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BTRC Expression Levels Impact HGSOC Progression Through Distinct Cellular Mechanisms

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High-grade serous ovarian cancer (HGSOC) is the commonest subtype of epithelial ovarian cancer. β-TrCP (encoded by *BTRC*) is a component of ubiquitin-proteasome system, a posttranslational process for protein regulation and homeostasis. The role of *BTRC* levels in HGSOC is not fully explored. The aim of this study was to investigate, using bioinformatics approach, the impact of *BTRC* levels on HGSOC. Publicly available transcriptomic data from HGSOC patients (TCGA) were used. First, the overall survival of patients in the lower quartile of *BTRC* expression was compared to those in the upper quartile. Next, differential gene expression analysis (DEA) was performed on the RNA-seq data to find genes that differ significantly in the two groups. Finally, gene set enrichment analysis (GSEA) using KEGG and GO databases were done to identify signaling pathways and mechanisms significantly upregulated in either of the two groups.

Our findings showed that HGSOC patients with high *BTRC* levels had significantly worse overall survival compared to those with low levels (log-rank = 0.0035). DEA of RNA-seq data returned a total of 371 significantly differentially expressed genes among the two groups. GSEA elucidated that high-*BTRC* expression patients were characterized by significant upregulation of many pathways and processes pertaining to cellular growth, proliferation, survival, stemness and development. In contrast, patients with low *BTRC* expression have many significantly upregulated pathways and processes related to mitochondrial function, immunity, and inflammation responses. Those differentially upregulated pathways and processes likely contribute to the variable survival outcomes of HGSOC patients. These findings suggest that *BTRC* expression levels, pending experimental validation, might be a candidate biomarker for informing combinatorial chemotherapy strategies that target implicated signaling pathways in HGSOC.

Keywords: HGSOC, RNAseq, Gene set enrichment analysis, BTRC, β-TrCP

INTRODUCTION

High grade serous ovarian carcinoma (HGSOC) is the most common histological subtype of the epithelial ovarian cancer (EOC). It comprises 70% to 80% of cases, and account for most fatalities (Prat and FIGO Committee on Gynecologic Oncology 2014). HGSOC is associated with unfavorable outcomes as most cases are diagnosed at an advanced stage, often following peritoneal metastasis(Levanon et al. 2008). The standard treatment involves cytoreductive surgery along with adjuvant or neoadjuvant platinum-base (carbo- or cisplatin) and taxane-based (paclitaxel) chemotherapy. Initially, most patients respond well but resistance develops and relapse occurs in the majority of patients shortly after (Matulonis et al. 2016). The 5-year overall survival rate for ovarian cancer patients is around 40%. Improved clinical outcomes are achieved with the use of tumor cell synthetic lethality-inducing drug Poly ADP ribose polymerase inhibitors (PARPi), especially in homologous recombination deficient (HRD) women with *BRCA1/2* mutations (Gadducci and Guerrieri 2017). A comprehensive understanding of molecular events leading to the development and progression of ovarian tumor, and resistance to therapies enables the development of targeted personalized treatments (Jayson et al. 2014).

Beta-transducin repeat-containing proteins (β-TrCP, or FBXW1, or BTRC) is an F-box protein that belongs to FBXW subfamily (encoded by *BTRC* gene). It serves as the substrate-specifying module in the E3 ubiquitin ligase SCF complex (Skp1–Cullin1–F-box protein) (Winston et al. 1999). It is part of the ubiquitin-proteasome system (UPS), an important post-translational modification process for proteins regulation and homeostasis. In this process, targeted proteins are ubiquitinated in a three-step reaction; initially, the ubiquitin protein is activated by

a ubiquitin-activating enzyme (E1) in an ATP-dependent reaction. Next, the activated ubiquitin is transferred to the ubiquitin-conjugating enzyme (E2). Finally, a ubiquitin ligase enzyme (E3) recruits a substrate protein and tags it with the activated ubiquitin. This process is repeated multiple times to add more ubiquitin tags to the substrate. Poly-ubiquitinated proteins are subsequently degraded by 26S proteasome in ATP-dependent manner (Hershko and Ciechanover 1998).

β-TrCP targets numerous regulatory proteins that function in a variety of physiological processes such as cell growth, cell cycle, cell survival, DNA damage repair, metabolism, angiogenesis, development and NF-kB signaling. The diverse β-TrCP substrates presumably gives it a dual role as both oncogene and tumor suppressor in a context- and tissue-specific manner (Bi et al. 2021). In general, β-TrCP was shown to be mostly oncogenic is several epithelial tissues as its mRNA expression was found to be upregulated in colorectal, lung, prostate, breast, pancreatic, ovarian and hepatoblastomas tumors (Frescas and Pagano 2008).

β-TrCP exhibits its oncogenic activity through targeting tumor suppressors that regulate a variety of signaling pathways. For example, β-TrCPs degrades the tumor suppressors IkB (inhibitor of NFkB)(Wu and Ghosh 1999), PDCD4 (inhibitor of eIF4a), and REST (inhibitor of neuronal genes in non-neuronal cells and PI3K pathway)(Westbrook et al. 2008). During cellular stress (e.g. infection and inflammation) β-TrCP stimulates NF-kB signaling through proteasomal destruction of IkB, the inhibitor of NF-kB transcription factor. This frees NF-kB and leads to its nuclear translocation where it transcribes various pro-survival target genes (Kanarek and Ben-Neriah 2012). In addition, β-TrCP stimulates cell cycle progression and cell proliferation through degradation of its target Rap1GAP, which is a tumor suppressor that controls cell proliferation through inactivation of Rap1 (D. Wang et al. 2014). Another substrate of β-TrCP is the tumor suppressor protein hDlg, which maintains cell-cell contact and regulate proliferation (Mantovani and Banks 2003). Additionally, through the ERK/RSK signaling axis, β-TrCP promotes cell survival by targeting the tumor suppressor BimEL for degradation in NSCLC (Dehan et al. 2009). β-TrCP also controls progression through cell cycle by targeting Emi1 for degradation. Emi1 is an inhibitor of APC in S and G2 phases (Margottin-Goguet et al. 2003).

On the other hand, β-TrCP shows tumor suppressing activity in certain conditions. For instance, in response to DNA damage or stalled replication, cdc25A phosphatase, which is an activator of cell cycle progression (G1 to S progression), is targeted for ubiquitination and degradation by β-TrCP. This leads to inhibition of cel cycle progression. Similarly, cdc25B phosphatase, another positive regulator of cell cycle, is also targeted by β-TrCP (Kanemori et al. 2005). In a similar fashion, β-TrCP targets casein kinase 1 phosphorylated VEGFR2 receptor for proteasomal destruction in endothelial cells and in papillary thyroid cancer cell line. This results in inhibition of angiogenesis and prevents tumor growth. An inverse correlation was found between β-TrCP expression and blood vessel formation (Shaik et al. 2012). The only lysine histone methyltransferase Set8 (KMT5A) is also targeted by β-TrCP in manner that relies on the kinase CKIδ. The regulatory functions of Set8, which is an oncoprotein, span many processes such as cell cycle, cell proliferation, migration and oncogenesis (Z. Wang et al. 2015). Similarly, $SCF^{b\text{-}TrCP}$ regulate β-catenin/tcf signaling through ubiquitination and proteasomal destruction of β-catenin. When Wnt signaling is activated, this inhibition is relieved and β-catenin translocate to nucleus to transcribe genes involved in cell growth and proliferation (Bharti and Aggarwal 2002), (Fuchs et al. 2004).

The impact of *BTRC* on high-grade serous ovarian cancer has not been explored enough. A previous study reported that higher mRNA expression of *BTRC* correlates with unfavorable prognosis and worse survival in patients with ovarian serous cystadenocaricinoma. A 5-year survival rate for ovarian serous cystadenocaricinoma patients with high *BTRC* expression is 20%. To the contrary, those with low *BTRC* expression have a 5-year survival rate of 35% (Uhlen et al. 2017). However, a full understanding of the cellular mechanisms behind this variable survival outcome is lacking. Unveiling those mechanisms might be useful in risk stratification and therapeutic decisions about combined targeted therapies. The aim of this study is to initially use publicly available RNA-seq datasets to compare the survival outcome in HGSOC patients in the lower quartile of *BTRC* expression against those in the upper quartile. Then, the biological mechanisms and signaling pathways contributing to variation in survival phenotype were explored using differential gene expression analysis and gene set enrichment analysis. The findings from this investigation uncovered many signaling pathways and cellular processes that are distinctly upregulated in the two HGSOC groups. Should future experimental validation is achieved, *BTRC* expression levels might be a candidate biomarker for risk stratification and combined targeted therapies for HGSOC patients.

MATERIALS AND METHODS

Data source

Normalized, log-transformed RNA-seq expression count data and clinical metadata of high-grade serous ovarian cancer patients (TCGA-OV) in the *BTRC* expression lower (Q1) and upper (Q4) quartiles were retrieved from the UCSC Xena database (Goldman et al. 2020) using the R package UCSCXenaTools (S. Wang and Liu 2019). In total, 153 samples were included in this study, of which 76 samples belong to *BTRC* expression lower quartile (Q1 group) and 77 samples belong to *BTRC* expression upper quartile (Q4 group).

Survival analysis

Survival analysis was conducted to compare the overall survival of low-*BTRC* and high-*BTRC* expressing groups using R package survival (Therneau and Grambsch 2001). Kaplan–Meier curves for overall survival (OS) were generated using R package survminer (Kassambara et al. 2016).

Differential gene expression analysis

Differential gene expression analysis (DEA) was performed on normalized, log-transformedl gene expression count data using the R package limma (version 3.65.3) (Ritchie et al. 2015). The threshold for significantly differentially expressed genes (DEGs) was defined as |logFC| > 1 and the adjusted p value < 0.05. The returned DEGs were visualized on a volcano plot created using the R packages ggplot2 (Wickham 2016), dplyr (Wickham et al. 2019), and ggrepel (Slowikowski 2026).

Enrichment analysis

Gene set enrichment analysis (GSEA) using KEGG (Kyoto Encyclopedia of Genes and Genomes) (Kanehisa et al. 2010) and GO (Gene Ontology) (Ashburner et al. 2000) databases was performed in R programming software using the R package clusterProfilter (Yu et al. 2012). Genes were identified using ENTREZ IDs. All DE genes were extracted and ranked according to their foldchanges (decreasing order). Then, GSEA was performed using the clusterProfiler functions gseGO() and gseKEGG(). Significance threshold for enrichment of KEGG signaling pathways was set to NES > |1.5| and adjusted pvalue < 0.05. Significance threshold for enrichment of GO categories was set to NES > |2| and adjusted pvalue < 0.05 Enriched terms were visualized using enrichplot (Guangchuang Yu 2018) and ggplot2 (Wickham 2016) R packages.

RESULTS

HGSOC Patients with high *BTRC* expression show worse overall survival outcome.

To evaluate whether *BTRC* expression dosage has an effect on HGSOC status, the overall survival (OS) of patients in the lowest quartile of *BTRC* expression (Q1 group) was compared to those in the highest quartile of *BTRC* expression (Q4 group). This univariate analysis shows that patients in the highest quartile *BTRC* expression displayed significantly worse overall survival compared to those of the lowest quartile *BTRC* expression (log-rank 0.0035, Figure 1) The median overall survival for *BTRC* Q1 patients was 1583 days while that of *BTRC* Q4 patients was 1088 days. This finding suggests that *BTRC* (encoding β-TrCP protein) might have an oncogenic role in HGSOC as elevated expression of *BTRC* appears to confer the ovarian tumor cells a survival advantage.

Low-*BTRC* and high-*BTRC* expressing HGSOC patients have different transcriptomes

Since the previous analysis demonstrated that differential *BTRC* expressions have a significant impact on the overall survival outcome in HGSOC patients, the biological processes that might contribute to this variation in overall survival were subsequently investigated. To that end, differential gene expression analysis was initially performed to identify genes that are differentially expressed in the Q1 and Q4 BTRC expression groups. This DEA was implemented on a total of 153 serous ovarian cancer RNA-seq expression count data retrieved from TCGA database (n of Q1 = 76 , n of Q4 = 77. This analysis uncovered a significant transcriptomic alteration between the two groups. A total of 371 statistically significant differentially expressed genes (DEGs) were returned between Q1 and Q4 *BTRC* gene expression groups; 124 genes were upregulated in the reference group Q1 (i.e. upregulated in Q4 group) and 249 genes were downregulated in Q1 group (or, upregulated in Q4 group) (Figure 2).

Distinct signaling pathways and biological mechanisms are activated in Low-*BTRC* and high-*BTRC* expressing HGSOC patients

To find out the signaling pathways that are differently enriched in the two *BTRC* expression-based HGSOC groups (lower and upper quartiles) and hence might be implicated in driving the variable survival outcomes, GSEA analysis using KEGG pathways was performed on the whole gene list obtained from the previous DEA analysis ranked by foldchange. This enrichment analysis revealed a significant upregulation of a total of 63 KEGG signaling pathways in the low *BTRC* expressing patients (Q1 group) (NES > 1.5 and adjusted pvalue < 0.05) (Figure 3A,). These activated signaling pathways are primarily associated with mitochondrial function (e.g. oxidative phosphorylation) and immune and inflammatory responses (e.g. antigen-processing and presentation, MHC class II protein complex, TNF and IL-7 signaling, Toll-like receptor, and NOD-like receptor) (Figure 3A, 3B right panel).

On the other hand, the high *BTRC* expressing (Q4) group was characterized by the significant upregulation of total of 60 KEGG signaling pathways (NES < -1.5 and adjusted pvalue < 0.05). Those pathways are mainly related to cellular proliferation, survival, stemness, and development. Examples of such enriched pathways include MAPK, PI3K-Akt, Ras, cAMP, cGMP-PKG, Notch, Hippo, hedgehog, and Wnt (Figure 3A, 3B left panel).

Further, GSEA analysis was performed using Gene Ontology (GO) database (biological processes (BP), molecular functions (MF), and cellular components (CC)) to identify mechanisms that might be involved in the differential survival outcome of Q1 and Q4 groups. This GO-based gene set enrichment analysis was also implemented using all of the DEA gene list ranked by foldchange. This analysis returned numerous biological process terms significantly upregulated in Q1 group (low *BTRC*) (150 BP, 44 CC, and 25 MF) (NES > 2 and adjusted pvalue < 0.05).

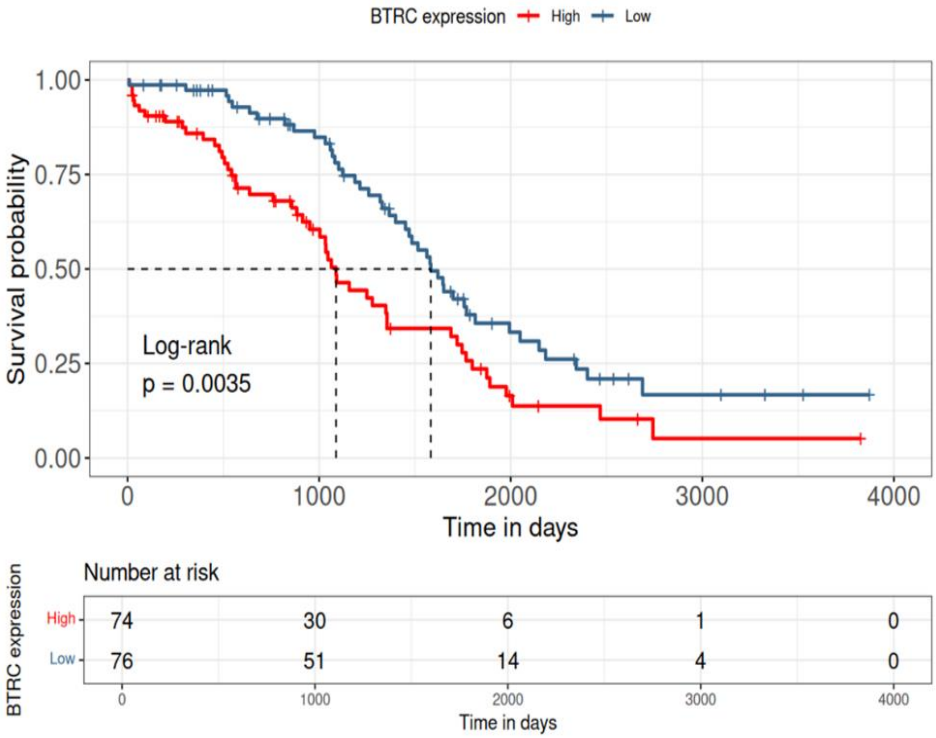

Figure 1. Kaplan Meir (KM) plot of overall survival of ovarian cancer patients with the highest BTRC expression (Q4) versus those with the lowest BTRC expression (Q1). Log-rank test (P = 0.0035). The median survival times of the Q1 and Q4 groups are indicated by the dashed lines.

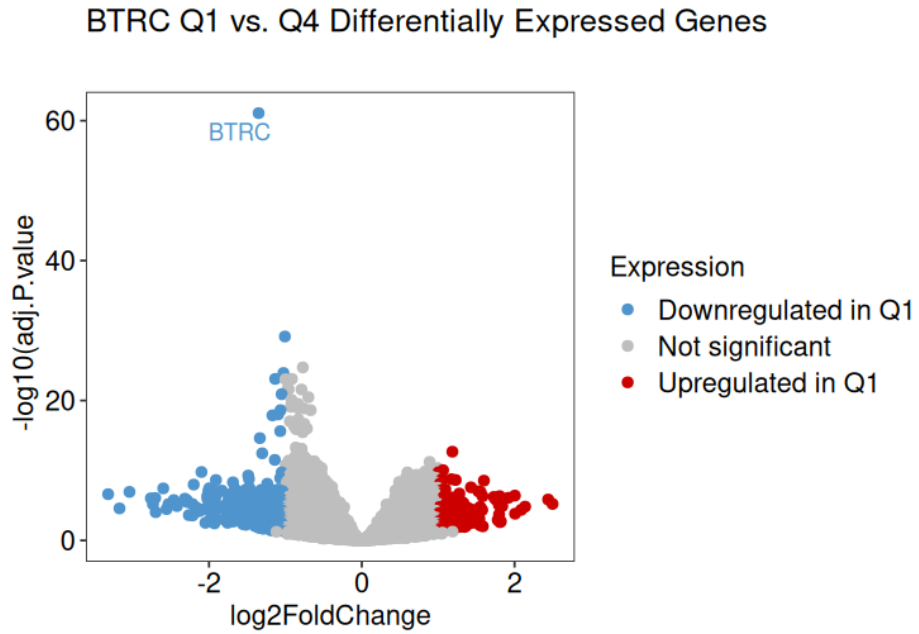

Figure 2. Volcano plot of the differential expression analysis of *BTRC* expression Q1 versus Q4 groups. The DEGs cutoffs were as follows: log fold change |logFC| > 1 and adjusted P value < 0.05. Red: significantly upregulated genes in Q1 patients. Blue: significantly downregulated genes in Q1 patients. Gray: non-significant genes.

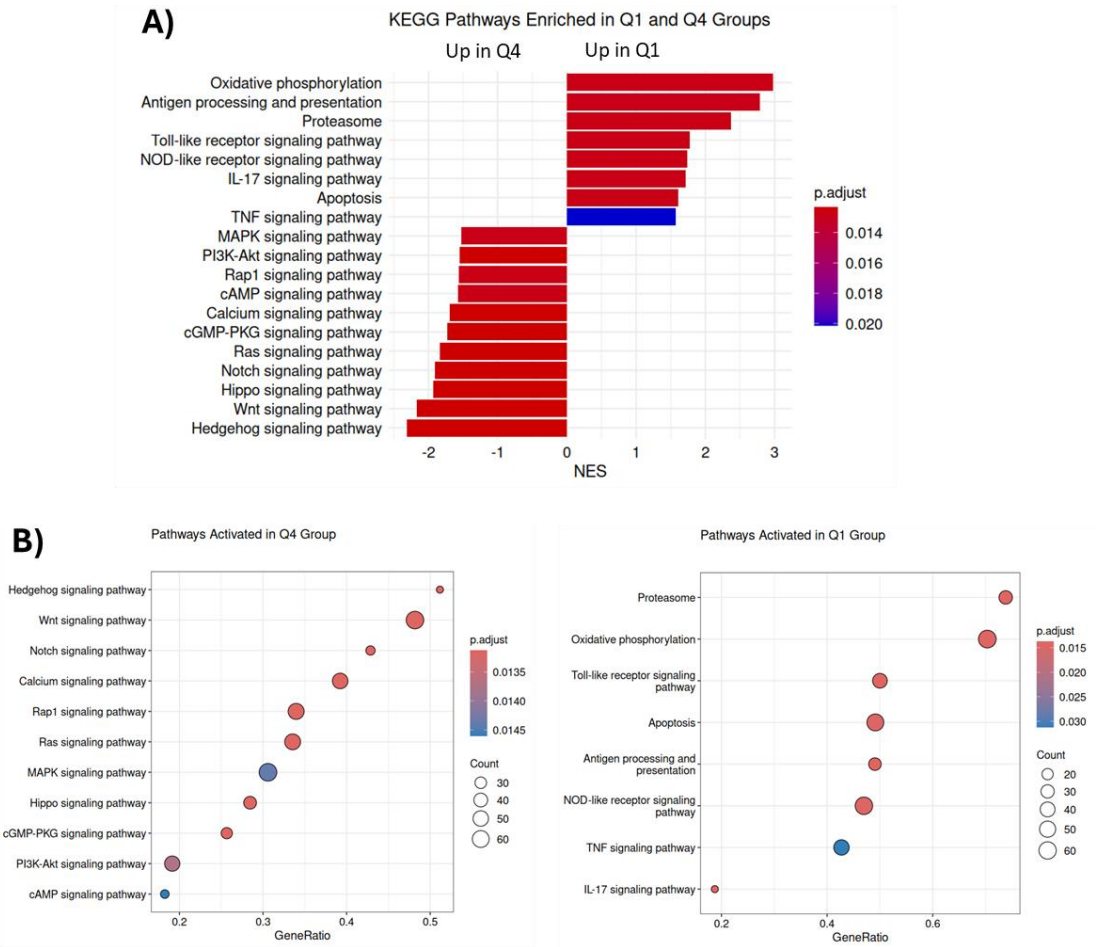

Figure 3 GSEA enrichment analysis shows enriched KEGG pathways in Q1 and Q4 BTRC expression groups. A) a diverging barplot of a selection of the significantly enriched KEGG pathways in the Q1 and Q4 groups. B) *Left panel*: dotplot displaying a selection of the significantly enriched KEGG pathways in Q4 group. *Right panel*: dotplot displaying a selection of the significantly enriched KEGG pathways in Q1 group. NES: normalized enrichment score.

The top 15 significantly enriched GO terms in the three categories of GO in Q1 group are shown in Figure 4. In general, the enriched GO terms in Q1 group can be grouped mainly into three major cellular processes; mitochondrial energy metabolism (e.g. ATP synthesis coupled electron transport and aerobic respiration), immunity and inflammatory responses (antigen processing and presentation, leukocyte mediated cytotoxicity, T cell mediated immunity, and acute inflammatory response), and metal ion homeostasis and stress response (e.g. response to copper ion, ferroptosis, stress response to metal ion, and response to zinc ion).

On the other hand, many distinct biological processes were significantly enriched in Q4 group (high *BTRC*) as well (142 BP, 20 CC, and 22 MF) (NES < -2 and adjusted p value < 0.05). The tope 15 significantly enriched GO terms in the three categories of GO in Q4 group are shown in Figure 4. Overall, the GO terms enriched in Q4 can be grouped into proliferation, migration, development and stem cell.

These findings show that higher *BTRC* expression (Q4 group) is associated with induction of signaling pathways that promote tumor progression, invasion, resistance to apoptosis, stemness, aggression and metastasis. To the contrary, lower *BTRC* expression correlates with the induction of oxidative phosphorylation, inflammation, and immunity pathways. These results suggest the variable survival between the Q1 and Q4 groups likely stem from these distinct biological mechanisms.

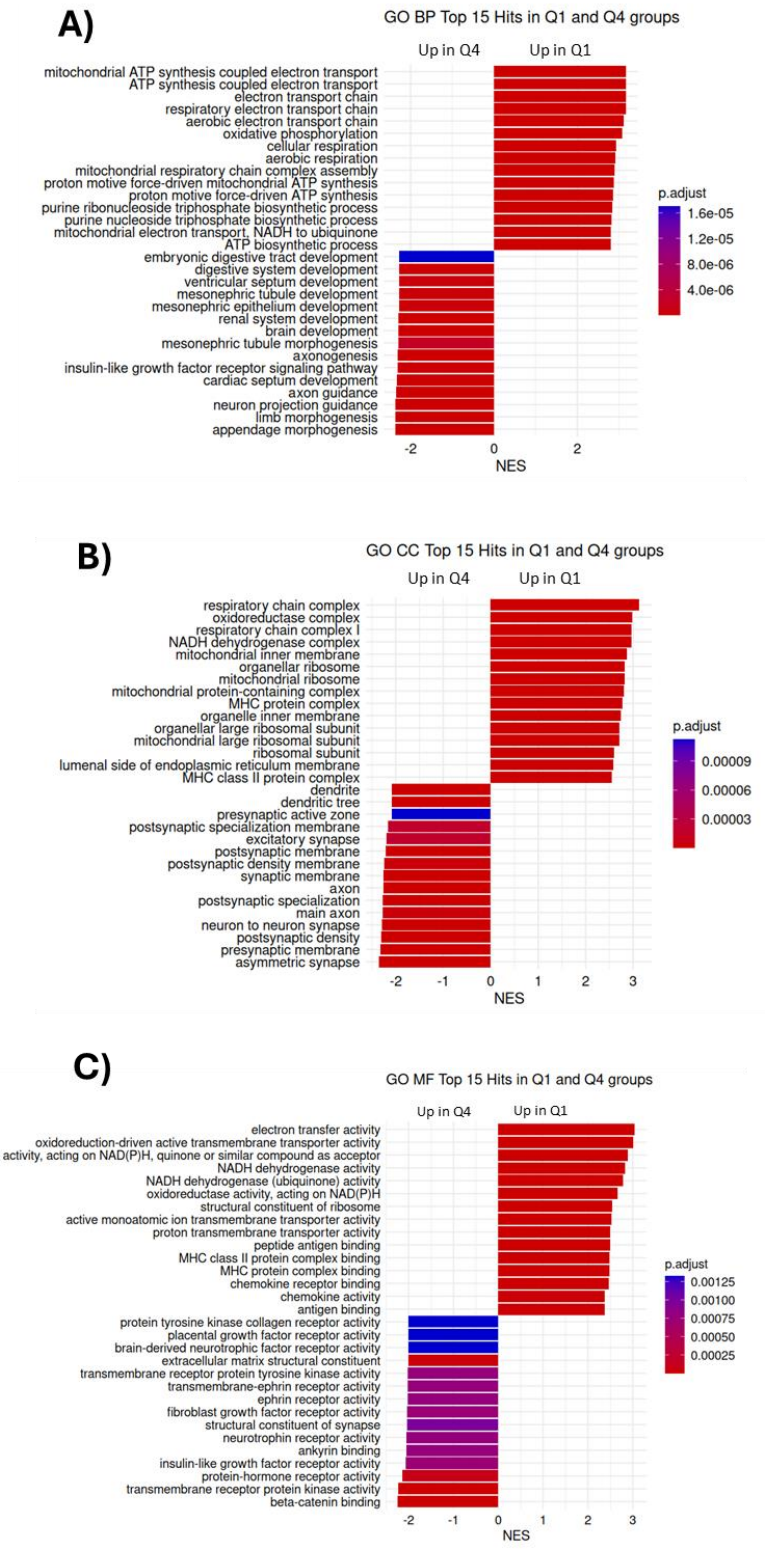

Figure 4 GSEA enrichment analysis using Gene Ontology terms. A) Top 15 enriched BP terms in Q1 and Q4 groups. B) Top 15 enriched CC terms in Q1 and Q4 groups. C) Top 15 enriched MF terms in Q1 and Q4 groups.

DISCUSSION

HGSOC is the deadliest subtype of all ovarian

cancers. Due to its late diagnosis, it has a dismal prognosis. In spite of an initial response to standard treatment by most patient, they eventually develop resistance to chemotherapy (Selvakumaran et al. 2003). Genetic and molecular biomarkers that enable targeted therapy are important for effective management of this tumor. The role of E3 ubiquitin ligase β-TrCP (encoded by *BTRC*) in tumors is context- and tissue-specific. It plays an essential role in regulating protein homeostasis through the proteasomal degradation both in physiological and pathological conditions (Bi et al. 2021). In this study, we retrieved publicly available HGSOC RNAseq dataset from UCSCXena database to explore the impact of differential *BTRC* gene expression levels on survival phenotypes and gene expression profiles HGSOC patients. Overall survival of patients in the lower quartile of *BTRC* mRNA expression (Q1) were compared to those in the upper quartile of *BTRC* mRNA expression (Q4). Our findings elucidate that patients with higher mRNA expression of *BTRC* have significantly worse survival outcome. This correlation between increasing *BTRC* expression and poor overall survival suggests that β-TrCP is likely oncogenic in HGSOC.

To identify cellular mechanisms that contribute to this variable overall survival outcome, differential gene expression analysis followed by KEGG- and GO-based gene set enrichment analyses were performed to compare HGSOC patients in the lower quartile of *BTRC* expression against those in the upper quartile. This returned a few hundred significantly differentially expressed genes in the two groups; 124 genes were upregulated in Q1 group, while 249 genes were upregulated in Q4 group. Many of the signaling pathways enriched in the higher *BTRC* expression Q4 group (worse survival group) are associated with the regulation of cellular growth, proliferation, survival, stemness and development, and are important drivers of cancer initiation, progression and metastasis (Kotsopoulos et al. 2014). For instance, among the top-ranking upregulated pathways in Q4 group is the hedgehog signaling pathway. Previous studies have shown that ovarian cancer stem cells (OCSCs) with aberrant components of Hedgehog signaling in HGSOC display induced self-renewal, EMT, invasion and resistance to chemotherapy (Sneha et al. 2020). In normal ovarian epithelium, the expression of Hedgehog signaling pathway components (SHH/DHH/PTCH/SMO/GLI1) is low or absent (Liao et al. 2009). However, hedgehog signaling is frequently induced in ovarian tumor tissues and is associated with poor survival outcomes. Experimental inhibition of hedgehog pathway interfered with ovarian tumor growth ((Liao et al. 2009), (Tang et al. 2025)). Additionally, this pathway is associated with malignant tumor progression, unfavorable prognosis, and death. Its aberrant upregulated is reported in several tumors such as glioma, prostate, medulloblastoma, liver, and pancreatic cancers (Jing et al. 2023).

Other stemness and development regulating pathways such as Hippo, Wnt, Notch signaling pathways were also stimulated in Q4 *BTRC* expression group. Several studies have reported that those pathways are dysregulated and they likely contribute to progression of ovarian cancer and resistance to chemotherapy (T. Han et al. 2023), (Barbolina et al. 2011), . Induced activity of the hippo signaling proteins YAP/TAZ is associated with poor survival outcome in ovarian serous cystadenocarcinoma (Y. Wang et al. 2018). Notch signaling pathways are frequently upregulated in high grade ovarian cancer (22% of cases) (The Cancer Genome Atlas Research Network 2011). Inhibitors of this pathway interfered with growth and induced apoptosis in ovarian cancer (Choi et al. 2008). Thus, higher *BTRC* expression might serve as a biomarker to help guide the use of combined targeted therapies against the molecules of activated signaling pathways.

In contrast, data from this study has revealed that HGSOC patients expressing low levels of *BTRC* gene are characterized by the activation of signaling pathways involved largely in oxidative phosphorylation, immunity, and inflammation. Previous research has shown that HGSOC patient samples exist in heterogenous OXPHOS states; high-OXPHOS and low-OXPHOS. Interestingly, unlike their low-OXPHOS counterparts, high-OXPHOS ovarian cancer cell lines viability was impacted in response to metformin, a mitochondrial complex I inhibitor (Gentric et al. 2019). Thus, low *BTRC* expression might have the potential to be a candidate biomarker to determine HGSOC patients that could benefit from synergetic therapy involving OXPHO inhibiting drugs such as metformin.

Antigen processing and presentation is involved in anti-tumor immunity and can predict immunotherapy outcomes (Balasubramanian et al. 2022). This study showed that in HGSOC patients with low *BTRC* levels, antigen processing and presentation, particularly MHC class II, were upregulated compared to those with higher *BTRC* levels. Previous work reported that antigen processing and presentation was downregulated in high-risk HGSOC patients (Yoshihara et al. 2012), indicating a positive correlation between antigen presentation and survival. Histone deacetylase (HDAC) inhibitors can stimulate antigen presentation activity in several tumors (Khan et al. 2008) and it shows synergetic effect in combination with standard ovarian tumor chemotherapy (Kitamura et al. 2007). Therefore, low *BTRC* expression might be explored as a candidate guiding biomarker for the use of this combination chemotherapy in HGSOC patients.

T cell-mediated immunity/cytotoxicity was also significantly induced in low *BTRC*-expressing HGSOC patients. This is consistent with previous findings that elucidated the correlation between intratumoral T lymphocytes infiltration and improved survival in epithelial ovarian cancer patients (L. Y. Han et al. 2008). This

suggests that HGSOC with low *BTRC* expression have enhanced antitumor immunity and might show beneficial response to immunotherapy such immune check point inhibitors ICIs.

An important limitation of this investigation is that it lacks empirical validation. Future *in vitro* and *in vivo* experiments are needed to validate the implication of *BTRC*, and its encoded protein β-TrCP, expression levels, on HGSOC. For instance, knocking out or ectopically overexpressing β-TrCP on HGSOC could be explored to find out whether these interventions show any impact on the growth and progression of HGSOC. Furthermore, examining the outcome of using inhibitors of signaling pathway and biological processes that we found upregulated either low-BTRC or high-BTRC groups might help validate the utility of co-targeting those pathways in the management of HGSOC.

CONCLUSIONS

In conclusion, our findings show *BTRC* expression levels correlated with overall survival phenotype in HGSOC patients. Different signaling pathways and cellular processes are upregulated in the low- and high-*BTRC* expressing patients. Therefore, *BTRC* expressions might be further explored as a biomarker for guided combinatory treatment of HGSOC.

Supplementary materials

Not applicable

Author contributions

The sole author of the paper confirms the sole responsibility for the study concept, methodology, validation, experimentation, data collection/validation, interpretation of results and manuscript preparation, revision and finalization.

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Not applicable

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Conflict of interest

The author declares no conflict of interest.

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