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RESEARCH ARTICLE

GGPS1 Gene Expression in Triple-Negative Breast Cancer: Impact on the Risk of Distant Metastasis and Potential Use as a Target for Therapy

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Abstract

Background: This in silico study aimed to investigate, in triple-negative breast cancers (TNBCs), the expression of genes involved in the production of geranylgeranyl-diphosphate (GGDP), an intermediate in the mevalonate/cholesterol pathway essential for the post-translational modification of the RhoA small GTPase, and their impact on distant-relapse-free survival (DRFS).

Methods: The study utilized a publicly available dataset to examine four genes (*HMGCR, FDPS*, *FDFT1*, and *GGPS1*) involved in the mevalonate/cholesterol pathway, as well as five essential components of the RhoA/ROCK signaling pathway: *RHOA, ROCK1, LIMK1, MYL1*, and *CFL1*. The impact of gene expression on DRFS was analyzed using the Cox regression model, with gene expression treated as continuous or categorical covariates.

Results: When stratified according to the optimal cutoff, the expression of *GGPS1, RHOA, ROCK1, LIMK1*, and *CFL1* significantly affected the occurrence of distant metastasis. *LIMK1* was associated with a 51% decreased risk of developing distant metastasis, whereas *GGPS1*, *RHOA, ROCK1*, and *CFL1* were associated with a substantially increased risk (100%, 108%, 80%, and 89%, respectively). In basal-like 2 (BL2), the TNBC subtype known for its poor prognosis, tumors with high levels of *GGPS1* were associated with a very short DRFS.

Conclusions: Given the crucial role of the RhoA small GTPase in activating the RhoA/ROCK pathway, preventing RhoA geranylgeranylation by inhibiting the expression of *GGPS1* gene by statins or the activity of the enzyme by bisphosphonates and GGPS inhibitors could be a promising therapeutic strategy to enhance the limited effectiveness of the current taxane-based chemotherapy used to treat TNBCs.

Keywords: Triple-Negative Breast Cancer, Distant Metastasis, Ggps1 Gene, Rhoa/Rock Signaling Pathway.

1. Introduction

Triple-negative breast cancer (TNBC) is a heterogeneous group of invasive breast cancers that do not express estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER2). Although TNBC accounts for only 12.7% of all breast cancer cases, it is responsible for 40% of breast cancer-related deaths due to its high growth rate and aggressive clinical behavior [1]. Given the lack of hormone receptors and HER2 overexpression, cytotoxic chemotherapy with taxanes is the standard treatment regimen for TNBC in both neoadjuvant and adjuvant settings [2,3]. However, systemic chemotherapy provided only limited benefits due to the substantial differences in pathological features and biological behavior among TNBCs,

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often leading to tumor chemoresistance and disease progression.

Initially categorized as basal-like tumors based on their gene expression profile [4,5], TNBCs have later been distinguished into six molecular subtypes: two basal-like (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), and a luminal androgen receptor (LAR) subtype [6]. In 2016, the classification was refined from six into four stable subtypes: BL1, BL2, LAR, and M, with the IM and MSL subtypes reassessed and reclassified [7]. Due to their distinct molecular profiles, the four TNBC subtypes exhibit different clinical behaviors. Thus, TNBCs belonging to the LAR subtype have lobular histology, predominantly metastasize to bone, may benefit from hormone therapy, and are associated with a favorable prognosis. In contrast, TNBCs in the BL2 subtype frequently show metaplastic histology, tend to metastasize to the lungs, and are associated with a short distant relapse-free survival (DRFS) [7].

Although the subtype classification of TNBCs could be beneficial for guiding treatment decisions, it is not currently used because of high costs, complex technological requirements, and potential variability in gene expression profiling results. Consequently, taxane-based chemotherapy remains the standard treatment for all TNBC patients, even though it is not sufficient to effectively prevent the metastatic spread of the most aggressive cancer cells. To overcome tumor chemoresistance and prevent cancer dissemination, researchers explored alternative strategies and identified new molecular targets that play crucial roles in the signaling pathways governing various aspects of metastatic spread, such as changes in cell shape and cell movement.

The Rho family of small GTPases plays a crucial role in cell migration and invasion [8,9]. These proteins require an irreversible covalent post-translational modification called geranylgeranylation to be properly targeted and anchored to the cytoplasmic surface of the plasma membrane [10]. Once anchored, they activated the Rho/Rho-associated protein kinases (ROCK) pathway (Figure 1), which is essential for coordinating the reorganization and dynamics of the actin cytoskeleton, regulating cell shape, and facilitating cell attachment and movement [11,12].

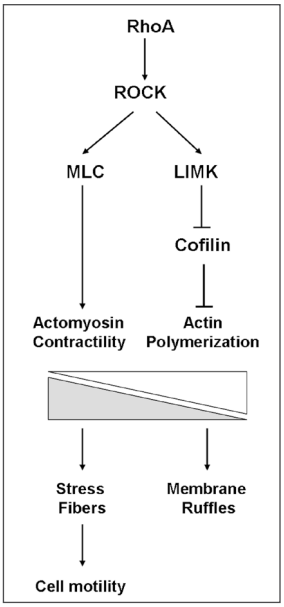

Figure 1. *RhoA is the most extensively studied member of the Rho small GTPase family. It acts as a master regulator at the leading edge of cells, coordinating signals that govern interactions between the cell and the extracellular matrix, leading to membrane ruffling, mediating the formation of stress fibers, and generating the contractile force necessary for cell motility. One of RhoA's most important downstream effectors is the Rho-associated protein kinase (ROCK). ROCK phosphorylates various downstream proteins, including LIM kinase (LIMK)[12]. LIMK, in turn, phosphorylates cofilin. Cofilin phosphorylation blocks the cofilin-mediated actin filament disassembly and induces cytoskeletal rearrangement. While increased actin polymerization enhances membrane ruffling, greater contractile forces lead to stress fiber formation and cell motility. Triangles visualize the reciprocity of the two opposite events: the formation of stress fibers and the membrane ruffles.*

This study examined the expression of genes involved in the production of geranylgeranyl-diphosphate (GGDP), a crucial intermediate in the mevalonate/cholesterol pathway, and its potential connection to the Rho/ROCK signaling pathway. We focused on TNBCs and explored how these gene expressions affect patients' distant relapse-free survival (DRFS).

2. Methods

2.1 Materials

The study used a clinically annotated dataset that is publicly available from the NCBI Gene Expression Omnibus (GEO) Repository (www.ncbi.nlm.nhi.gov/geo/), identified by the GEO accession number GSE25066. As detailed in the original article [13], the dataset generated by MD Anderson Cancer Center (MDACC) consists of 508 breast cancer gene expression profiles from HER2-negative breast cancer patients who participated in neoadjuvant chemotherapy trials. These patients received an anthracycline-based and taxane regimen, either in combination or sequentially. For the present study, only the cohort of 178 patients with TNBC was considered. The original research [13] was conducted with the approval of the respective Institutional Review Board (protocols LAB99-402, USO-02-103, 2003-0321, I-SPY-1), and patients provided prospective consent for a research tumor biopsy by fine needle aspiration (FNA) or core biopsy (CBX) before any systemic therapy. They also consented to the future assessment of pathologic response and survival endpoints. Estrogen receptor (ER) and progesterone receptor (PR) status of the tumors were determined using immunohistochemistry (IHC) on diagnostic CBX samples, with a cut-off of 1% nuclear staining in tumor cells for ER or PR positivity. HER2 status was assessed either by fluorescence in situ hybridization or IHC. For 130 of the samples classified as triple-negative samples by immunohistochemistry, the TNBC subtyping according to the Lehmann classification [7] was also available. Global gene expression was assessed using the Affymetrix U133A GeneChip (GEO accession GPL96) on FNAs, which were independent of the diagnostic CBXs used for routine determination of ER, PR, and HER2 status. The expression estimates were filtered, normalized, and log2-transformed before being uploaded to the GEO repository. Because in the GPL96 array, some genes were recognized by more than one probeset, the best probeset was selected based on its specificity and sensitivity values. If two or more probesets met this criterion, the mean value was calculated.

2.2 Gene Selection

Nine genes were selected for the study. Four of these

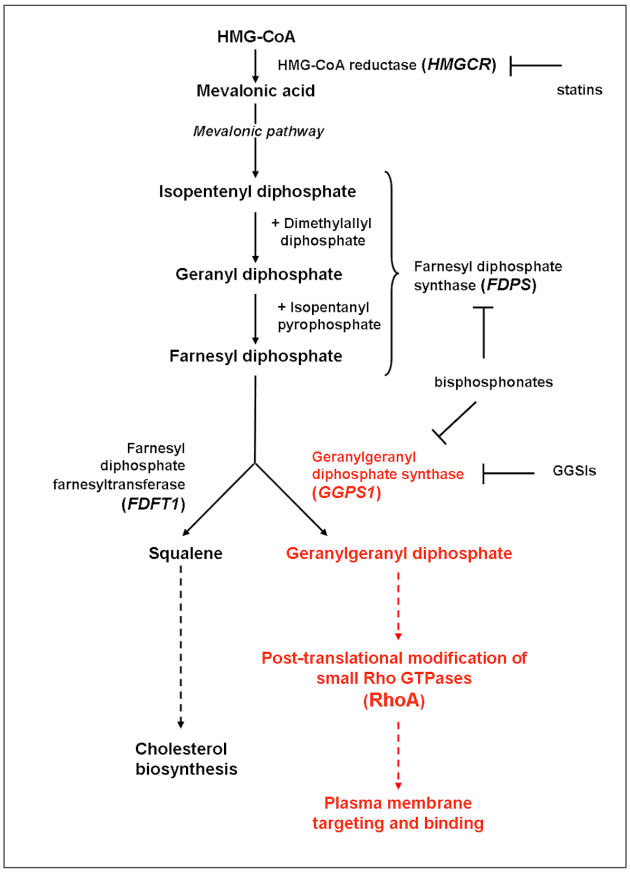

Figure 2. *Schematic description of the core mevalonate/cholesterol pathway involved in the synthesis of isoprenoids. The pathway branch leading to the production of geranylgeranyl diphosphate is highlighted in red. In parenthesis, there are the genes that code for the corresponding enzyme. Statins, bisphosphonates, and geranylgeranyl transferase inhibitors (GGSIs) can block the production of GGDP through different mechanisms. The subsequent depletion of the intracellular pool of GGDP could be a therapeutic strategy to prevent the trans-localization of Rho GTPase to the plasma membrane and the activation of the Rho-ROCK signaling cascade.*

genes are involved in the mevalonate/cholesterol pathway (Figure 2): *HMGCR* (3-hydroxy-3-methylglutaryl coenzyme A reductase) codes for the enzyme that converts HMG-CoA into mevalonic acid, the rate-limiting step in cholesterol and isoprenoids synthesis. *FDPS* (farnesyl-diphosphate synthase) encodes the key enzyme in isoprenoids biosynthesis; through a two-step reaction, it catalyzes the synthesis of geranyl-diphosphate, which is the substrate for protein farnesylation and geranylgeranylation, as well as farnesyl diphosphate, a key intermediate in the biosynthesis of cholesterol and sterols. *FDFT1* (farnesyl-diphosphate farnesyltransferase 1) codes for the first specific enzyme in cholesterol biosynthesis. It catalyzes the dimerization of two molecules of farnesyl diphosphate in a two-step reaction to form squalene, the committed intermediate in the production of cholesterol and sterols. *GGPS1* (geranylgeranyl-diphosphate synthase 1) codes for the enzyme that catalyzes the synthesis of geranylgeranyl diphosphate, which is essential for the post-translational modification of several proteins, including Rho small GTPases.

The other five genes code for components of the Rho-ROCK signal cascade: *RHOA* (Ras Homolog Family Member A) encodes the main member of the Rho family of small GTPases; *ROCK1* (Rho-associated protein kinase 1) codes for ROCK, the primary effector of Rho; *LIMK1* (LIM Domain Kinase 1) codes for the downstream LIM-kinase of ROCK; *CFL1* (Cofilin 1) and *MYL1* (Myosin Light Chain 1) code, respectively, for cofilin and myosin light chain, both terminal effectors of the signaling pathway (Figure 1).

2.3 Statistical Analysis

The Shapiro-Wilk test was used to assess the normal distribution of the variables. The results indicated that the expression level of most genes did not follow a normal distribution. Consequently, non-parametric tests were applied to analyze the variables. The chi-squared test was used to evaluate the statistical significance of the frequency distribution of qualitative variables.

DRFS was defined as the interval from the initial diagnostic biopsy to the diagnosis of distant metastasis or death from any cause. Accordingly, sixty-four patients (36%) experienced distant metastasis within a median follow-up period of 14 months (1 - 67 months). Since the median follow-up for the entire cohort was 26 months, the primary endpoint for prediction was DRFS at 3 years, for a total of 62 events.

All analyses were conducted using the open-source software R Core Team version 4.4.2 (http://www.R-project.org). The function *coxph*() [in the *survminer* R package] was used to perform the Cox proportional hazards regression, assessing the effect size of the covariates singly or in combination on DRFS, described in terms of hazard ratio (HR). The function *cox.zph*() [in the *survival* R package] was used to test the proportional hazards (PH) assumption for each covariate included in the Cox regression model. To assess the functional form (nonlinearity) of each continuous variable in a Cox proportional hazards model, the function *ggcoxfunctional*() [in the *survminer* R package] was used. The function *ggforest*() [in the *survminer* R package] was used to create the forest plot that summarizes the results of the multivariate analysis and the function *cutpointr*() [in the *cutpointr* R package] was utilized to identify the optimal cutoff for each covariate within this dataset, using the variable 'event' as the benchmark.

Kaplan-Meier plots were generated to visualize survival curves, and the log-rank test was applied to compare the survival curves between two groups. A two-sided $P < 0.05$ was considered statistically significant.

Table 1. *Univariate Cox regression analysis of the association between gene expression (as continuous or categorical covariate) and distant-relapse free survival.*

	Continuous				Stratified according to the optomal cutoff			
Gene	**Beta coefficient**	**HR (95% CI)**	**Wald test**	**P**	**Beta coefficient**	**HR (95% CI)**	**Wald test**	**P**
HMGCR	-0.23	0.79 (0.63-1.01)	3.87	0.050	0.14	1.15 (0.69-1.92)	0.29	0,59
FDPS	0.17	1.18 (0.85-1.63)	0.98	0.322	0.35	1.41 (0.83-2.39)	1.65	0.199
FDFT1	-0.24	0.79 (0.59-1.06)	2.44	0.118	-0.40	0.67 (0.41-1.11)	2.47	0.116
GGPS1	0.66	1.93 (1.08-3.47)	4.90	0.027	0.69	1.99 (1.20-3.33)	7.01	0.0081
RHOA	0.17	1.19 (0.71-1.99)	0.42	0.515	0.73	2.08 (1.23-3.53)	7.39	0.0066
ROCK1	0.39	1.47 (0.80-2.70)	1.57	0.209	0.59	1.80 (1.10-2.96)	5.36	0.0206
LIMK1	-0.19	0.83 (0.56-1.23)	0.85	0.358	-0.71	0.49 (0.29-0.82)	7.33	0.0068
MYL1	0.16	1.17 (0.92-1.48)	1.65	0.198	0.50	1.64 (0.97-2.78)	3.41	0.065
CFL1	0.35	1.42 (0.91-2.22)	2.34	0.126	0.64	1.89 (1.14-3.13)	6.13	0.0133

The Hazard Ratio (HR) is a measure of the risk of distant relapse

3. Results

3.1 Gene Expression and Distant-Relapse Free Survival

Univariate analysis by the Cox regression model indicated that, when considered as a continuous variable, only the expression of the *GGPS1* gene significantly impacted the occurrence of distant metastasis (Table 1).

Specifically, tumors with high expression of *GGPS1* were associated with a hazard ratio (HR) of 1.93 (95% CI: 1.08-3.47, P = 0.027). This means that patients with high-expressing *GGPS1* tumors had a 93% increased risk of developing distant metastasis compared to those with low levels of *GGPS1* expression. Cox model diagnostic indicated no pattern with time (chisq = 0.0002, P = 0.99), thus satisfying the proportional hazards assumption. However, when assessing the functional form of each continuous covariate graphically, it was noted that all genes lacked a linear relationship with the risk of developing distant metastasis (in Supplementary Figure 1). Consequently, the optimal cutoff for each covariate was determined, and gene expression was stratified accordingly.

Univariate Cox regression analysis showed that, when stratified by the optimal cutoff, five genes significantly impacted the occurrence of distant metastasis (Table 1). In addition to *GGPS1*, which retained the significant impact found using the expression as continuous covariate (HR = 2.00, 95% CI: 1.20-3.33, P = 0.0081), the genes *RHOA, ROCK1, LIMK1*, and *CFL1* were also significantly associated with DRFS. Specifically, *RHOA, ROCK1*, and *CFL1* expression were associated with an increased risk of developing distant metastasis (108%, 80%, and 64%, respectively), while *LIMK1* expression was associated with a 51% reduction in risk. Kaplan-Meier curves (Figure 3) visualized how low and high expressions of *GGPS1, RHOA, ROCK1, LIMK1*, and *CFL1* gene differently impacted the probability of developing distant metastasis.

The forest plot (Figure 4) summarizes the results of the multivariate analysis that included five genes in the Cox regression model. Except for *ROCK1*, all

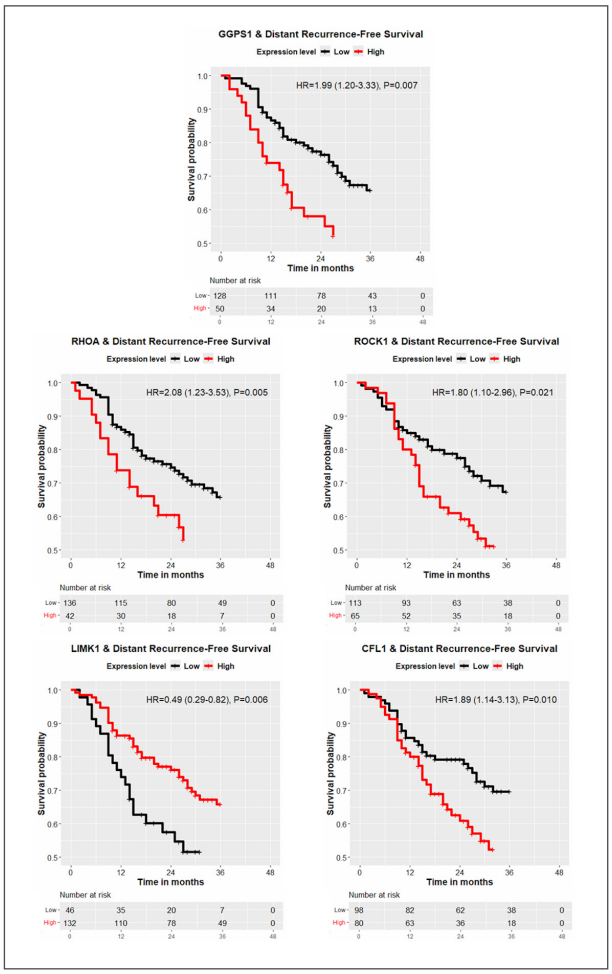

Figure 3. *Kaplan-Meier estimates of distant relapse-free survival according to the expression of GGPS1, RHOA, ROCK1, LIMK1, and CFL1 gene stratified by the optimal cutoff. The Hazard Ratio (HR) quantifies the risk of distant relapse for the unfavorable class, and the P-value is from the log-rank test.*

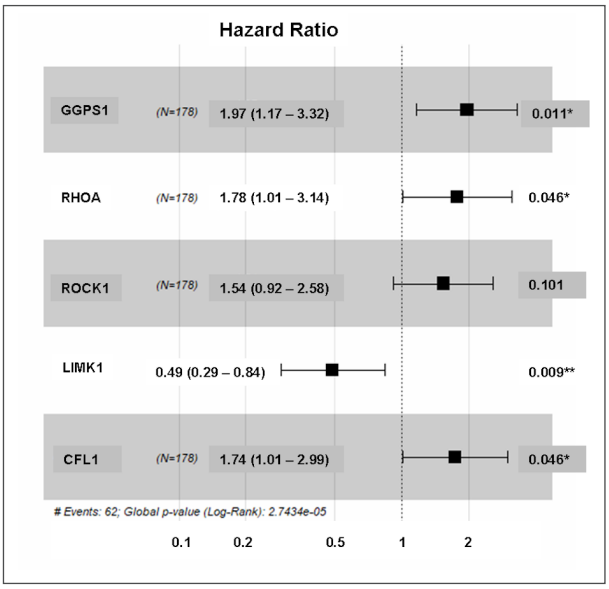

Figure 4. *Forest plot visualizes the multivariate Cox regression analysis, including the GGPS1, RHOA, ROCK1, LIMK1, and CFL1 genes in the model.*

genes retained their independent and statistically significant association with the risk of developing distant metastasis.

3.2 GGPS1 and FDFT1 Gene Expression and TNBC Subtypes

According to the Lehmann classification [7], 32% (42/130) of TNBCs belong to the BL1 subtype, 23% (30/130) to the BL2 subtype, 18% (24/130) to the LAR subtype, and 26% (34/130) to M subtype. The log-rank test indicated that patients with a tumor classified as BL2 had a lower survival probability compared to the patients with a tumor classified as LAR, especially at the early follow-up time. As visualized by the Kaplan-Meier curves (Figure 5A), at 18 months, the patients with a TNBC classified as BL2 had a statistically significant increase (70%) in the risk of developing distant metastasis when compared to the patients with a TNBC classified as LAR. Notably, the expression of *GGPS1* and *FDFT1*

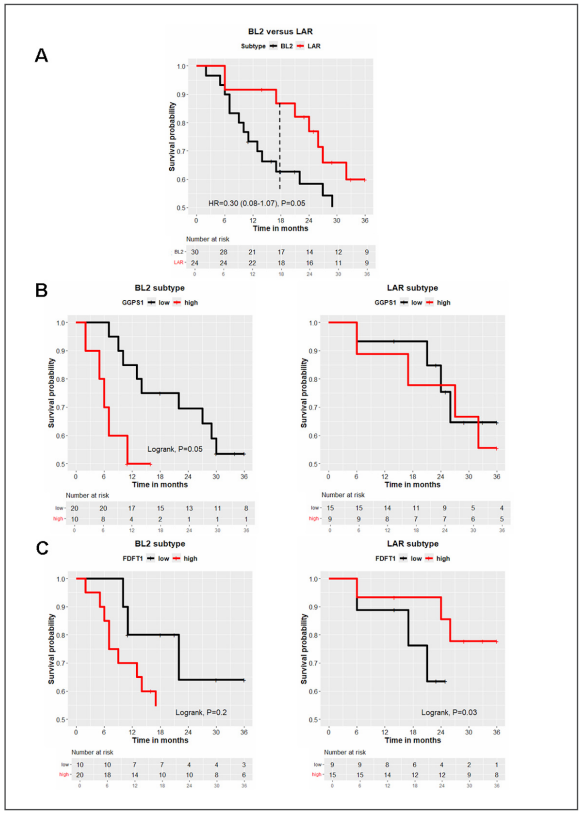

Figure 5. *Kaplan-Meier estimates of distant relapse-free survival in (A) LAR versus BL2 TNBC subtypes and according to the expression of the GGPS1 (B) or FDFT1 (C), stratified by the optimal cutoff. The Hazard Ratio (HR) quantifies the risk of distant relapse for the unfavorable class, and the P-value is from the log-rank test.*

genes had different impacts on these two subtypes: in LAR TNBC, *GGPS1* expression did not distinguish between patients with better or worse prognoses, whereas in the BL2 subtype, patients with high *GGPS1*-expressing tumors experienced early relapse (Figure 5B). Conversely, high expression levels of *FDFT1* were associated with a better prognosis in LAR TNBC but not in the BL2 subtype where *FDFT1* expression did not distinguish between patients with better or worse prognoses (Figure 5C). It is important to note that the expression of *GGPS1* was similar in the two TNBC subtypes (BL2 *versus* LAR: 8.81 *versus* 8.89, $P = 0.987$), whereas the expression of *FDFT1* was significantly higher in the LAR compared to the BL2 subtype (BL2 *versus* LAR: 11.17 *versus* 11.58, $P = 0.042$).

4. Discussion

The clinical evidence indicates that TNBC is the most aggressive form of breast cancer. In agreement with this notion, 35% (62 out of 178) of patients in this study developed distant metastasis within 36 months of follow-up, and 25% (45 out of 178) experienced a distant recurrence already after 18 months. The finding indicated that, despite the effectiveness of taxane-based treatments, TNBC often develops drug resistance, which leads to cancer progression and the dissemination of metastases. To do this, cancer cells require increased cell motility which is driven by remodeling of the cytoskeletal system and interactions with the extracellular matrix. Therefore, controlling cell motility through the actin cytoskeleton offers a potential strategy for regulating tumor cell dissemination. In this context, inhibiting the Rho/ROCK pathway emerges as a promising therapeutic approach for patients at high risk of developing distant metastasis. The observation that the gene expression of *RHOA, ROCK1, LIMK1*, and *CFL1* significantly impacts DRFS supports this strategy. Indeed, the Rho/ROCK signaling pathway (Figure 1) regulates a delicate balance between actin polymerization, which promotes membrane ruffling, and myosin-mediated contraction of actin filaments, leading to the formation of stress fiber formation and increased cell motility. When phosphorylated by the ROCK-activated LIM kinase, the actin-depolymerizing activity of cofilin is inhibited, contributing to the reorganization of the actin cytoskeleton induced by Rho [14,15]. Thus, blocking the Rho/ROCK signaling cascade upstream by preventing the prenylation of Rho GTPase using prenyltransferase inhibitors appeared as a viable alternative treatment strategy.

Several drugs have been developed with promising results in preclinical studies [16-18]; however, they have yet to gain approval for medical use due to undesirable side effects and compensatory mechanisms that lead to drug resistance. Although the introduction of dual inhibitors has reduced some of these effects, their potency remains suboptimal for clinical development.

An attractive and alternative approach focuses on preventing Rho prenylation by depleting the necessary isoprenoids, specifically geranylgeranyl diphosphate for RhoA, by inhibiting the enzymes involved in their synthesis. Present findings support this hypothesis, showing that increased expression of *GGPS1*, the gene encoding the enzyme that synthesizes geranylgeranyl diphosphate, is significantly associated with a higher risk of developing distant metastases.

Located at the crucial branch point of the mevalonate/cholesterol pathway (Figure 1), GGDP synthase competes with FDP farnesyltransferase, which is encoded by the *FDFT1* gene and is responsible for committing the synthesis of cholesterol and steroid hormones. The effects of this competition were particularly pronounced in the two subtypes of TNBC known for having the worst prognosis (BL2) and best prognosis (LAR). Present findings indicate that the impact of *GGPS1* to *FDFT1* expression varies significantly in the two subtypes of TNBC. In the BL2 subtype, high expression levels of *GGPS1* are associated with a shorter DRFS (Figure 5B). Conversely, in the LAR subtype, higher expression of *FDFT1*, which plays a role in the synthesis of cholesterol and steroid hormones, is linked to a more favorable prognosis (Figure 5C).

Preventing the post-translational modification of RhoA by inhibiting geranylgeranyl diphosphate synthase, and subsequently depleting intracellular levels of geranylgeranyl diphosphate, is emerging as a promising therapeutic strategy [19,20]. Clinically approved statins are among the potential candidates for achieving this goal. These compounds downregulate the mevalonate pathway and inhibit the biosynthesis of isoprenoids by blocking HMG-CoA reductase [21]. Preliminary results suggest that among women with TNBC, initiating statin therapy within 12 months after breast cancer diagnosis is associated with improved overall survival and breast cancer-specific survival [21]. In particular, simvastatin has been shown to selectively prevent the translocation of RhoA from the cytosol to the membrane by depleting intracellular levels of GGDP, independent of its cholesterol-lowering effects [22].

Due to the homology of GGDP synthase with FDP synthase, bisphosphonates, have also been considered as potential therapeutic options. In particular, triazole bisphosphonate-based GGDPS inhibitors (GGSIs) are emerging as a novel strategy to induce cancer cell death [23]. When used in combination with statins such as lovastatin or pravastatin, GGSIs enhance the statin effect, disrupt protein geranylgeranylation *in vivo*, and significantly slow tumor growth in xenograft models. This combined approach provides a framework for future clinical exploration.

5. Conclusions

While the current findings need to be validated in independent case series of triple-negative breast cancer (TNBC), they suggest that *GGPS1* expression may serve as a prognostic factor to identify TNBC patients who are at high risk for distant recurrence. Additionally, considering the essential role that GGDP plays in activating the RhoA/ROCK signaling pathway, these results indicate that inhibiting the gene expression upstream using statins or inhibiting the enzymatic activity of GGDPS with bisphosphonates and specific inhibitors could be an effective strategy to prevent the progression of all TNBCs, particularly those classified as BL2, which are known for their aggressiveness.

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Footnote

Funding: This research did not receive funding.

Conflicts of Interest: The author declares no conflicts of interest

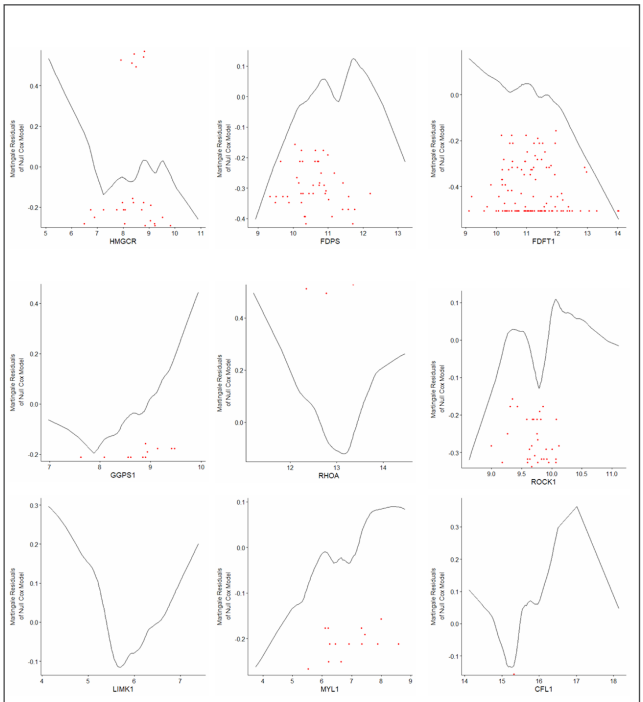
Informed consent: This study analyzed secondary data from the NCBI Gene Expression Omnibus (GEO) Repository, therefore, the consent to participate is not required.

Ethical Statement: The study utilized summary statistics from the publicly available dataset, the NCBI Gene Expression Omnibus (GEO) Repository. The original study was approved by the respective Institutional Review Board (protocols LAB99-402, USO-02-103, 2003-0321, I-SPY-1). As such, this research did not involve direct contact with human participants or the collection of new personal data, and therefore, ethical approval was not required.

Data availability: The datasets analyzed for this study can be found in the NCBI Gene Expression Omnibus (GEO) Repository (www.ncbi.nlm.nhi.gov/geo/).

Supplementary Material: This article contains supplementary material

Supplementary Material



Supplementary Figure 1. Graphs of continuous covariates against martingale residuals of null cox proportional hazards model. For each covariate, the function is not linear.

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