RESEARCH ARTICLE

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Integrated Analysis of the STING1-IRF1 Signaling Pathway and Genomic Alterations in Breast Cancer: Implications for Immune Evasion and Patient Prognosis

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Abstract

Background: The *STING1-IRF1* axis plays a crucial role in sensing innate immunity within the tumor microenvironment. However, the genomic landscape of this axis and its clinical implications in breast cancer still require a deeper understanding, more comprehensive explanation, and greater detail. **Methods:** This study adopted a multi-cohort integrated analytical approach. Gene expression and clinical survival data were retrieved from the GEO database under the serial number GSE42568, while somatic mutation data were obtained from the TCGA-BRCA database. A comprehensive bioinformatics analysis was performed, including survival analysis (Kaplan–Meier), differential gene expression analysis (volcano plots), and genomic mutation characterization (Oncoprint), using the R programming language and suitable packages. **Results:** The results in cohort GSE42568 showed high expression of the *STING1-IRF1* axis it is associated with a positive trend towards improved survival rates. Transcriptional analysis also revealed a decrease in the expression of *HLA-B* and *HLA-C* genes, immunotropic chemokines (*CXCL9, CXCL 10*) in tumors with low *STING1* expression this suggests a "cold" immune pattern. Conversely parallel genomic analysis of the TCGA cohort has identified high frequency of mutations in the *MAP3K1* (56%) and *PIK3CA* (53%), *TP53* (46%) genes in addition to mutations in *STING1*which was directly linked to a disruption in tumor signaling pathways particularly in cell cycle pathways and *TP53* and *PIK3CA* this contributes to strengthening immune escape mechanisms. **Conclusion:** Our results indicate that the *STING1-IRF1* axis is a prognostic biomarker for predicting the course of the disease, targeting this pathway may help overcome immune evasion resulting from specific genomic changes in breast cancer patients.

Keywords: Breast Cancer, *STING1*, *IRF1*, *TCGA-BRCA*, GEO, Immune Evasion, Genomic Mutations, Prognosis

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Introduction

Breast cancer is the most common type of cancer among women worldwide with more than 2.3 million new cases reported annually [1]. this disease still exhibits considerable biological heterogeneity ,despite significant progress in early diagnosis strategies and targeted treatments. This may be leads to significant variation in treatment response rates and disease progression "prognosis" [2]. Aggressive subtypes , present particular challenge due to their lack of traditional therapeutics targets and their heavy reliance on immune escape mechanisms [3].

The Tumor Microenvironments and the Concept "Cold Tumors" : Some recent studies indicate that the success of treatments depends not only on the genetic characteristics of the cancer cell but also on the nature of the Tumor Microenvironment(TME) , Tumors are classified into "Hot" (inflamed) tumors characterized by a dense infiltration of T cells, and "Cold" tumors lacking immune activity [4]. To understanding how to turn cold tumors into hot ones is a cornerstone of new , modern immunotherapy research, and this is where the role of innate DNA sensing pathway comes into play [5, 6]. Breast cancer exhibits considerable biological variability due to its diverse molecular classifications, distinct mutational landscapes, and the composition changed of the immunological microenvironment, and the altered composition of the immunological microenvironment, all of which contribute to the emergence of different diagnostic profiles [7, 8].

cGAS-STING pathway

The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway acts as the molecular immune guardian as a innate defence mechanism that senses the presence of double strand DNA (dsDNA) in the cytoplasm ,while this often occurs in cancer cells as a result of genomic imbalance. .

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The *STING1* protein, upon activation, catalyzes a series of chemical reactions that end with the activation of *IRF1* and IRF3 factors , which in turn lead to the production of type I interferons (IFN-I) and immunogenic chemokines such as CXCL10 [9]. As shown in the Figure 1.

Studies have shown that disruption of this pathway is closely linked to tumors ability to evade the immune system's radar [10, 11].

HLA-B/C molecules and immune vision

The *STING1-IRF1* axis not attracts immune cells, and other immunology systems , but also enhances "antigen presentation " , this axis a regulatory role in the expression of major histocompatibility complex class I (MHC-I/*HLA-B*/C) molecules, these are the platforms very necessary for cytotoxic T cells (CD8+) to recognize cells [12]. Loss of expression of these molecules is a common strategy employed by invasive breast tumors to escape immune killing [13].

Despite growing evidence regarding the importance of *STING1*, there is a lack of studies which links its transcriptional activity and overall "mutational landscape" in breast cancer using data from independent cohorts. This study aimed to to bridge this gap through an integrated analysis that combines gene expression and survival data from the Gene Expression Database (GEO) from the National Center for Biotechnology Information (NCBI) with somatic mutation data from the Cancer Genome Atlas Project (TCGA-BRCA) via the Genomic Data Commons (GDC) dataset, through this approach, we aim to demonstrate how common mutations affect the efficacy of the *STING1* axis, and to know how is reflected in immune infiltration and disease prognosis in patients.

Materials and Methods

Data Collection and Processing

This study integrated data from two independent sources to provide a multi-level genomic perspective. Clinical data (RNA-Seq/Microarray) for invasive breast cancer were retrieved from the Gene Expression Database (GEO) from the National Center for Biotechnology Information (NCBI) under accession number GSE42568 (number of samples = 104) analyzed using the Affymetrix platform (GPL570). Data was also retrieved Somatic mutations (MAF files) from the Cancer Genome Atlas Project (TCGA-BRCA) via the Genomic Data Commons (GDC) dataset, to characterize the mutational landscape. This cross-platform validation approach allowed to link the genetic abnormalities discovered in TCGA based on the immune phenotypes observed in the GEO group.

Survival analysis

To assess the predictive value of the *STING1-IRF1* axis, Patients in GSE42568 were classified into two groups: a high-expression group and a low-expression group, the overall survival rate was estimated using the Kaplan-Meier method, statistical significance was determined using the log-rank test across two packages: survival and survminer in the R programming language.

Differential gene expression analysis (DEA)

To identify genes associated with *STING1* differential expression analysis was performed on the GSE42568 dataset, a Volcano plot was created to visualize genes with significant upregulated and significant downregulated genes using a threshold of (log2 FC >1) and an adjusted

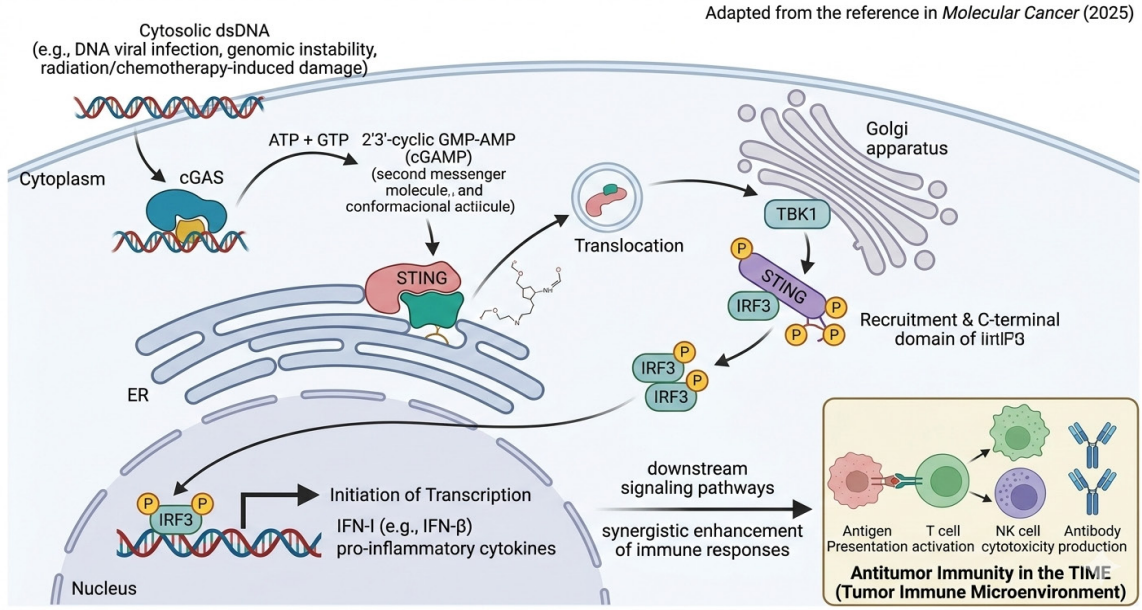

Figure 1. Schematic Diagram of the cGAS-STING Signaling Pathway in Tumor Immunity. This pathway begins when the enzyme cGAS detects double-stranded DNA (dsDNA) in the cell's cytoplasm, this often results from genetic disorder or cell damage caused by radiation or chemotherapy when activation, cGAS produces a second transporter, cGAMP, which binds to the STING protein in the endoplasmic reticulum, following this , the STING protein transfers to the Golgi apparatus to polarize the enzyme TBK1, this leads to the activation and translocation of transcription factors (particularly IRF3 and IRF1) into the nucleus. This cascade of signals stimulates the production of type I interferons (IFNs) and pro-inflammatory cytokines, This enhances the process of antigen presentation and T-cell infiltration within the breast cancer's immune microenvironment. (Adapted from Luo et al., 2025 [11]).

(P-value < 0.05) this analysis highlighted the role of *STING1*in regulating Major Histocompatibility Complex Class I (MHC-I) molecules and T-cell chemoattractants.

Genomic Landscape and Pathway Analysis

Mutation data from TCGA-BRCA cohort were analysed using the 'maftools' package. A mutational map (Oncoplot) was constructed to visualization the most mutant genes and their potential interaction with the *STING1* pathway .Also was performed analysis to enrich tumor signalling pathways to identify molecular abnormalities in cellular processes with particular emphasis on the *TP53*, *PI3K*, and cell cycle axes as the drivers of immune exclusion .

Analysis of the Immunological Microenvironment

The CIBERSORT algorithm was used to quantify the proportions of immune cells. This method employs linear regression using support vector (SVR) to separate the RNA-seq sequence data into 22 distinct immune cell subtypes.

Results

Survival results and the STING1 axis

To assess the predictive significance of the *STING1-IRF1* axis in breast cancer, we performed a 100-month long-term survival analysis. As shown in the Kaplan-Meier plot (Figure 2A) ,the patients with high *STING1* expression showed a significant survival advantage compared to patients with low expression . Multivariate Cox regression analysis was performed, to further evaluate the prognostic significance. The *STING1-IRF1* axis showed a hazard ratio (HR) of 0.74 (95% CI: 0.38–1.42; p = 0.34) after adjusting for age and stage, indicating a 26% reduction in the risk of death in the high gene expression group. Although the statistical significance did not reach the traditional threshold (p = 0.34), but the early and sustained divergence of the survival curves indicates a significant a positive trend.

Identifying the "hot" immune fingerprint

We performed a differential expression analysis to analyze the molecular mechanisms underlying these clinical trends, in the , reveals volcano plot of the differential gene expression (Figure 2B) a strong genomic signature, with elevated *STING1-IRF1* expression levels closely associated with the upregulation of several inflammatory mediators, including CXCL9, CXCL10, and TMEM173 (*STING1*). Moreover to further analyze expression patterns between both groups of samples, a heatmap was plotted it observed increase in MHC-I molecules, specifically *HLA-B* and *HLA-C*, in the high-expression group, Figure 3.

Increased immune infiltration

The results of the microenvironment analysis (Figure 4A) also showed where we measured the relative

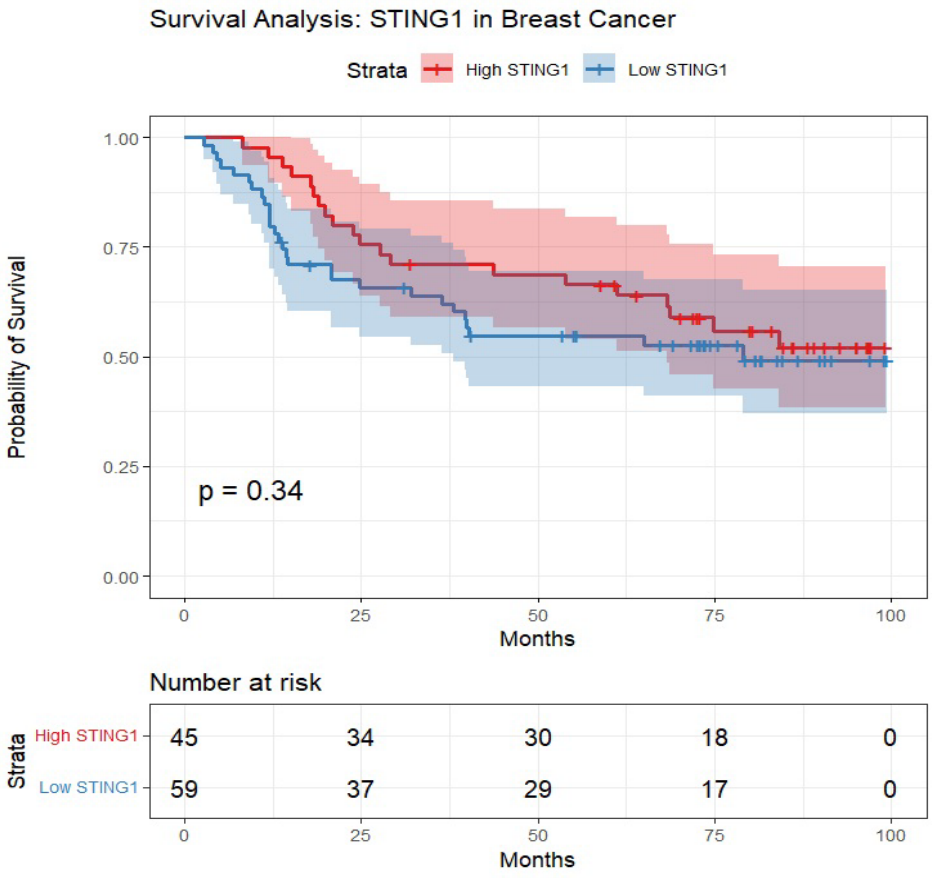

Figure 2. A. (Survival Analysis - Kaplan-Meier): Shows a positive trend towards increased survival rates in patients with high *STING1* gene expression. B. (Volcano Plot): Identifies immune genes (such as *HLA-B* and *CXCL9)* that are strongly activated in conjunction with *STING1-IRF1* axis expression.

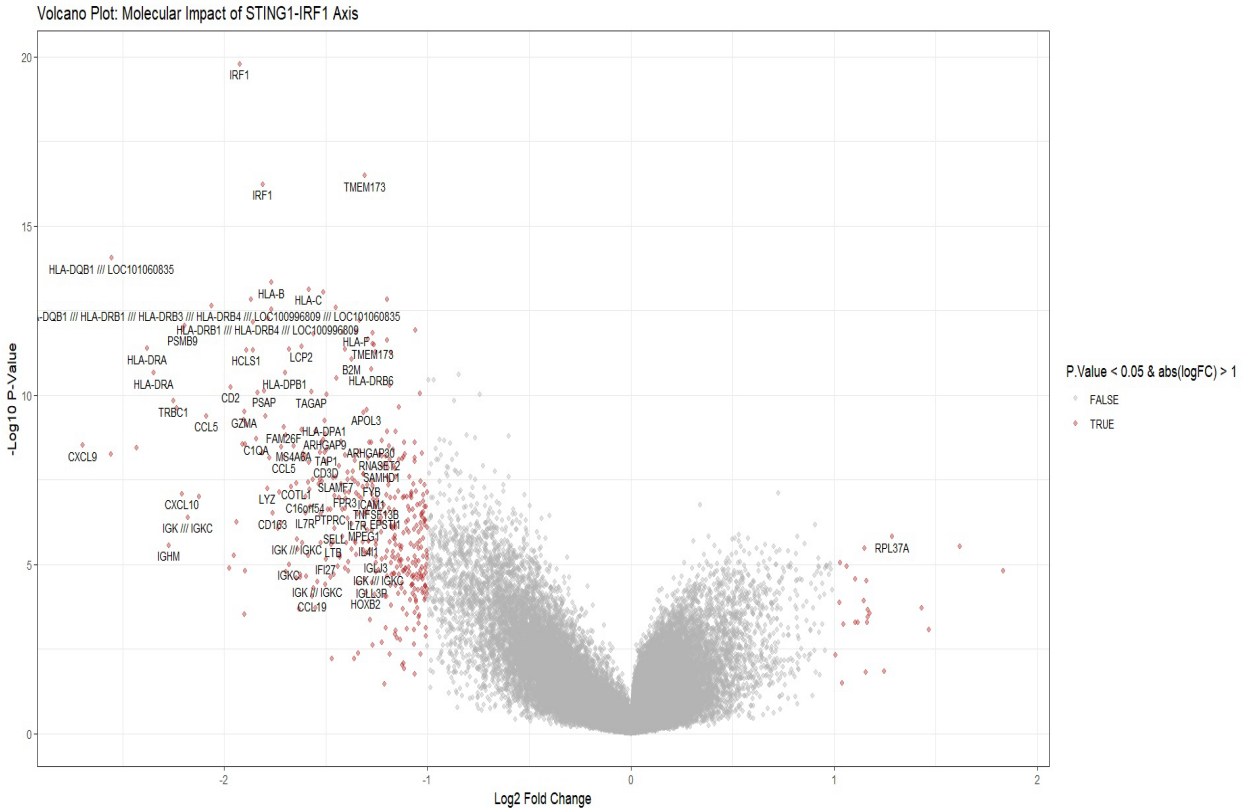

Figure 2.B. (Volcano Plot): Identifies immune genes (such as *HLA-B* and *CXCL9*) that are strongly activated in conjunction with *STING1-IRF1* axis expression.

abundance of tumor-infiltrating lymphocytes, showed increase in CD8+ cytotoxic T cells and macrophages within the high-*STING1-IRF1*group compared to the low-level group, that this increase likely indicates that the *STING1* axis it may be a key driver in transforming "cold" tumors into an inflammatory state capable of triggering an antitumor response

Cellular Functional and Pathways Analysis

Following the differential gene expression results, the Gene Set Enrichment Analysis (*GSEA*) was performed to determine whether distinct pathways could characterized

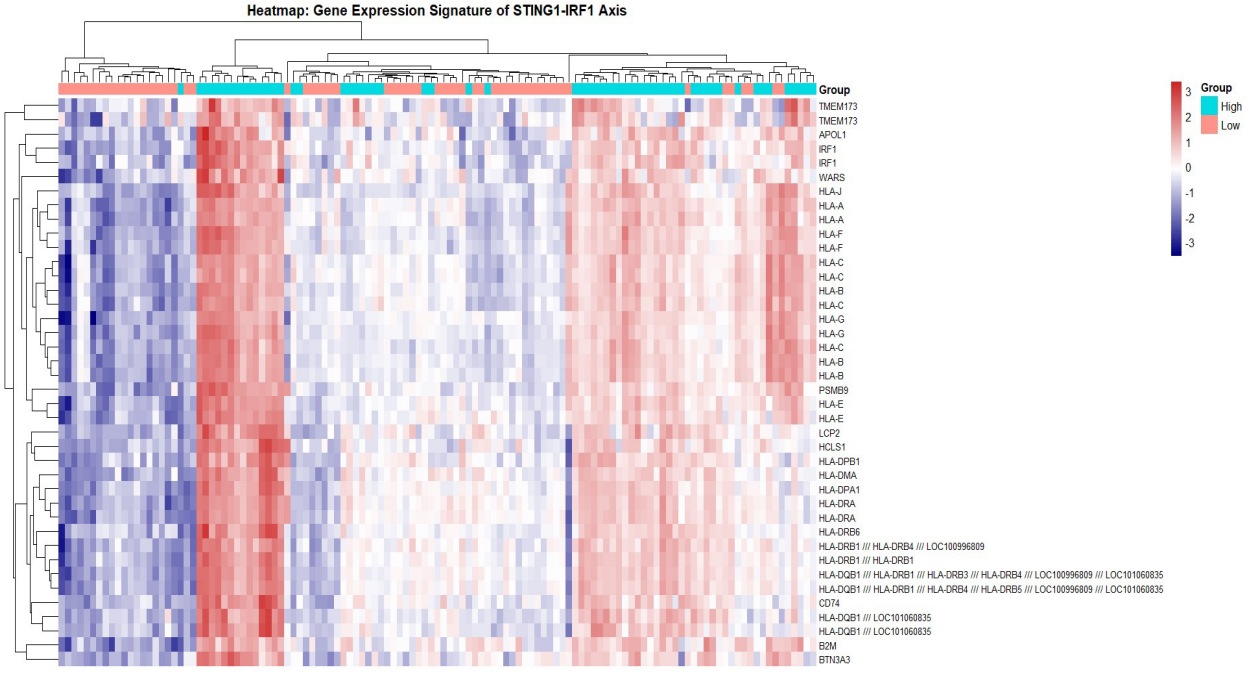

Figure 3. The Heatmap Shows the Division of Patients Into Two Clear Groups; an "immunologically hot" group (high expression) and a "cold" group (low expression).

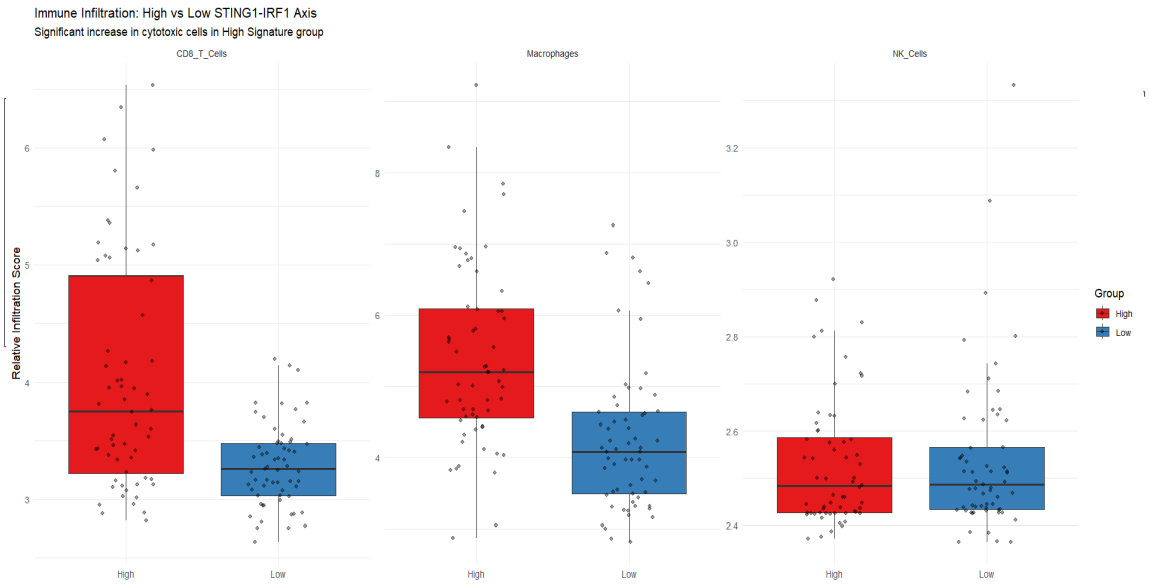

Figure 4 A. (- Boxplots showing immune infiltration demonstrates an actual increase in cytotoxic T cells (CD8+ T cells) and macrophages within the tumor in the high expression group.

each group. The dot plot (Figure 4 B) shows a functional enrichment analysis which observed that leukocyte-mediated immunity and antigen processing and presentation are the two biological processes most strongly associated with *STING1* expression, this means that *STING1* may act as a key coordinator, facilitating communication between cancer cells and the systemic immune response by recruiting and activating lymphocytes.

The STING1-IRF1-HLA Interaction Hub

Using a protein-protein interaction network (Figure 5), the expanded network, composed of 27 proteins, confirmed that *STING1* and *IRF1* function as central signaling hubs. can see *IRF1* appears to be the primary mediator between *STING1* and the *HLA* subset (*HLA-B*, *HLA-C*, *HLA-E*) This provides a clear molecular roadmap (*STING1* → *IRF1* → *HLA*) this is provides a map of how these tumors

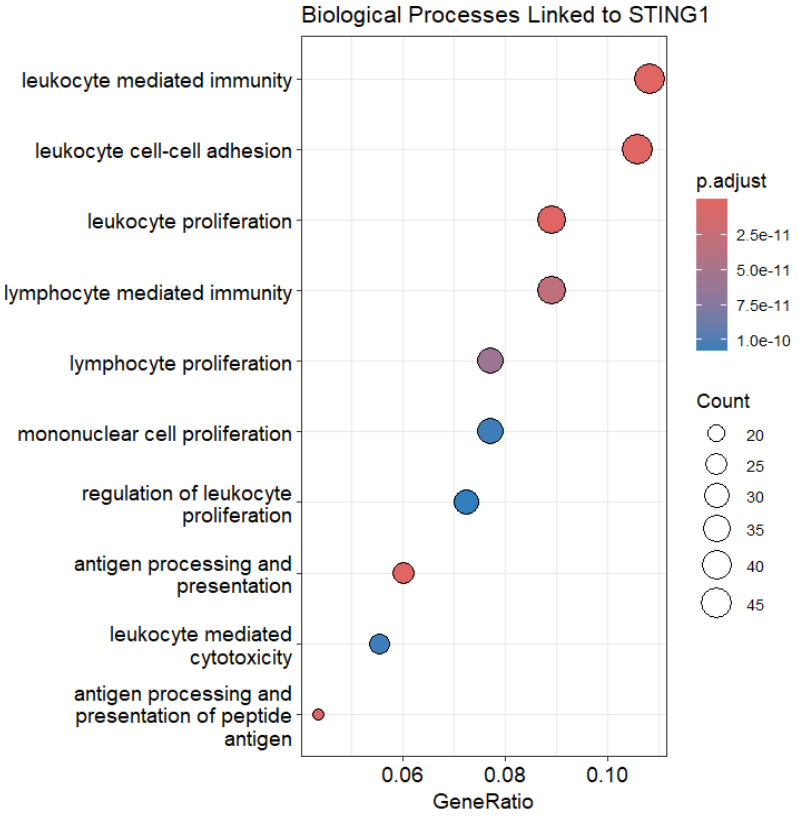

Figure 4. B (Dotplot): reveals that the most important biological processes associated with the outcomes are the summoning of immune cells and the presentation of antigens to recognize cancer.

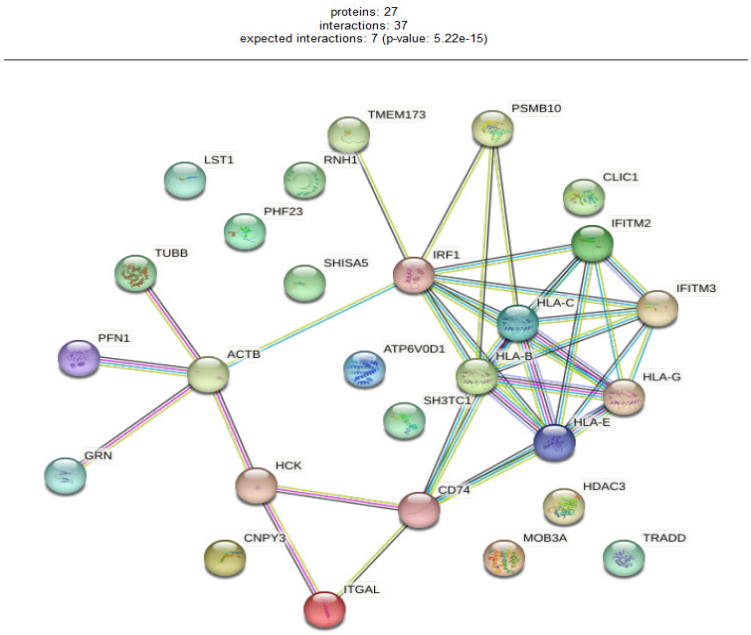

Figure 5. PPI Network Draws the Molecular "Roadmap" Linking *STING1* and *IRF1* to the Activation of *HLA* Genes

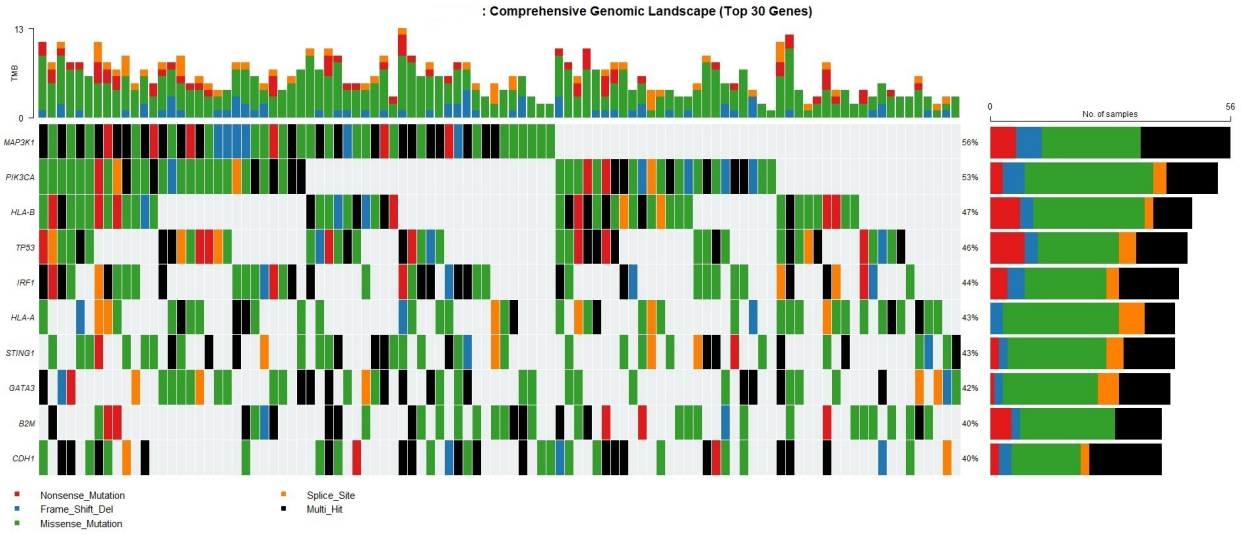

Figure 6. Oncoplot: Identifies gene mutations (*TP53, MAP3K1,* ...) that may be responsible for disrupting the immune response in some samples, by different colors, described in the legend below the oncoplots (Missense Mutation, Splice Site, Frame-Shift inser tion, In-Frame Insertion, In-Frame Deletion, Nonsense Mutation, Frame-Shift deletion, Multi-hit, Altered pathway)

regain their ability to present themselves to the host's immune system.

Precipitating Factors and Mutational Barriers

To better characterize the samples, we further analyze their somatic mutational profile . We examined the genetic alterations that may disrupt this immune axis, Figure 6, and observed high genomic alterations rates in *MAP3K1* (56%) and *PIK3CA* (53%) genes across the entire cohort. Furthermore somatic genomic alterations in the *HLA-B* (47%), *TP53* (46%), and *STING1* (43%) genes were also common. The high mutational burden at these genetic loci, in particular *TP53*, provides genetic explanation for why some tumors fail to activate the *STING1*-mediated immune response.

Discussion

Based on the survival analysis and the *STING1* axis, Kaplan-Meier analysis described in Figure 1, The results indicated a positive correlation between high expression of the *STING1* gene and improved long-term survival (100 months) in breast cancer patients. Although the p-value ($p = 0.34$) did not reach the level of traditional statistical significance, the continuous separation between curves favors the highly expressive group It reflects clinical

significance this cannot be overlooked in the context of tumor immunity.

This result is consistent with the important role of the cGAS-STING pathway as a cellular defense mechanism capable of sensing oncogenic DNA and thus triggering an adaptive immune response. A previous study by Woo et al. [14] demonstrated that activation of this pathway is an indispensable condition for the spontaneous generation of killer T cells (CD8+) against tumors, which explains the improved survival observed in your study.

Furthermore, Parkes et al. [15] found that the STING gene signature is associated with improved clinical outcomes and response to chemotherapy in breast cancer, particularly in genomically unstable species. The results of the differential gene expression analysis revealed a sharp molecular difference between the two study groups. Samples with high *STING1-IRF1* gene expression showed strong activation of a range of inflammatory mediators and genes associated with the immune response. Among the most important of these genes are *CXCL9* and *CXCL10*, In addition to the major histocompatibility complex type 1 (MHC-1) molecules such as *HLA-B* and *HLA-C*.

These results mean that the *STING1* axis is not neglected in isolation, but rather stimulates a series of reactions and molecular processes that increase inflammation in the tumor environment, the importance of the *STING1-IRF1* axis is not limited to transcriptional changes, but extends to the actual reshaping of the tumor microenvironment (TME). was also observed an increase in macrophage presence in the *STING1*-high-expression environment. From a biological perspective, activation of the *STING1* pathway may promote the transformation of macrophages towards the anti-tumor M1 subtype. This is according to what he mentioned Ohkuri et al. [16], STING stimulation not only attracts T cells but also reprograms tumor-associated macrophages (TAMs) to become more capable of presenting immune antigens and secreting inflammatory cytokines this explains the strong correlation we observed in the current study between *STING1* and improved survival. The *STING1-IRF1* axis may be the key to transforming immunocompromised tumors into responsive tumors. This aligns with some studies supporting this approach in clinical trials, such as those by Corrales et al. [17] and Zhou et al. [18], regarding the use of STING inducers to overcome the immune resistance barrier, particularly in cases of immunosuppression due to specific gene mutations

The marked increase in the chemokines CXCL9 and CXCL10 explains the mechanism by which T-cells are recruited.This was confirmed by a previous study by Noblejas-López et al. [19], which showed that CXCL10 expression stimulated by the interferon pathway is a crucial factor in predicting the response of breast cancer patients to immunotherapies.

Furthermore, the results shown by the heatmap indicated a clear increase in the expression of *HLA-B* and *HLA-C* genes specifically in the high-expression group. This is consistent with a study by Reschke et al. [20]which supported this argument, indicating that the restoration of *HLA-B* gene expression is closely associated with increased cytotoxic T cell infiltration and improved clinical prognosis .

The results of the *GSEA* and Dotplot analysis are shown in Figure 4B , the biological processes most strongly associated with elevated *STING1* expression are "Leukocyte-mediated immunity" and "Antigen processing and presentation". This finding is significant because it suggests that *STING1* may not only send out distress signals, but may actually enhance the efficiency and ability of cancer cells to identify themselves to the immune system by boosting Major Histocompatibility Complex Class I) MHC-I (pathways, this is entirely consistent with what was published in a recent study by Mpakali et al. [21], Which confirmed that the disruption in antigen presentation pathways is the main means by which breast tumors escape immune control, *STING1*'s ability to restore these pathways reactivates the cancer-immunity cycle.

This important link between *STING1* and other pathways indicates the presence of "cellular communication" between cancer cells and infiltrating immune cells, This communication and stimulation in the *STING1-IRF1* axis ensures the continued vital production of immune cells and a pathway that prevents or reduces the exposure of immune components such as cytokines to immune exhaustion [22]

Analysis of the interaction network (Figure 6) showed that *IRF1* acts as a central hub linking *STING1* and *HLA* genes such as (*HLA-B*, *HLA-C, HLA-E*). This hierarchical organization (*STING1* → *IRF1* → *HLA*) can provide an important mechanistic explanation, the *STING1* protein the *STING1* protein does not directly affect genes, but rather stimulates the transcription factor *IRF1*, which is the genetic engineer of the interferon response, this result is consistent with the study by Nagai et al. (2021), which showed that *IRF1* is the main regulator of MHC-I molecules in breast cancer, and its absence leads to a complete failure of tumors to respond to immunotherapy, even in the presence of primary stimuli [19, 23].

Among the notable results, illustrated in Figure 7, we found high mutation rates in several genes for example, *MAP3K1* (56%) and *PIK3CA* (53%), in addition to mutations in *TP53* and *STING1* itself, while this also revealed a remarkably high percentage of *STING1* gene mutations (43%), It also suggests that direct somatic changes in the *STING1* gene itself may be the primary driver of its loss of function in sensing innate immunity. These genetic disorders are likely to impair the subsequent activation of the *IRF1* pathway this provides a direct genetic explanation for the pattern of "immune inactivity" and the subsequent escape from immune surveillance.

Which was observed in a large subset of breast cancer patients, these mutations explain "why" some tumors fail to activate the *STING1* axis despite the presence of triggers , mutations in *TP53* and *PIK3CA* are known to inhibit and suppress interferon production changing the *STING1* signaling pathway from a benign inflammation pathway to a tumor growth promotion pathway, This is consistent with what Tian et al. (2022) stated in their study, they pointed out that the genetic background of the tumor (Somatic Mutations) these may act as "genetic brakes"

preventing the success of STING stimulators in the clinic [24] . Recent research has indicated that activation of the *PIK3CA* pathway leads to direct inhibition of the STING pathway via phosphorylation mechanisms that prevent its signals from reaching the nucleus and suppress its activity [25] . This is what we found in our results above, where the percentage of mutations in *PIK3CA* exceeded 50%, and this represents a major obstacle for tumors with a high mutational burden in this gene often show low expression of immunological markers.

We also observed in the current study the presence of mutations in the *GATA3* gene (42%) and B2M (40%). The B2M gene is a key component of MHC-I, and its mutation means that the tumor has lost its structural ability to present immune antigens this makes even STING 1 activation insufficient to restore tumor immunological recognition, this result is consistent with what Zaretsky et al. (2016) presented in their study on the role of B2M mutations in acquired immunotherapy resistance [26].

The high mutation rate (46%) in the p53 gene this may explain why the immune response failed to be activated in a wide range of samples, whereas in normal conditions, the healthy p53 protein works synergistically with STING to promote tumor aging and inflammation.

In conclusion, this study has provided a comprehensive analysis of the functional and clinical role of the *STING1-IRF1* axis in breast cancer. Highlighting it as a key driver of immune infiltration and antitumor response by combining gene expression data with the mutational landscape we obtained, this means that restoring the activity of this pathway is capable of breaking the state of "immune inertia" in cold tumors, by enhancing antigen presentation pathways and attracting lymphocytes.

However, our results show that the mutational burden in genes such as *PIK3CA* and *TP53* represents a critical obstacle to the efficiency of this system, this necessitates the adoption of combined therapeutic strategies that combine STING inducers, inhibitors of mutational pathways, and immune stimulation in general. These findings not only contribute to understanding the mechanisms of immune escape it could even open new horizons for developing accurate biomarkers to predict the response to modern immunotherapies in breast cancer. We propose that clinical trials should be conducted combining STING inducers and *PIK3CA* inhibitors.

Study Limitations and Clinical Implications

Despite strong bioinformatics evidence supporting the predictive role of the *STING1-IRF1* axis, no, this study has certain limitations. Firstly, the analysis relied on retrospective datasets (GEO and TCGA), the sample size for the survival analysis was relatively average (n = 104). Secondly, although our results are statistically significant however, further verification is needed through future clinical trials and in vitro functional assays to elucidate the precise molecular interactions. however, these results have important clinical implications; *STING1* and *IRF1* expression levels can serve as potential biomarkers, to identify breast cancer patients with 'hot' immune profiles who are likely to respond to immunotherapies. Furthermore, targeting this axis may provide a new therapeutic strategy to boost immunity against tumors.

Author Contribution Statement

M. Alzeyadi: Concept, Methodology, Analysis, Supervision. I. Alhamadani: Investigation, Software, Writing-review. Both authors approved the final version.

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Conflict of Interest

The authors declare no conflict of interest.

Ethical Statement

This study analyzed de-identified public data from TCGA and GEO. Thus, no institutional review board (IRB) approval was required, following the 1964 Helsinki Declaration.

Data Availability

All analyzed datasets (TCGA and GEO) and generated results are included within this article.

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