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PROFILING OF S6K1 ISOFORM EXPRESSION ACROSS MOLECULAR SUBTYPES OF HUMAN BREAST TUMORS

Aim. To investigate the transcriptional profiles of RPS6KB1 mRNAs encoding canonical (p70/p85-S6K1) and novel (p60-S6K1) isoforms in clinical human breast tumor (BC) samples across major molecular subtypes (Luminal A, Luminal B (HER2+), and triple-negative (TNBC)) compared to adjacent histologically normal tissue. **Methods.** Total RNA was isolated from clinical breast tumors and paired adjacent tissues. Expression levels of ESR1, HER2, and specific S6K1 isoform transcripts were quantified using real-time qPCR. Statistical analysis was performed to evaluate relative gene expression and p70/p85-S6K1/p60-S6K1 transcript ratios. **Results.** Transcriptional profiling confirmed clinical subtyping and revealed distinct S6K1 isoform expression patterns. Canonical p70/p85-S6K1 transcript levels were markedly upregulated across all tumors, with the highest expression observed in HER2-positive Luminal B samples. Conversely, expression of the novel p60-S6K1 isoform was dramatically downregulated in all tumor types, with the lowest levels detected in TNBC. The p70/p85-S6K1/p60-S6K1 mRNA ratio was significantly altered in cancer tissues compared to normal counterparts. **Conclusions.** These findings corroborate the pro-oncogenic role of canonical S6K1 signaling and provide the first evidence that the p60-S6K1 isoform may exert tumor-suppressive functions.

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Divergent expression profiles highlight the importance of considering isoform-specific signaling when designing targeted mTOR/S6K therapies.

Keywords: *RPS6KB1, p85S6K1, p70S6K1, p60S6K1, breast cancer molecular subtypes, qPCR.*

Introduction

Breast cancer (BC) is the most common malignancy among women both worldwide and in Ukraine, ranking second in cancer-related mortality. In 2022, the disease claimed approximately 670,000 female lives globally. Timely diagnosis at stages I–II ensures a 90–95% curability rate, whereas late detection significantly reduces this probability [1]. BC is a highly heterogeneous disease classified into molecular subtypes based on the expression of estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2), and the proliferation marker Ki-67. The four primary subtypes are Luminal A (ER+/PR+/HER2–), Luminal B (ER+/PR+/HER2+/-), HER2-enriched (ER–/PR–/HER2+), and triple-negative breast cancer (TNBC; ER–/PR–/HER2–).

Determining the molecular subtype is a fundamental diagnostic step, as it dictates both the therapeutic strategy and disease prognosis due to substantial differences in recurrence risk and treatment response dynamics among the subtypes.

Estrogen receptor-positive (ER+) tumors account for approximately 70–80% of all breast cancer cases, making anti-estrogen (endocrine) therapy the cornerstone of treatment for all patients with hormone receptor-positive (ER+/PR+) breast cancer. However, resistance to endocrine therapy poses a major clinical challenge, developing in approximately 20–30% of patients with early-stage disease and in nearly all patients with metastatic ER+ breast cancer over time. One of the key molecular mechanisms underlying acquired resistance is the activation of bypass signaling cascades — particularly the PI3K/AKT/mTOR pathway — allowing tumor cells to switch to alternative growth and survival mechanisms. Notably, this pathway is simultaneously capable of driving ligand-independent activation of ER (ESR1). Dysregulation of

PI3K/mTOR/S6K1 signaling is implicated in severe human pathologies, including cancer, neurodegenerative and cardiovascular diseases, metabolic disorders, and age-related conditions.

Ribosomal protein S6 kinase (S6K1), encoded by the *RPS6KB1* gene, is among the primary effectors of this signaling cascade. Importantly, S6K1 can phosphorylate ESR1, thereby modulating its activity as a transcription factor by regulating its nuclear translocation. S6K1 exists as several variants, with the two most thoroughly investigated isoforms being p85-S6K1 and p70-S6K1. These are translated from a common mRNA transcript via alternative translation initiation sites (the first and second AUG codons), resulting in p85-S6K1 possessing an additional 23 N-terminal amino acid residues compared to the p70 isoform [2–9].

Elevated expression and activation of p70-S6K1 correlate with a poor prognosis in several cancer types, suggesting its potential utility as a biomarker for disease monitoring. Activated p70-S6K1 contributes to various facets of cancer progression, including the epithelial-mesenchymal transition (EMT), cancer cell stemness, and drug resistance [10, 11].

Recently, in addition to the well-characterized p70 and p85 isoforms, a novel p60-S6K1 isoform has been identified [12, 13]. According to our previous data, p60-S6K1 arises from the translation of an alternative splice variant of S6K1 mRNA containing an additional exon 1a. The presence of this exon ensures translation exclusively from a third, p60-S6K1-specific initiation codon, thereby preventing p70/p85-S6K1 expression.

Utilizing the CRISPR/Cas9 genome-editing system, we generated MCF-7 breast carcinoma cell sublines with differential expression of S6K1 isoforms [14]. We demonstrated that altering the expression balance among S6K1 isoforms initiates EMT, indicating the activation of invasive and

metastatic capacities [15]. Thus, the ratio of S6K1 isoform expression could potentially serve as a diagnostic marker for tumor cells that have undergone EMT, thereby providing an additional parameter for refining molecular subtyping, which is a critical factor for both treatment selection and disease prognosis.

Therefore, the present study aimed to determine the transcriptional characteristics of RPS6KB1 mRNAs responsible for translating p70/p85-S6K1 and p60-S6K1 in human breast tumors of different molecular subtypes (Luminal A, Luminal B (HER2+), and triple-negative) compared to histologically normal adjacent breast tissue. Real-time PCR analysis revealed a significant upregulation of p70/p85 isoform expression across all analyzed tumor types, accompanied by a marked downregulation of the p60 isoform. Although the highest S6K1 expression level was observed in Luminal B tumors, no statistically significant differences in S6K1 expression were detected across the different molecular subtypes. Similarly, no significant differences were found in the expression ratio of p70-S6K1 to p60-S6K1 among the tumor groups. Consequently, these findings confirm the established oncogenic properties of canonical S6K1 and provide the first evidence that the p60 isoform may possess tumor-suppressive functions, warranting further detailed investigation.

Materials and Methods

Total RNA isolation

Total RNA was isolated from human breast tumor tissue samples (0.2–1.5 g) using the guanidinium isothiocyanate method with innuSOLV reagent (Analytik Jena) or RNA Go (BioLabTech), according to the manufacturers' instructions. The tissue samples were snap-frozen in liquid nitrogen immediately after resection and stored at -80°C . Total RNA from mammalian cells was isolated using the RNeasy Mini Plus Kit (Qiagen) according to the manufacturer's instructions. The cells were first trypsinized, washed twice with ice-cold phosphate-buffered saline (PBS), and subsequently collected by centrifugation. After washing, the cell

pellet was divided into two portions and transferred into microcentrifuge tubes. One portion was used for total RNA isolation. The concentration, purity, and integrity of the isolated RNA were assessed spectrophotometrically at $\lambda = 260\text{ nm}$ and $\lambda = 280\text{ nm}$ and by agarose gel electrophoresis with ethidium bromide staining.

cDNA synthesis from total RNA

cDNA was synthesized by reverse transcription using total RNA isolated from human breast tumor samples. The reaction mixture, with a final volume of $20\text{ }\mu\text{L}$, contained 1–5 μg of total RNA pretreated with DNase I, $100\text{ }\mu\text{M}$ oligo(dT)15 primer, $4\text{ }\mu\text{L}$ of $5\times$ reaction buffer, $2\text{ }\mu\text{L}$ of 10 mM dNTPs, $0.5\text{ }\mu\text{L}$ of RiboLock RNase inhibitor ($40\text{ U}/\mu\text{L}$), and $1\text{ }\mu\text{L}$ of RevertAid H Minus Reverse Transcriptase ($50\text{ U}/\mu\text{L}$). For RNA denaturation and annealing of the oligo(dT)15 primer to mRNA, the RNA and primer were incubated separately from the remaining reaction components at 65°C for 10 min. The remaining components were then added, and reverse transcription was performed at 42°C for 1–2 h. The enzymes were inactivated by incubation at 65°C for 10 min. The resulting cDNA was diluted twofold by adding $20\text{ }\mu\text{L}$ of H_2O and stored at -20°C .

Real-time quantitative PCR (qPCR)

Real-time quantitative PCR was performed using the Maxima SYBR Green/Fluorescein qPCR Master Mix (Thermo Fisher Scientific, USA) and a CFX96 Real-Time System thermal cycler (BioRad, Singapore).

The $20\text{-}\mu\text{L}$ qPCR reaction mixture contained $0.5\text{ }\mu\text{L}$ of cDNA, $10\text{ }\mu\text{L}$ of $2\times$ Master Mix, $1\text{ }\mu\text{L}$ of a mixture of forward and reverse primers ($5\text{ }\mu\text{M}$ each), and $8.5\text{ }\mu\text{L}$ of nuclease-free H_2O . Amplification was performed under the following thermal cycling conditions: initial denaturation at 95°C for 10 min; 40 amplification cycles consisting of denaturation at 95°C for 15 s, annealing at 60°C for 20 s, and extension at 72°C for 25 s.

Primer sequences used for real-time quantitative PCR:

p60-S6K1 for Ex1a TTCTGTCTGGGAGTAGCACTG
 p60-S6K1 rev Ex3 CACAATGTTCCATGCCAAGTT
 S6K1 for Ex2 GACCATATGAACTTGGCATGG
 S6K1 rev. Ex4 TCCCAGTATTTGCTCCTGTTAC
 TBP for TGCACAGGAGCCAAGAGTGAA
 TBP rev. CACATCACAGCTCCCCACCA
 ESR1 for AGGTGGACCTGATCATGGAG
 ESR1 rev AAGCTTCGATGATGGGCTTA
 Her2+ for GTCCTGGAAGCCACAAGG
 Her2+ rev GGTTTTCACACATCCTCT

To determine relative gene expression, the ΔC_t method was used. TBP was used as the reference gene, and the expression levels of the target mRNAs were calculated relative to TBP expression. Each reaction was performed in three technical replicates. Statistical analysis was performed using analysis of variance (ANOVA) followed by Tukey's HSD test, with $p < 0.05$ considered statistically significant.

The clinical samples of breast cancer tumor tissue and adjacent tumor-surrounding tissue were obtained from the National Cancer Institute. All subjects provided written informed consent.

Results and Discussion

Validation of clinical samples and expression of ESR1/HER2

The present study aimed to determine the mRNA expression profiles of S6K1 isoforms (p70/p85-S6K1 and p60-S6K1) in primary tumors of various

breast cancer (BC) molecular subtypes: Luminal A, Luminal B (HER2+), and triple-negative breast cancer (TNBC), comparing them to samples of histologically normal adjacent breast tissue (Table 1). Since the preliminary classification of the clinical samples into molecular subtypes was based on routine immunohistochemical (IHC) analysis of ESR1 and HER2/neu protein levels, we first verified these clinical parameters using real-time qPCR to assess the corresponding mRNA expression.

As shown in Figures 1 and 2, the expression profiles of the studied genes at the transcriptional level largely corroborated the clinical distribution of the samples by molecular subtype. A significant upregulation of the *ESR1* mRNA transcript was observed in Luminal A and Luminal B (HER2+) tumors compared to adjacent normal tissues, particularly within the Luminal B cohort. Furthermore, *HER2* mRNA levels were significantly higher in Luminal B samples than in the Luminal A group, which is consistent with a higher clinical aggressiveness typically associated with the Luminal B subtype.

Notably, isolated cases exhibited a discrepancy between mRNA and protein expression profiles. For instance, qPCR analysis of sample T42, clinically classified as TNBC (which characteristically lacks HER2 expression), revealed high *HER2* mRNA levels comparable to those of Luminal B tumors. This finding underscores the potential for transcriptional-translational discordance or highlights the possibility of false-negative IHC results, suggesting that re-evaluation of such anomalous cases is critical to determine the feasibility of anti-HER2 targeted therapy. Additionally, the analysis of *ESR1* expression in tumor-adjacent tissues was heterogeneous, with relatively high levels observed in certain samples (e.g., N85, N89, N15—2). This elevated expression could be attributed to undetected microscopic tumor cell invasion or a broader “field effect” exerted by the primary tumor on its surrounding microenvironment, indicating that adjacent tissue may serve as an informative supplementary marker for post-operative monitoring.

Table 1. Clinical profile of the breast tissue samples used in the study

Tissue samples	Quantity
Luminal A	10
Luminal B (HER2+)	11
TNBC	10
Adjacent tumor normal tissue	10

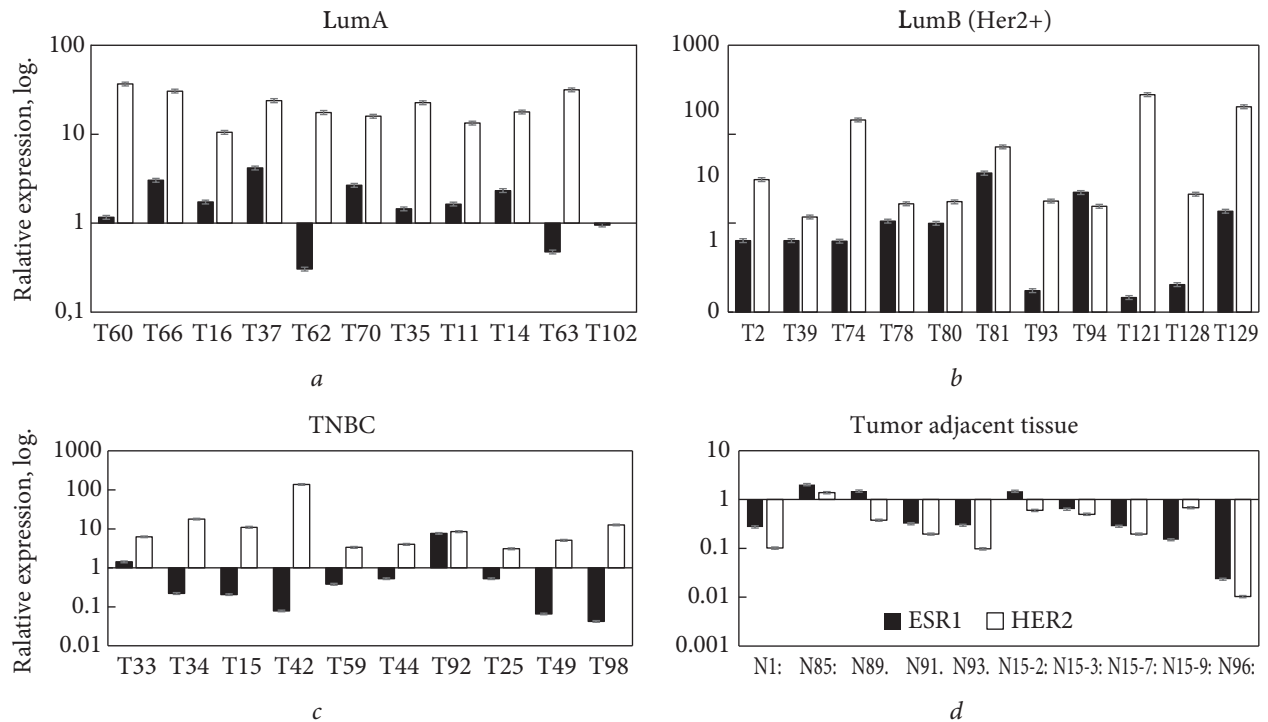


Fig. 1. PCR analysis of ESR1 and HER2 mRNA expression levels in breast tumors of different molecular subtypes and in tumor-adjacent tissue (*d*). T — tumor samples from different patients; N — unpaired tumor-adjacent tissue from different patients

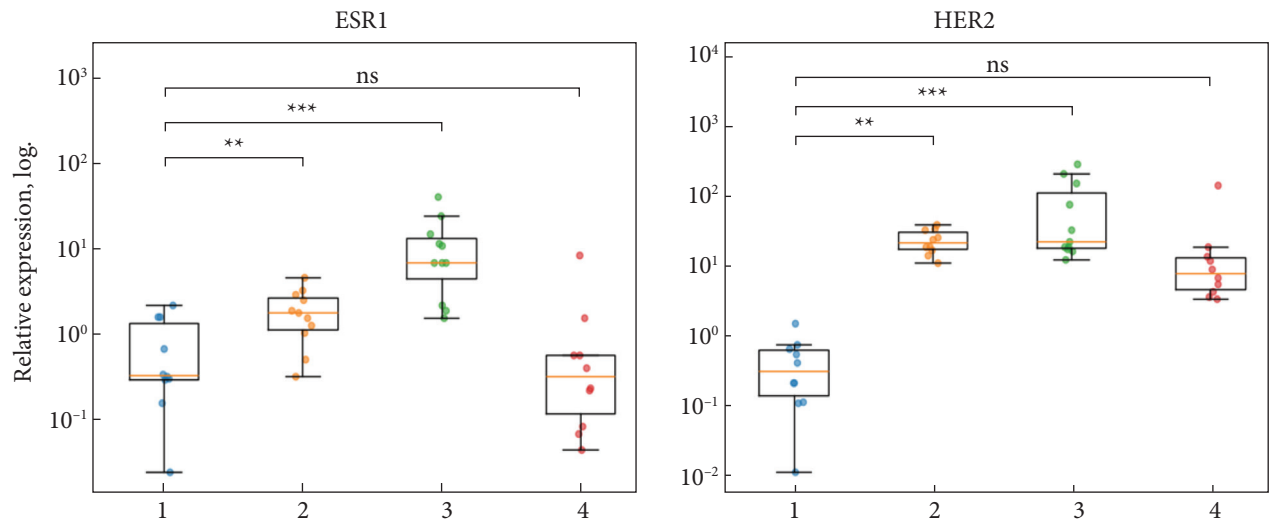


Fig. 2. Averaged ESR1 and HER2 expression levels determined by quantitative PCR (qPCR) in tumor-adjacent tissues and breast tumors of different molecular subtypes. Data are presented as boxplots (median and interquartile range) with individual values overlaid. A logarithmic scale is used. Statistical significance was assessed using the Kruskal-Wallis test followed by Dunn's post-hoc test (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, ns — not significant). Breast tissue samples: 1 — tumor-adjacent tissue, 2 — Luminal A tumors, 3 — Luminal B (HER2/neu+) tumors, 4 — triple-negative tumors

Upregulation of canonical p70/p85-S6K1 isoforms is associated with HER2 status

Following cohort validation, we investigated the expression of specific S6K1 isoforms. Translation of S6K1 isoforms relies on two distinct mRNA transcripts: a 15-exon transcript (NM_003161, RefSeq, NCBI) containing open reading frames for all three initiation sites (p60, p70, p85), and an alternative splice variant containing an additional exon 1a (NM_001272044, RefSeq, NCBI), which ensures translation exclusively from a third initiation codon specific to the p60-S6K1 isoform (12). Based on our previous findings using exon 1a-specific shRNA, the latter transcript is primarily responsible for the p60-S6K1 expression (13). Thus, our qPCR analysis allowed us to differentiate the

combined expression of the canonical p70/p85-S6K1 isoforms from the strictly p60-S6K1-specific transcript.

Our data revealed significant differences in the expression levels of the p70/p85-S6K1 isoforms among the BC molecular subtypes compared to the control group (Fig. 3, 4). Elevated expression of p70/p85-S6K1 was detected in both Luminal A and Luminal B tumors. Moreover, we observed a trend in which increased p70/p85-S6K1 expression correlated with greater aggressiveness in the Luminal B (HER2+) subtype. This finding has a clear biological rationale: HER2 overexpression in Luminal B tumors triggers hyperactivation of the PI3K/AKT/mTOR signaling cascade, thereby necessitating a coordinated upregulation of its downstream effectors, notably S6K1. Conversely, in TNBC — the most aggressive BC subtype — the

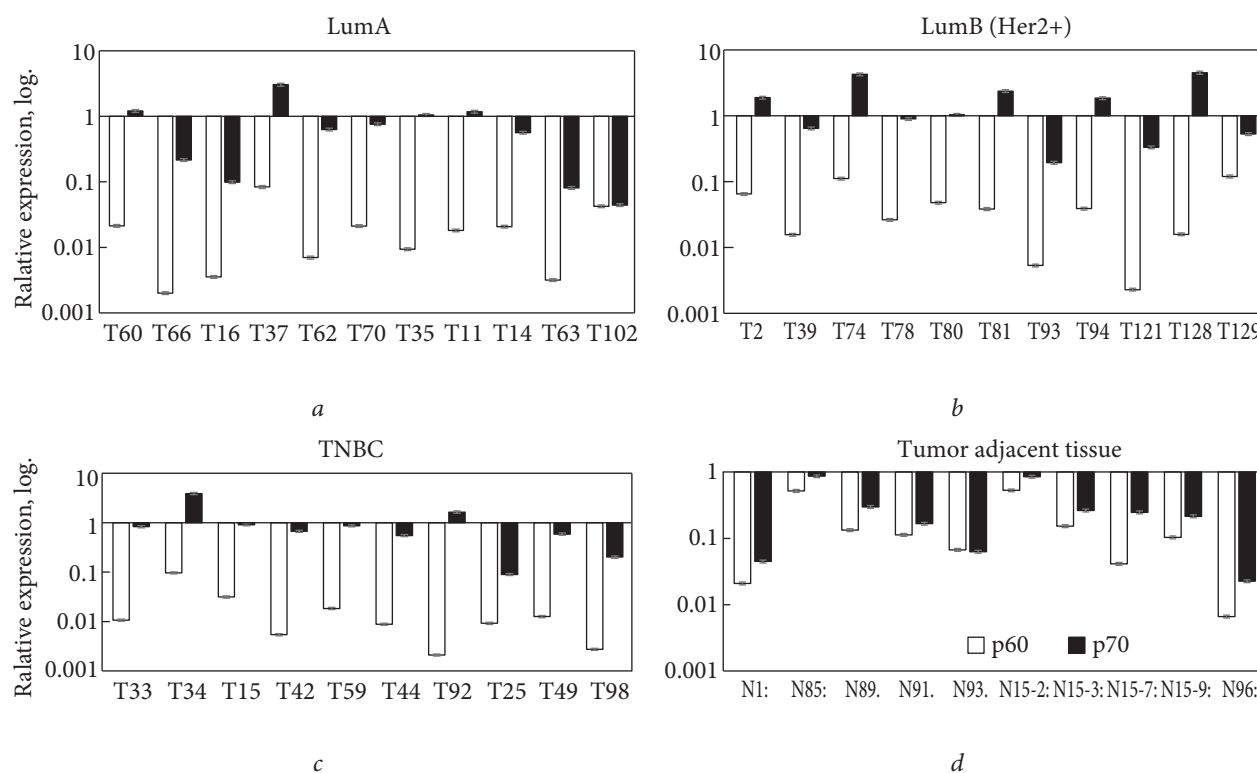


Fig. 3. PCR analysis of S6K1 isoform mRNA expression (p70/85-S6K1 and p60-S6K1) in breast tumors of different molecular subtypes and in tumor-adjacent tissue. T — tumor samples from different patients; N — unpaired tumor-adjacent tissue from different patients

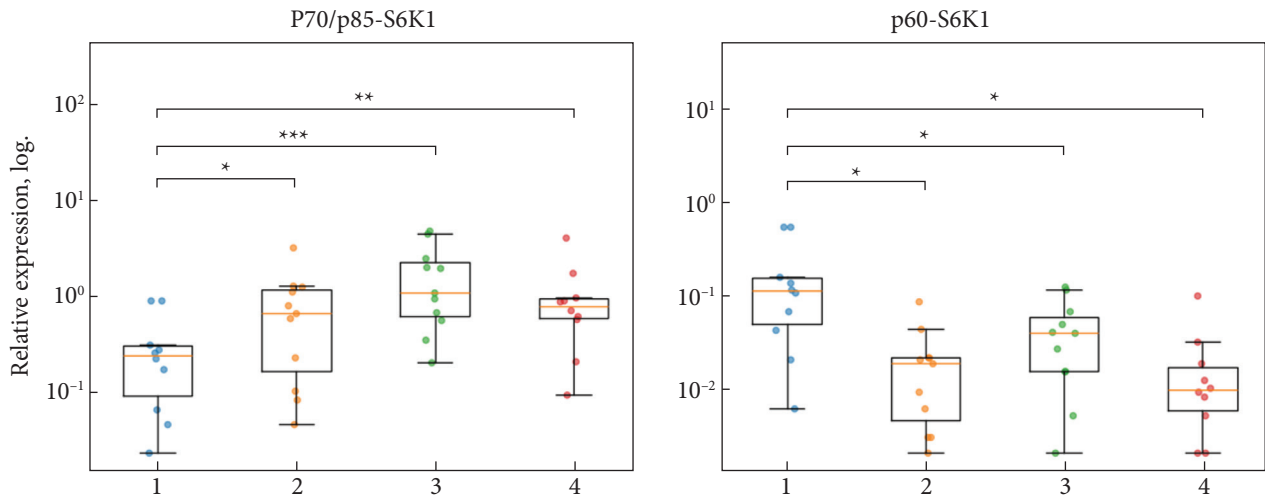


Fig. 4. Averaged expression levels of the p70/p85-S6K1 and p60-S6K1 isoforms, determined by quantitative PCR (qPCR), in tumor-adjacent tissues and breast tumors of different molecular subtypes. Data are presented as boxplots (median and interquartile range) with individual values overlaid. A logarithmic scale is used. Statistical significance was assessed using the Kruskal-Wallis test followed by Dunn's post-hoc test (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Breast tissue samples: 1 — tumor-adjacent tissue, 2 — Luminal A tumors, 3 — Luminal B (HER2+) tumors, 4 — TNBC

expression of p70/p85-S6K1 tended to be lower than in Luminal B and was roughly comparable to Luminal A. This suggests that the high invasive and metastatic potential of TNBC, which lacks the HER2 driver, relies heavily on alternative mechanisms, such as the early initiation of the epithelial-mesenchymal transition (EMT).

Downregulation of the novel p60-S6K1 isoform highlights its putative tumor-suppressive role

In striking contrast to the canonical isoforms, analysis of the p60-S6K1 transcript revealed a diametrically opposite trend. A dramatic downregulation of the p60-S6K1 mRNA was observed across all analyzed tumor types compared to adjacent normal tissue, with the most profound decrease detected in the highly aggressive TNBC samples (Fig. 3, 4).

This clinical finding provides critical validation of our previous *in vitro* experimental models. We previously demonstrated, using CRISPR/Cas9 genomic editing in the Luminal A-derived MCF-7 cell line [14], that selectively altering the expression

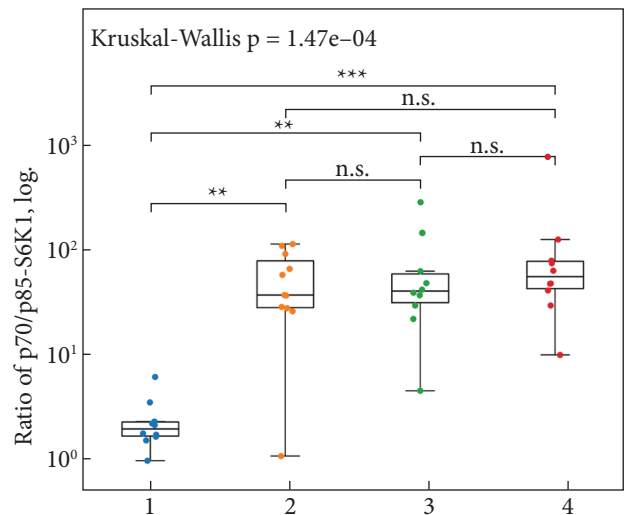


Fig. 5. The p70/p85-S6K1/p60-S6K1 ratio in tumor-adjacent tissues and breast tumors of different molecular subtypes. Data are presented as boxplots (median and interquartile range) with individual values overlaid. A logarithmic scale is used. Statistical significance was assessed using the Kruskal-Wallis test followed by Dunn's post-hoc test (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, ns — not significant). Cancer molecular types: 1 — tumor-adjacent tissues, 2 — Luminal A, 3 — Luminal B (HER2+), 4 — TNBC

balance among S6K1 isoforms initiates the onset of EMT, accompanied by a dramatic silencing of ESR1 expression and the activation of invasive capacities [15]. The consistent downregulation of p60-S6K1 observed in primary human breast tumors in the present study strongly supports the hypothesis that the loss of this specific isoform is a critical molecular event in malignant transformation and tumor progression. Together, these data provide the first clinical evidence that the novel p60-S6K1 isoform may possess inherent tumor-suppressive functions.

The balance of S6K1 isoforms and its therapeutic implications

Finally, we analyzed the relative expression ratio of the canonical p70/p85-S6K1 isoforms to the novel p60-S6K1 isoform. While calculating this ratio did not reveal statistically significant differences among the distinct molecular subtypes of breast cancer, a highly significant shift in the p70/p60 ratio was evident when comparing primary tumors to conditionally normal adjacent tissues (Fig. 5).

Overall, our data demonstrate that the transcript encoding the p70 and p85 isoforms represents the dominant *RPS6KB1* mRNA in both normal breast tissue and breast cancer, regardless of molecular subtype. However, malignant transfor-

mation is characterized by a significant uncoupling of S6K1 isoform expression: the canonical pro-oncogenic p70/p85-S6K1 signaling is upregulated (particularly in HER2-driven contexts), while the putative tumor-suppressive p60-S6K1 isoform is concurrently repressed. These divergent properties are likely governed by distinct intracellular functional activities and alternative substrate specificities of the isoforms.

Crucially, these findings have direct translational relevance. The widespread clinical use of broad-spectrum mTOR/S6K1 inhibitors as anti-tumor therapeutics generally targets all kinase isoforms indiscriminately [2, 3]. By demonstrating the opposed roles of p70/p85 and p60 isoforms in breast cancer progression, our data strongly suggest that non-selective inhibition may yield suboptimal or unpredictable clinical outcomes. Therefore, a detailed functional analysis of these individual kinase isoforms is imperative to guide the development of precise, isoform-specific therapeutic strategies for breast cancer management.

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ПРОФІЛЮВАННЯ ЕКСПРЕСІЇ ІЗОФОРМ S6K1 СЕРЕД МОЛЕКУЛЯРНИХ ПІДТИПІВ ПУХЛИН МОЛОЧНОЇ ЗАЛОЗИ ЛЮДИНИ

Мета. Дослідити транскрипційні профілі мРНК гена RPS6KB1, що кодують канонічні (p70/p85-S6K1) та нову (p60-S6K1) ізоформи, у пухлинах молочної залози людини основних молекулярних підтипів (люмінальний А, люмінальний В (HER2+) і тричі негативний) порівняно з прилеглою гістологічно нормальною тканиною молочної залози. **Методи.** Загальну РНК виділяли з клінічних зразків пухлин молочної залози та парних прилеглих тканин. Рівні експресії ESR1, HER2 та транскриптів специфічних ізоформ S6K1 оцінювали методом кількісної ПЛР у реальному часі (кПЛР). Статистичний аналіз проводили для визначення відносної експресії генів і співвідношення транскриптів p70/p85-S6K1/p60-S6K1. **Результати.** Транскрипційне профілювання підтвердило клінічні підтипи та виявило відмінні патерни експресії ізоформ S6K1 у зразках пухлин. Рівень транскрипту для канонічних p70/p85-S6K1 був помітно підвищений у всіх проаналізованих пухлинах, досягаючи найвищих показників у зразках HER2-позитивного люмінального підтипу В. Натомість рівень мРНК нової ізоформи

p60-S6K1 критично знижувався в усіх типах пухлин, причому найвиразніше падіння спостерігалось при тричі негативному раку молочної залози. Хоча співвідношення експресії мРНК p70/p85-S6K1 до p60-S6K1 суттєво не відрізнялося між окремими молекулярними підтипами пухлин, воно достовірно змінювалося в пухлинній тканині порівняно з прилеглою тканиною. **Висновки.** Отримані клінічні дані підтверджують проонкогенну роль канонічного сигналіну S6K1 і надають перші докази того, що ізоформа p60-S6K1 може виконувати пухлиносупресорні функції. Різнострамовані профілі експресії цих ізоформ підкреслюють вирішальне значення врахування ізоформ-специфічного сигналіну під час розробки таргетної терапії mTOR/S6K для лікування раку молочної залози.

Ключові слова: RPS6KB1, p85S6K1, p70S6K1, p60S6K1, молекулярні підтипи раку молочної залози, кПЛР.