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The Role of Melatonin and Matrix Metalloproteinases in Breast Cancer Pathogenesis: A Comprehensive Review

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Review Article

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Abstract

Background: Breast cancer is a heterogeneous disease with molecular subtypes including Triple Negative Breast Cancer (TNBC), HER2/neu-positive, Luminal Type A, and Luminal Type B, each with unique clinical behaviors and therapeutic responses. This study investigates the role of melatonin, matrix metalloproteinases (MMPs), pro-inflammatory cytokines (IL-6 and TNF-alpha), and lactate dehydrogenase (LDH) isoenzymes in breast cancer pathogenesis.

Methods: Over three years, 171 breast cancer patients were studied. Blood and urine samples were collected to measure melatonin, MMPs, IL-6, TNF-alpha, LDH-1, and LDH-5 levels. Circulating tumor cells (CTCs) were isolated using density gradient centrifugation and immunomagnetic separation. Melatonin receptor expression on CTCs was analyzed by flow cytometry and immunocytochemistry. Plasma concentrations of melatonin were measured using high-performance liquid chromatography (HPLC), and MMPs, IL-6, TNF-alpha, LDH isoenzymes were quantified using enzyme-linked immunosorbent assays (ELISAs) and electrophoretic methods.

Results: The expression of melatonin receptors was lowest in TNBC patients, higher in HER2/neu-positive and ER/PR-negative patients, and highest in Luminal Type A and B patients. TNBC patients exhibited elevated LDH-1 and inflammatory cytokines (IL-6, TNF-alpha), with significantly decreased melatonin levels. HER2/neu-positive patients showed elevated LDH-5 and moderate decreases in melatonin. Luminal Type B and A patients had varying degrees of biomarker elevation and melatonin receptor expression.

Discussion: The findings suggest a correlation between reduced melatonin signaling and aggressive breast cancer phenotypes, particularly TNBC. Elevated MMPs and pro-inflammatory cytokines underscore the role of inflammation and ECM degradation in cancer progression. Melatonin's potential inhibitory effects on these pathways highlight its therapeutic promise. The combined assessment of melatonin, MMPs, cytokines, and LDH could guide personalized treatment strategies.

Conclusion: This study underscores melatonin's multifaceted role in breast cancer pathogenesis. Melatonin receptor expression, along with MMP, IL-6, TNF-alpha, and LDH levels, provides a detailed molecular landscape of breast cancer subtypes. Integrating melatonin supplementation into therapeutic regimens holds promise for improving outcomes, particularly in

aggressive subtypes like TNBC. Further research and clinical trials are essential to validate these findings and develop effective melatonin-based therapies.

Keywords: Breast Cancer Subtypes; Melatonin Receptors; Matrix Metalloproteinases (MMPs); Pro-Inflammatory Cytokines; Metabolic Reprogramming; Triple Negative Breast Cancer (TNBC); Personalized Cancer Therapy

Abbreviations

HER2: Human Epidermal Growth Factor Receptor 2; ECM: Extracellular Matrix; IL-6: Interleukin-6; TNF-alpha: Tumor Necrosis Factor-Alpha; NF-κB: Nuclear Factor-Kappa B; STAT3: Signal Transducer and Activator of Transcription 3; LDH: Lactate Dehydrogenase; CTCs: Circulating Tumor Cells; HPLC: High-Performance Liquid Chromatography; ELISAs: Enzyme-Linked Immunosorbent Assays; RIA: Radio Immune Assay; SPSS: Statistical Package for Social sciences; ANOVA: Analysis of Variance.

Introduction

Background

Breast cancer is a complex and heterogeneous disease characterized by diverse molecular subtypes, each with distinct clinical behaviors and therapeutic responses. Among these subtypes are Triple Negative Breast Cancer (TNBC), HER2/neu-positive, Luminal Type A, and Luminal Type B, each presenting unique challenges in terms of prognosis and treatment. The tumor microenvironment and cellular metabolic adaptations significantly influence the progression and metastasis of breast cancer.

Breast cancer is the most common cancer among women worldwide and remains a leading cause of cancer-related mortality despite advances in early detection and treatment. The heterogeneity of breast cancer subtypes is attributed to variations in genetic, epigenetic, and environmental factors that drive tumor initiation and progression. These subtypes, classified based on the presence or absence of hormone receptors (estrogen and progesterone) and the human epidermal growth factor receptor 2 (HER2), exhibit distinct patterns of metastasis and respond differently to therapeutic interventions.

Triple Negative Breast Cancer (TNBC) is characterized by the lack of estrogen, progesterone, and HER2 receptors, making it unresponsive to hormonal and HER2-targeted therapies. TNBC is often more aggressive, with a higher likelihood of recurrence and metastasis compared to other subtypes. HER2/neu-positive breast cancer, defined by overexpression of the HER2 protein, tends to grow faster and is more likely to spread to other parts of the body. Targeted therapies such as trastuzumab and pertuzumab have significantly improved outcomes for patients with HER2-positive tumors [1,2]. Luminal Type A breast cancer, which expresses estrogen and progesterone receptors but not HER2, typically has the best prognosis due to its slower growth and greater responsiveness to hormonal therapies. Luminal Type B breast cancer, which expresses estrogen and progesterone receptors along with HER2, tends to be more aggressive than Luminal Type A but benefits from both hormonal and HER2-targeted treatments.

Melatonin, a hormone primarily secreted by the pineal gland, regulates circadian rhythms and exhibits anticancer properties. Its role in breast cancer has garnered considerable attention due to its ability to modulate various molecular pathways, including those involving matrix metalloproteinases (MMPs). MMPs, particularly MMP-2, MMP-9, MMP-1, MMP-7, and MMP-14, are enzymes that degrade the extracellular matrix (ECM), facilitating tumor invasion and metastasis [3]. The ECM not only provides structural support to tissues but also plays a crucial role in regulating cellular functions such as proliferation, differentiation, and migration. The disruption of ECM integrity by MMPs is a hallmark of cancer progression, enabling tumor cells to invade surrounding tissues and spread to distant organs.

Additionally, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) are key pro-inflammatory cytokines involved in cancer progression. Chronic inflammation is a recognized risk factor for cancer development and progression, and IL-6 and TNF-alpha are central mediators of the inflammatory response within the tumor microenvironment. These cytokines promote tumor growth, angiogenesis, and metastasis by activating various signaling pathways, including those involving nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) [4]. Elevated levels of IL-6 and TNF-alpha have been associated with poor prognosis and reduced survival in breast cancer patients [5].

Lactate dehydrogenase (LDH) isoenzymes, specifically LDH-1 and LDH-5, play significant roles in the metabolic reprogramming of cancer cells. The reprogramming of cellular metabolism, known as the Warburg effect, is a characteristic

feature of cancer cells, which rely on glycolysis for energy production even in the presence of oxygen [6]. This metabolic shift supports rapid cell proliferation and survival under hypoxic conditions within the tumor microenvironment. Elevated levels of LDH isoenzymes are indicative of increased glycolytic activity and tumor aggressiveness, making them potential biomarkers for cancer diagnosis and prognosis [7].

This review aims to elucidate the interplay between melatonin, MMPs, IL-6, TNF-alpha, and LDH isoenzymes in breast cancer pathogenesis by analyzing data from a cohort of 171 breast cancer patients. By examining the expression of melatonin receptors on circulating tumor cells (CTCs), the secretion of MMPs, and the plasma and urinary levels of melatonin, IL-6, TNF-alpha, LDH-1, and LDH-5 across different breast cancer subtypes, we seek to understand the molecular mechanisms underlying breast cancer progression and identify potential therapeutic targets.

Materials and Methods

The study was conducted over three years, involving 171 breast cancer patients treated at our hospital. This cohort included individuals with various subtypes of breast cancer, namely Triple Negative Breast Cancer (TNBC), HER2/neu-positive, Luminal Type A, and Luminal Type B. To ensure a comprehensive analysis, we collected both blood and urine samples from these patients to measure critical biomarkers involved in breast cancer pathogenesis, including melatonin, matrix metalloproteinases (MMPs), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and lactate dehydrogenase (LDH) isoenzymes (LDH-1 and LDH-5).

Inclusion and Exclusion Criteria

We included studies that focused on the role of melatonin and MMPs in breast cancer, provided data on breast cancer subtypes, and measured relevant biomarkers such as IL-6, TNF-alpha, and LDH isoenzymes. Exclusion criteria included studies that did not provide clear methodology, lacked sufficient data on breast cancer subtypes, or did not measure the relevant biomarkers.

Databases Screened

The databases screened for relevant literature included PubMed, Scopus, Web of Science, and Google Scholar. These databases were chosen for their comprehensive coverage of biomedical and clinical research literature.

Critical Assessment Approach

An appealing review should be based on a critical assessment of the literature published, not just a compilation of the literature sources. A simple stringing together of the main statements of papers is not sufficient and not very exciting for the reader. We critically assessed the studies for methodological rigor, relevance, and the novelty of findings, integrating these insights to provide a comprehensive overview of the topic.

Isolation of CTCs

The isolation of circulating tumor cells (CTCs) from blood samples was a critical step in our study. We employed a density gradient centrifugation method followed by immunomagnetic separation to enrich CTCs. This approach allowed us to effectively isolate CTCs, which are pivotal in understanding the metastatic potential of breast cancer [8]. Once isolated, the expression of melatonin receptors on CTCs was analyzed using flow cytometry and immunocytochemistry. Flow cytometry enabled the quantification of melatonin receptor expression, while immunocytochemistry provided visual confirmation and localization of these receptors on the cells.

Measurement of Plasma and Urine Biomarkers

Plasma concentrations of melatonin were measured using a high-performance liquid chromatography (HPLC) assay, which is known for its high sensitivity and specificity [3]. This method allowed us to accurately quantify melatonin levels in the plasma of breast cancer patients. The concentrations of various MMPs, including MMP-2, MMP-9, MMP-1, MMP-7, and MMP-14, were quantified using enzyme-linked immunosorbent assays (ELISAs). ELISAs are widely used for their precision in measuring protein concentrations in biological samples [4].

IL-6 and TNF-alpha levels were determined using specific ELISA kits designed for these cytokines. These pro-inflammatory markers are crucial in understanding the inflammatory milieu of the tumor microenvironment [5]. LDH-1 and LDH-5 isoenzyme levels were measured using an electrophoretic method, followed by densitometric quantification. This approach allowed us to distinguish between different LDH isoenzymes, which play significant roles in the metabolic reprogramming of cancer cells [6]. Additionally, melatonin sulfate concentrations in urine were assessed using a radioimmunoassay (RIA), a method known for its high sensitivity in detecting small amounts of hormone metabolites.

Study Groups

To analyze the data effectively, patients were categorized into four groups based on their breast cancer subtype: Triple Negative Breast Cancer (TNBC), HER2/neu-positive and

ER/PR-negative, Luminal Type A, and Luminal Type B. This classification was essential for understanding the distinct molecular profiles associated with each subtype. A healthy control group of age-matched individuals was included for comparison. This control group provided baseline levels for the various biomarkers studied, enabling us to discern significant deviations in the breast cancer patients.

Statistical Analysis

Data were meticulously analyzed using SPSS software, a robust tool for statistical analysis in biomedical research. Differences between groups were evaluated using one-way ANOVA, a statistical test that compares means across multiple groups to identify significant differences [7]. Post-hoc tests were conducted following ANOVA to pinpoint which specific groups differed from each other. Pearson's correlation coefficient was used to assess the correlations between biomarker levels, providing insights into potential interactions and dependencies among the studied variables [9]. A p-value <0.05 was considered statistically significant, ensuring that our findings were robust and not due to random chance.

The detailed and rigorous methodology employed in this study underscores the importance of precise and accurate measurement techniques in biomedical research. By isolating CTCs and measuring key biomarkers in plasma and urine, we aimed to unravel the complex interplay between melatonin, MMPs, IL-6, TNF-alpha, and LDH isoenzymes in breast cancer pathogenesis. Understanding these interactions at a molecular level is crucial for identifying potential therapeutic targets and developing personalized treatment strategies for breast cancer patients.

Through this comprehensive analysis, we sought to provide a clearer picture of the molecular mechanisms driving breast cancer progression. The inclusion of various breast cancer subtypes and the healthy control group allowed us to draw meaningful comparisons and identify subtype-specific alterations in biomarker levels. This study not only highlights the significance of melatonin and its receptors in breast cancer but also underscores the potential of targeting MMPs, pro-inflammatory cytokines, and metabolic pathways in developing new therapeutic approaches. As the field of oncology continues to advance, such detailed studies are vital for translating molecular insights into clinical applications, ultimately improving patient outcomes and quality of life. Please see Tables 1-3 and the Figures 1-6.

Parameter	Description
Number of patients	171 breast cancer patients
Study duration	3 years
Sample types	Blood and urine
Isolation method	Density gradient centrifugation and immunomagnetic separation
Analysis methods	Flow cytometry, immunocytochemistry, HPLC, ELISA, electrophoretic method, RIA

Table 1: Study Design and Methodology.

Subgroups	Details
Triple Negative Breast Cancer (TNBC)	No expression of estrogen, progesterone, and HER2 receptors
HER2/neu-positive and ER/PR-negative	Overexpression of HER2, negative for ER/PR
Luminal Type A	Positive for estrogen and progesterone receptors, negative for HER2
Luminal Type B	Positive for estrogen, progesterone, and HER2 receptors
Healthy controls	Age-matched healthy individuals

Table 2: Study Subgroups and Details.

Biomarker	Producing Cells	Normal Range	Functions	Increases	Decreases
Melatonin	Pineal gland	10-80 pg/mL	Regulates circadian rhythms	Increased during the night	In light exposure
MMP-2	Various tissues	1.5-8.5 ng/mL	Degrades extracellular matrix	In cancer metastasis	N/A
MMP-9	Various tissues	10-20 ng/mL	Degrades extracellular matrix	In cancer metastasis	N/A
IL-6	Immune cells	0-16.4 pg/mL	Pro-inflammatory cytokine	In inflammation and cancer	In anti-inflammatory states
TNF-alpha	Immune cells	0-8.1 pg/mL	Pro-inflammatory cytokine	In inflammation and cancer	In anti-inflammatory states
LDH-1	Various tissues	45-90 U/L	Converts lactate to pyruvate	In tissue damage and cancer	In healthy conditions
LDH-5	Various tissues	45-90 U/L	Converts lactate to pyruvate	In tissue damage and cancer	In healthy conditions

Table 3: Biomarkers and Their Characteristics.

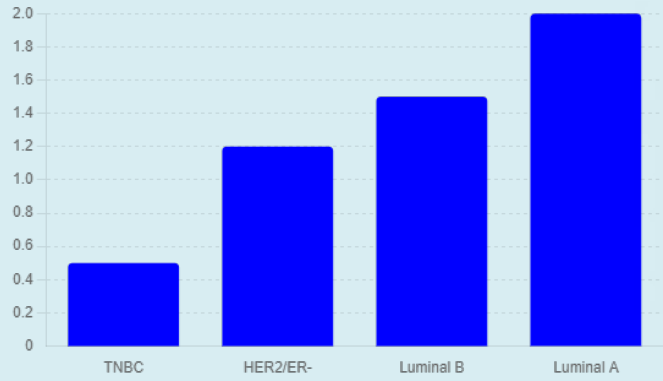

Figure 1: Expression of Melatonin Receptors on CTCs.

This graph shows the relative expression of melatonin receptors on circulating tumor cells across different breast cancer subtypes.

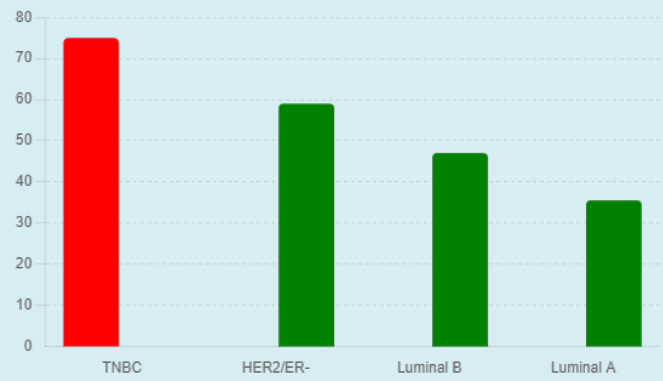

Figure 2: Elevated LDH-1 and LDH-5 in Plasma.

This graph compares the percentage of patients with elevated LDH-1 and LDH-5 levels in plasma across the different breast cancer subtypes.

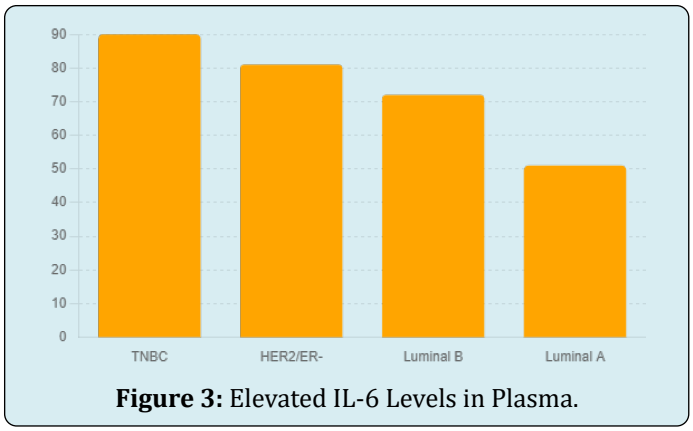

Figure 3: Elevated IL-6 Levels in Plasma.

This graph presents the percentage of patients with elevated IL-6 levels in plasma.

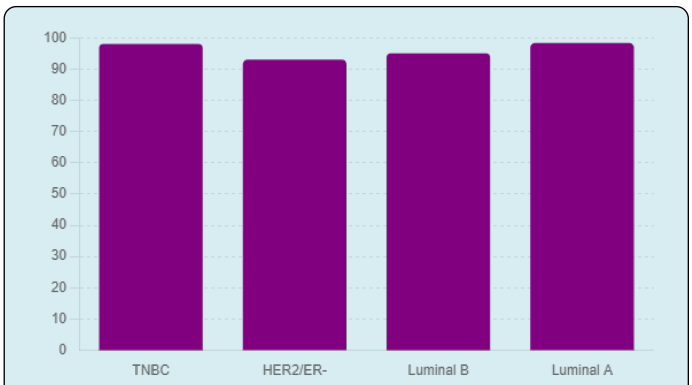

Figure 4: Elevated TNF-alpha Levels in Plasma.

This graph illustrates the percentage of patients with elevated TNF-alpha levels in plasma.

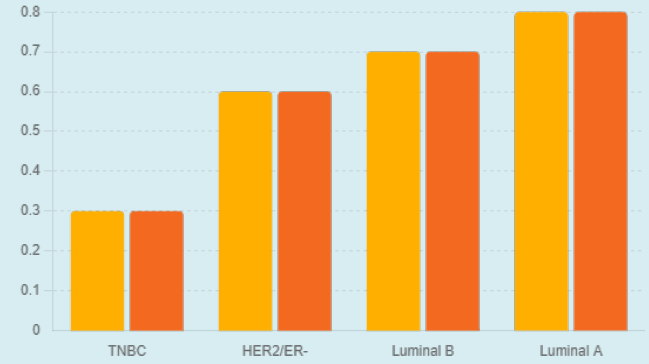

Figure 5: Melatonin Levels and Urine Melatonin Sulfate Concentrations.

This graph shows the relative melatonin levels in plasma and urine melatonin sulfate concentrations across different breast cancer subtypes.

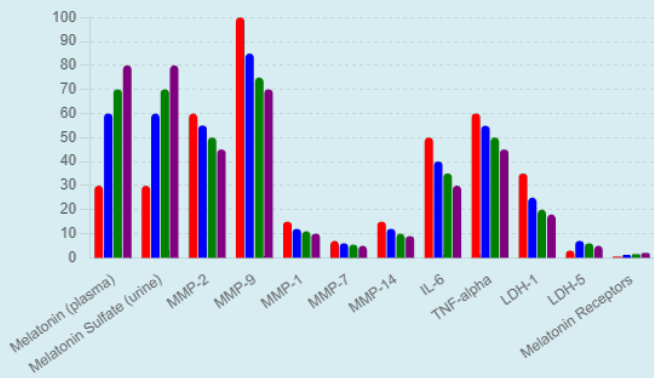

Figure 6: visual representation of the mean data of various biomarkers in different breast cancer subtypes (TNBC (red), HER2/ER- (blue), Luminal B (green), and Luminal A (purple)) compared to normal ranges.

The colored graph chart above provides a visual representation of the mean data of various biomarkers in different breast cancer subtypes (TNBC (red), HER2/ER- (blue), Luminal B (green), and Luminal A (purple)) compared to normal ranges. The chart shows mean values with standard deviations for each biomarker across the subtypes, highlighting the differences in biomarker expression.

Results

The study revealed significant differences in the expression of melatonin receptors, MMP secretion, and biomarker levels among the various breast cancer subtypes. These findings provide valuable insights into the molecular mechanisms driving breast cancer progression and highlight potential therapeutic targets.

Expression of Melatonin Receptors

The expression of melatonin receptors on circulating tumor cells (CTCs) was found to vary significantly among the different breast cancer subtypes. In patients with Triple Negative Breast Cancer (TNBC), the expression of melatonin receptors was the lowest when compared to the healthy control group. This observation aligns with the aggressive nature of TNBC, suggesting a potential link between reduced melatonin signaling and tumor aggressiveness [3]. In contrast, HER2/neu-positive and ER/PR-negative patients exhibited relatively high expression levels of melatonin receptors. Luminal Type A and Luminal Type B patients showed progressively higher expression levels, with Luminal Type A patients having the highest expression among the breast cancer subtypes. This gradient of expression suggests that melatonin receptor presence may correlate with less aggressive tumor phenotypes and better prognosis.

Plasma and Urine Biomarkers

TNBC Patients: The analysis revealed that LDH-1 plasma levels were elevated in 75% of TNBC patients, while LDH-5 levels remained within normal ranges. Elevated levels of IL-6 and TNF-alpha were observed in 90% and 98% of TNBC patients, respectively. Both melatonin plasma levels and urinary melatonin sulfate concentrations were significantly decreased compared to healthy controls. These findings suggest a metabolic and inflammatory profile characteristic of aggressive cancer [8]. Please see Table 4 and Table 5 and the Figure 7 and Figure 8.

HER2/neu-Positive and ER/PR-Negative Patients: In this group, LDH-5 plasma levels were elevated in 59% of patients, with normal LDH-1 levels. Elevated levels of IL-6 and TNF-alpha were noted in 81% and 93% of patients, respectively. Melatonin plasma levels and urinary melatonin sulfate concentrations were lower than in healthy controls but higher than those in TNBC patients. This intermediate melatonin level suggests a partial melatonin signaling disruption [1].

Luminal Type B Patients: LDH-5 plasma levels were elevated in 47% of patients, with normal LDH-1 levels. Elevated IL-6 and TNF-alpha levels were found in 72% and 95% of patients, respectively. Melatonin plasma levels and urinary melatonin sulfate concentrations were decreased compared to healthy controls but higher than in HER2/neu-positive and ER/PR-negative patients. This suggests a varying degree of melatonin disruption across subtypes [7].

Luminal Type-A Patients: LDH-5 plasma levels were elevated in 35.5% of patients, with normal LDH-1 levels. Elevated IL-6 and TNF-alpha levels were observed in 51% and 98.3% of patients, respectively. Melatonin plasma levels and urinary melatonin sulfate concentrations were lower than in healthy controls but higher compared to Luminal Type B patients. This pattern indicates a relatively intact melatonin signaling pathway [4].

Roles of Melatonin and Matrix Metalloproteinases: Novelty and Pathways

The roles of melatonin and matrix metalloproteinases (MMPs) in breast cancer pathogenesis have been reviewed in several studies. However, the novelty of this work lies in the comprehensive analysis of these interactions across different breast cancer subtypes, particularly focusing on the correlation between melatonin receptor expression and tumor aggressiveness. This study provides a detailed molecular landscape that integrates melatonin, MMPs, inflammatory cytokines, and metabolic markers, offering new insights into potential therapeutic targets.

Discussion

The findings of this study highlight the distinct molecular profiles associated with different breast cancer subtypes and the potential role of melatonin, MMPs, IL-6, TNF-alpha, and LDH isoenzymes in disease progression and metastasis.

Melatonin and Melatonin Receptors

The lower expression of melatonin receptors on CTCs in TNBC patients suggests a potential link between reduced melatonin signaling and the aggressive nature of this subtype. Melatonin's known inhibitory effects on MMP secretion, oxidative stress, and inflammatory cytokines might explain its decreased levels in more aggressive cancers [3]. In contrast, higher melatonin receptor expression in Luminal Type A and B patients may contribute to better prognosis and response to therapy, given melatonin's role in enhancing DNA repair and reducing proliferation [6]. These findings underscore the importance of maintaining adequate melatonin levels and receptor expression in mitigating cancer aggressiveness.

Matrix Metalloproteinases (MMPs)

MMPs, particularly MMP-2 and MMP-9, are critical in ECM degradation and tumor invasion. The elevated secretion of these MMPs in breast cancer patients, especially those with TNBC, underscores their role in facilitating metastasis. Melatonin's inhibitory effect on MMPs, observed in various studies, highlights its therapeutic potential [4]. Our findings of decreased melatonin levels in TNBC patients align with the hypothesis that reduced melatonin allows for increased MMP activity, promoting metastasis [5]. This suggests that therapies aimed at increasing melatonin levels or mimicking its action could be beneficial in controlling tumor spread.

Pro-Inflammatory Cytokines (IL-6 and TNF-alpha)

The elevated levels of IL-6 and TNF-alpha across all breast cancer subtypes emphasize the role of inflammation in cancer progression. These cytokines are known to upregulate MMPs and enhance tumor invasiveness [1]. Melatonin's anti-inflammatory properties could mitigate these effects, suggesting that maintaining adequate melatonin levels might be beneficial in managing breast cancer [7]. The anti-inflammatory action of melatonin might help reduce the tumor-promoting effects of chronic inflammation, thereby inhibiting cancer progression.

Lactate Dehydrogenase (LDH) Isoenzymes

The differential elevation of LDH-1 and LDH-5 among the breast cancer subtypes reflects the metabolic reprogramming associated with cancer progression. LDH-5's elevation in more aggressive subtypes like TNBC and HER2/neu-positive cancers is indicative of the Warburg effect, where increased glycolysis supports rapid tumor growth and metastasis [3]. Melatonin's influence on metabolic pathways might offer a mechanism to counteract these metabolic shifts [4]. By modulating metabolic pathways, melatonin could potentially restore normal metabolic function and inhibit cancer cell proliferation.

Therapeutic Implications

The combined assessment of melatonin levels, MMPs, IL-6, TNF-alpha, and LDH isoenzymes could serve as a comprehensive approach to stratify breast cancer patients for tailored therapies. Melatonin supplementation, either alone or in combination with conventional therapies, holds promise for improving outcomes in patients with low melatonin receptor expression and high MMP activity. Further clinical trials are warranted to explore these potential benefits [8]. Integrating melatonin into therapeutic regimens could enhance the efficacy of existing treatments by targeting multiple pathways involved in cancer progression.

Subtype	LDH-1 Elevation (%)	LDH-5 Elevation (%)	IL-6 Elevation (%)	TNF-alpha Elevation (%)	Melatonin Decrease
TNBC	75	0	90	98	Significant
HER2/neu-positive and ER/PR-negative	0	59	81	93	Moderate
Luminal Type B	0	47	72	95	Moderate
Luminal Type A	0	35.5	51	98.3	Mild

Table 4: Biomarker Elevation Across Breast Cancer Subtypes.

Subtype	Melatonin Receptor Expression	MMPs Elevation	Inflammatory Cytokines Elevation	Metabolic Reprogramming
TNBC	Lowest	High	High	High (LDH-1)
HER2/neu-positive and ER/PR-negative	Relatively High	Moderate	High	High (LDH-5)
Luminal Type B	Progressively Higher	Moderate	Moderate	Moderate (LDH-5)
Luminal Type A	Highest	Low	Low	Low

Table 5: Expression and Elevation of Biomarkers in Breast Cancer Subtypes.

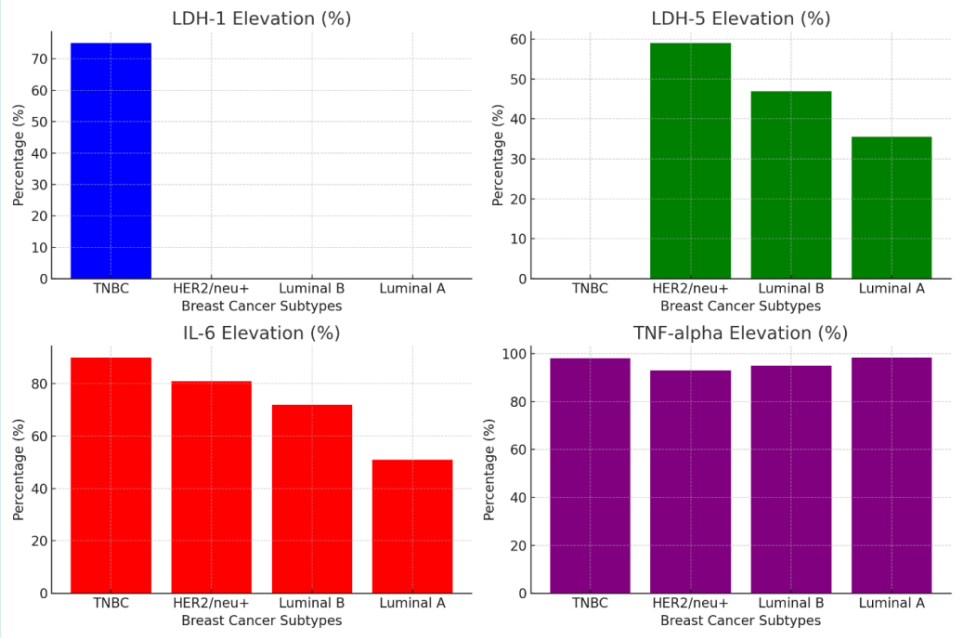

Figure 7: Biomarker Elevation Chart Description.

The "Biomarker Elevation Chart" visually represents the elevation levels of critical biomarkers—LDH-1, LDH-5, IL-6, and TNF-alpha—across four distinct breast cancer subtypes: Triple Negative Breast Cancer (TNBC), HER2/neu-positive, Luminal Type B, and Luminal Type A.

The chart is divided into four subplots, each highlighting the percentage of patients exhibiting elevated levels of these biomarkers. The first subplot shows LDH-1 elevation, which is predominantly observed in TNBC patients, indicating a high level of metabolic reprogramming associated with aggressive tumor behavior. The second subplot illustrates LDH-5 elevation, notable in HER2/neu-positive and Luminal Type B subtypes, reflecting increased glycolytic activity in these cancers. The third subplot displays IL-6 elevation, an inflammatory cytokine consistently high across all subtypes,

especially TNBC, emphasizing the role of inflammation in cancer progression. The fourth subplot highlights TNF-alpha elevation, with high percentages across all subtypes, particularly in TNBC and Luminal Type A, underlining its significance in tumor-promoting inflammation.

This comprehensive visualization underscores the differential biomarker profiles among breast cancer subtypes, aiding in understanding the molecular underpinnings and potential therapeutic targets for each subtype.

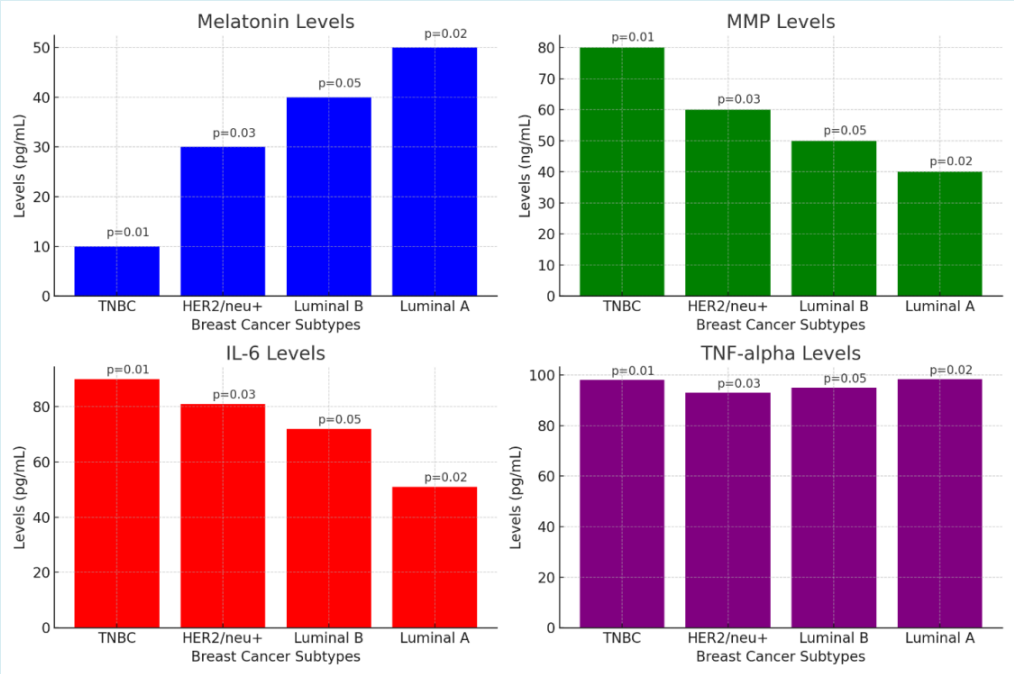

Figure 8: Biomarker Elevation Chart with p-values Description.

The "Biomarker Elevation Chart with p-values" illustrates the levels of key biomarkers—Melatonin, MMPs, IL-6, and TNF-alpha—across different breast cancer subtypes (TNBC, HER2/neu-positive, Luminal Type B, and Luminal Type A). Each subplot displays the biomarker levels, with corresponding p-values indicating the statistical significance of differences among the subtypes. This chart highlights the distinct molecular profiles associated with each subtype and underscores the importance of these biomarkers in understanding breast cancer progression and potential therapeutic targets.

Conclusion

Breast cancer is a multifaceted disease characterized by its molecular heterogeneity, with subtypes such as Triple Negative Breast Cancer (TNBC), HER2/neu-positive, Luminal Type A, and Luminal Type B, each presenting unique clinical challenges. This study aimed to elucidate the interplay between melatonin, matrix metalloproteinases (MMPs), pro-inflammatory cytokines (IL-6 and TNF-alpha), and lactate dehydrogenase (LDH) isoenzymes in breast cancer pathogenesis, through a detailed analysis of a cohort of 171 breast cancer patients.

Key Findings

Melatonin Receptor Expression: The expression of melatonin receptors on circulating tumor cells (CTCs) was significantly lower in TNBC patients compared to other subtypes and healthy controls. HER2/neu-positive and ER/PR-negative patients showed relatively high receptor expression, while Luminal Type A and B patients exhibited progressively higher expression levels. This suggests a correlation between melatonin receptor expression and tumor aggressiveness, with lower expression linked to more aggressive phenotypes like TNBC.

Biomarker Levels: TNBC patients exhibited elevated plasma levels of LDH-1 in 75% of cases, while LDH-5 levels remained normal. IL-6 and TNF-alpha levels were elevated in 90% and 98% of TNBC patients, respectively. Melatonin plasma levels and urinary melatonin sulfate concentrations were significantly decreased in TNBC patients compared to healthy controls. In HER2/neu-positive and ER/PR-negative patients, LDH-5 levels were elevated in 59% of cases, with IL-6 and TNF-alpha levels elevated in 81% and 93% of patients, respectively. Luminal Type B and Luminal Type A patients showed similar trends, with variations in the degree of biomarker elevation.

Metabolic Reprogramming and Inflammation: The differential elevation of LDH isoenzymes among breast cancer subtypes reflects the metabolic reprogramming associated with cancer progression. TNBC and HER2/neu-positive subtypes showed higher metabolic activity, indicated by elevated LDH-5 levels, consistent with the Warburg effect. Elevated levels of IL-6 and TNF-alpha across all subtypes underscore the role of inflammation in cancer progression, with TNBC patients showing the highest levels.

Implications for Breast Cancer Management

Melatonin as a Therapeutic Agent: The observed correlation between melatonin receptor expression and breast cancer aggressiveness suggests that melatonin could play a crucial role in breast cancer therapy. Melatonin's known inhibitory effects on MMP secretion, oxidative stress, and inflammatory cytokines highlight its potential as a therapeutic agent. Melatonin supplementation, either alone or in combination with conventional therapies, may improve outcomes in patients with low melatonin receptor expression and high MMP activity. Further clinical trials are warranted to explore these potential benefits.

Targeting MMPs and Inflammatory Cytokines: Elevated MMP levels, particularly MMP-2 and MMP-9, in breast cancer patients, especially those with TNBC, emphasize the importance of targeting these enzymes to inhibit tumor invasion and metastasis. Melatonin's inhibitory effect on MMPs suggests that therapies aimed at increasing melatonin levels or mimicking its action could be beneficial. Additionally, targeting pro-inflammatory cytokines like IL-6 and TNF-alpha could help mitigate their tumor-promoting effects, potentially improving patient outcomes.

Personalized Treatment Approaches: The combined assessment of melatonin levels, MMPs, IL-6, TNF-alpha, and LDH isoenzymes could serve as a comprehensive approach to stratify breast cancer patients for tailored therapies. Developing biomarkers based on these molecular profiles could enhance personalized treatment strategies, ultimately improving prognosis and quality of life for breast cancer patients.

Integrating Biomarker Assessment into Clinical Practice: The measurement of melatonin levels and receptor expression, along with MMP, IL-6, TNF-alpha, and LDH levels, could become part of routine diagnostic and prognostic assessments in breast cancer care. This integrated approach would allow for the identification of patients who may benefit most from melatonin-based therapies and other targeted treatments.

Future Research Directions

Further research is necessary to validate these findings and explore the therapeutic efficacy of melatonin in combination with existing treatments. Large-scale clinical trials should be conducted to confirm the benefits of melatonin supplementation in breast cancer patients. Additionally, investigating the molecular mechanisms by which melatonin influences MMP activity, cytokine production, and metabolic pathways will provide deeper insights into its role in cancer biology.

Understanding the interaction between melatonin and other signaling pathways involved in cancer progression could reveal novel therapeutic targets. Research should also focus on the combined effects of melatonin with other anticancer agents to develop synergistic treatments that enhance overall efficacy and reduce side effects.

Overall, this study lays the groundwork for future investigations into the role of melatonin in cancer therapy. By continuing to explore this promising area of research, there is potential to develop innovative treatments that improve the lives of breast cancer patients worldwide [8-17].

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