear that only the ABCC1 pump appears in DF patients, while recurrent patients present besides ABCC1, ABCB1, and ABCG2. Therefore, in the DF group, POU5F1 is potentially phosphorylated only by MAPK1 and MAPK3. In contrast, in the recurrent group, this transcription factor is targeted by four different kinases: MAPK1, MAPK3, PIM1, and PRKACA, which have been related to drug resistance (Marques et al. 2019).

To further investigate the role of PRKACA and PIM1 kinases, Gene Set Enrichment Analysis (GSEA) was performed. The same 7 target genes (ABCB1, ABCG2, ABCC1, POU5F1, SOX2, NANOG, and SALL4) were used to make a geneset and run GSEA on the TGCT cohort, split into 2 patient groups within recurrent patients. One group of patients with elevated PIM1 mRNA expression, and the other contained the rest of recurred patients. The first group showed higher expression, with an FDR score of 0.097 (Figure 5a), using 1000 permutations. The same comparison, separating the TGCT cohort between disease-free patients, had no significant result, with an FDR Score of 0.745 with the same number of permutations. UCEC separated into the same groups, showing an FDR Score of 0.103 (Figure 5b) within the patients with PIM1 mRNA expression elevated and 0.376 in the remaining disease-free patients Figure 5.

To further support and validate the data presented earlier, we confirmed the main

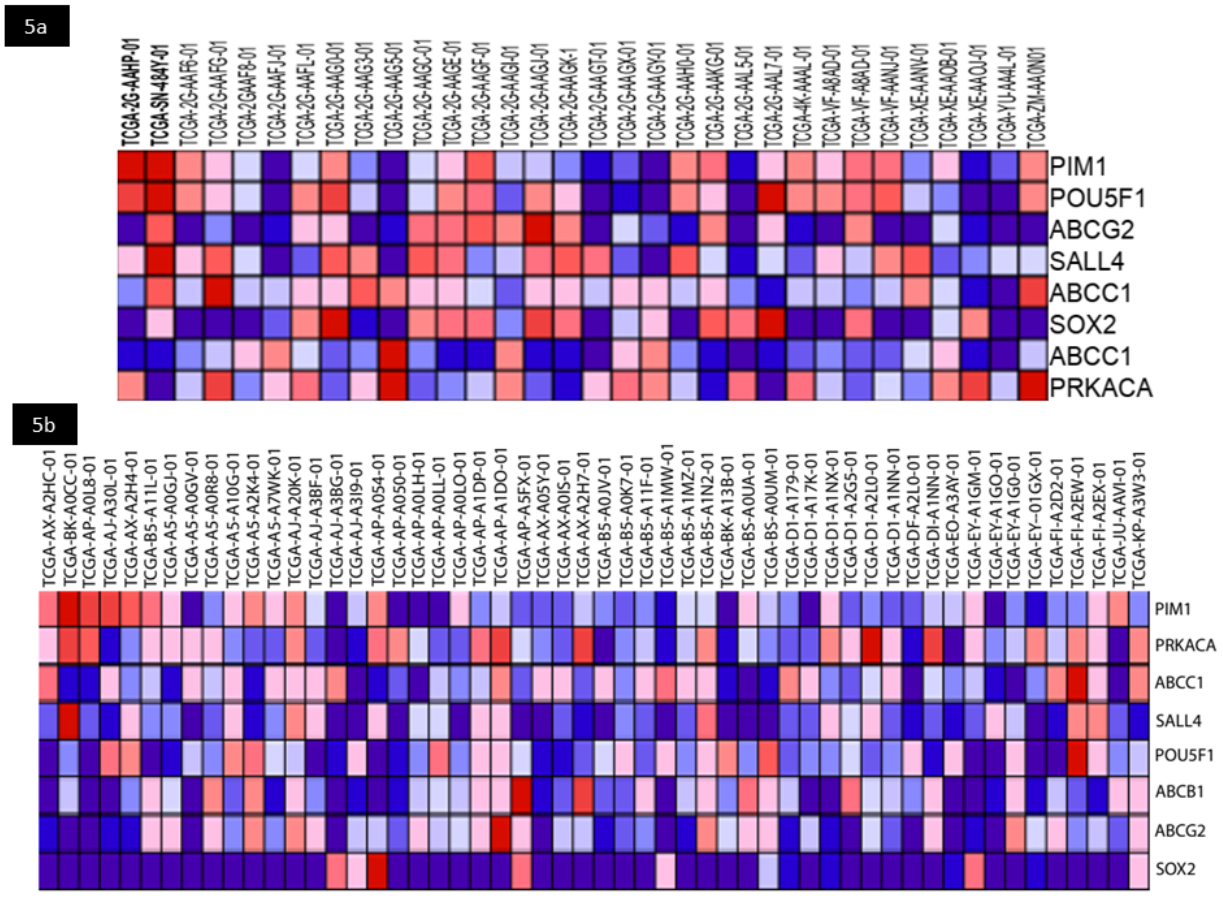


Figure 5. GSEA PIM1 gene expression in TGCT and UCEC patients. 5A: Recurred TGCT, PIM1 High x Low Pim1. 5B: Disease Free TGCT, PIM1 High x Low Pim1.

findings on two other platforms, Gen e Omnibus (GEO) and the International Cancer Genome Consortium (ICGC). On the GEO platform, we were able to verify the connection between ABCB1 and ABCG2 with the UCEC and TGCT patient groups. We observed increased activity of both pumps in utero, particularly ABCG2 (accession number: GSE238158) (Edgar et al. 2022). This strengthens the role of these proteins in cancer development.

We analyzed the UCEC cohort from the ICGC portal (https://dcc.icgc.org/) and found that both ABCB1 and ABCG2 show equal or lower expression in patients in "progression." We also observed the same trend in TCGA, where there was no difference in gene expression. This suggests that an increase in the expression of these genes (Zhang et al. 2011) may be the only plausible explanation for tumor recurrence or progression. These strong findings further support studies on the phosphorylation and activation of these proteins.

Altogether, our phosphonetwork and Geneset Enrichment Analysis lead us to conclude that PRKACA and PIM1 are novel targets to overcome drug resistance. This work's results may help improve new drug development targeting such kinases in TGCT and UCEC recurrent patients.

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SUPPLEMENTARY MATERIAL

Figure S1.

How to cite

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BRO and AVW contributed to the study conception and design, data acquisition, analysis and interpretation, manuscript drafting, and critical revision. MBM and LFM contributed to the drafting of the manuscript and critical revision.