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Research Article

The Role of Systemic Inflammation, Neurotransmitter Dysregulation, and Tumor Markers in the Progression of Metastatic NSCLC: Pathophysiological Insights and Therapeutic Implications

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Abstract

Metastatic non-small cell lung cancer (NSCLC), particularly adenocarcinoma, remains a leading cause of cancer mortality worldwide, with advanced stages presenting complex challenges in both management and treatment. The progression of NSCLC, especially when metastases are involved, is closely tied to systemic inflammation and alterations in the neuroendocrine system. This study aims to elucidate the septic processes associated with advanced NSCLC by examining the role of inflammatory markers, neurotransmitters, and tumor markers in patients with metastatic disease. We conducted a comparative analysis between two distinct patient groups: the first group included 41 patients with advanced NSCLC (adenocarcinoma, stage IV, G3-G4), all presenting multiple metastases in the liver, bones, brain, and adrenal glands, with detectable circulating tumor cells (CTCs) and cell-free DNA (ctDNA) in their blood. The second group, serving as a control, consisted of 41 patients with early-stage NSCLC (adenocarcinoma, stage I, G1-G3) who were free of CTCs and ctDNA in their blood. Inflammatory markers, including TNF-alpha, CRP, ferritin, IL-1beta, IL-6, serum amyloid A (SAA), erythrocyte sedimentation rate (ERS), and leukocytes, were measured in both groups. Our results revealed significant increases in all inflammatory markers in the advanced NSCLC group compared to the control group. Specifically, TNF-alpha levels were elevated by 70%, CRP by 20%, ferritin by 11%, IL-1beta by 29%, IL-6 by 49%, and SAA by 27%. The ERS was 19% higher, and the leukocyte count increased by 12.9%. These findings underscore the profound systemic inflammation associated with metastatic NSCLC, which likely contributes to the aggressiveness and metastatic potential of the disease.

In addition to inflammation, we assessed the levels of key neuromediators, including melatonin, dopamine, serotonin, adrenalin, noradrenalin, cortisol, and histamine, to explore the neuroendocrine alterations associated with cancer progression. Our analysis demonstrated a dramatic 90% reduction in both melatonin and dopamine levels in the advanced NSCLC group compared to the control group. In contrast, serotonin levels were increased by 11.2%, adrenalin by 2.5%, noradrenalin by 9.8%, cortisol by 21.7%, and histamine by 17.7%. The significant decrease in melatonin and dopamine, both of which play critical roles in immune regulation and anti-cancer defense, suggests that metastatic NSCLC patients may suffer from impaired immune responses and increased tumor growth. Furthermore, the elevations in serotonin, adrenalin, noradrenalin, cortisol, and histamine point to a hyperactive stress-response system in these patients, which may further exacerbate tumor progression through immune suppression and the promotion of a tumor-friendly microenvironment.

Tumor markers, including CYFRA, carcinoembryonic antigen (CEA), CTCs, and ctDNA, were also quantified in both groups. As expected, the advanced NSCLC group exhibited significant increases in all tumor markers. CYFRA levels were 19% higher, CEA increased by 29.5%, CTCs were elevated by 87.1%, and ctDNA was 84.3% higher compared to the control group. The substantial presence of CTCs and ctDNA in the blood of stage IV patients indicates a higher degree of tumor shedding and metastasis, which correlates with the heightened inflammatory and neuroendocrine changes observed. In conclusion, this study provides compelling evidence that metastatic NSCLC (adenocarcinoma) is characterized by pronounced systemic inflammation, significant dysregulation of neurotransmitter levels, and elevated tumor markers. The interplay between these factors likely contributes to the aggressive nature of advanced NSCLC and its metastatic spread. Our findings suggest that targeting both inflammation and neuroendocrine pathways could offer novel therapeutic strategies for improving outcomes in patients with metastatic NSCLC. Future research should focus on exploring potential interventions aimed at reducing inflammation, restoring neurotransmitter balance, and inhibiting tumor marker activity to mitigate disease progression.

Keywords: Metastatic NSCLC, Inflammation, Neurotransmitter dysregulation, Tumor markers, Immunotherapy, Angiogenesis and Melatonin

1. Introduction

Non-small cell lung cancer (NSCLC) is one of the most prevalent and fatal types of cancer globally, accounting for approximately 85% of all lung cancer cases. Lung cancer itself remains the leading cause of cancer-related mortality worldwide, claiming millions of lives annually. NSCLC encompasses several histological subtypes, with adenocarcinoma being the most common, constituting approximately 40% of all lung cancer cases. While NSCLC is associated with high mortality, the disease trajectory and patient outcomes vary significantly based on the stage at diagnosis. Early-stage NSCLC may be potentially curable with surgical resection or localized therapies, but advanced-stage NSCLC, especially when metastasis has occurred, is challenging to manage and is generally associated with a poor prognosis. Understanding the underlying biological and biochemical mechanisms that drive NSCLC progression, particularly in its metastatic forms, is crucial for developing more effective treatments and improving patient survival.

A hallmark of metastatic NSCLC is its ability to spread to distant organs, most commonly the liver, bones, brain, and adrenal glands. This widespread dissemination not only compromises organ function but also triggers systemic inflammatory responses that further contribute to cancer progression. In the context of NSCLC, inflammation is a double-edged sword. While acute inflammation serves as a defense mechanism to eliminate harmful agents and repair tissue damage, chronic inflammation can create a tumor-promoting microenvironment. Tumors, particularly those in advanced stages like metastatic NSCLC, often exploit inflammatory pathways to promote their growth, resist immune detection, and enhance their metastatic potential.

The association between cancer and inflammation was first proposed over a century ago, and since then, numerous studies have established a strong link between chronic inflammation and various malignancies, including lung cancer. Inflammatory cytokines, such as TNF-alpha, IL-6, and IL-1beta, are often upregulated in the tumor microenvironment, where they facilitate cancer cell proliferation, invasion, and survival. Furthermore, inflammatory markers like C-reactive protein (CRP), ferritin, and serum amyloid A (SAA) have been implicated in the pathogenesis of cancer and are commonly elevated in patients with advanced malignancies. These markers not only reflect the systemic inflammatory state but also contribute to the creation of a favorable environment for tumor growth and metastasis by inducing angiogenesis, enhancing tumor cell migration, and suppressing anti-tumor immunity.

In metastatic NSCLC, septic processes related to chronic inflammation are particularly prominent. The presence of circulating tumor cells (CTCs) and cell-free DNA (ctDNA) in the blood further complicates the clinical scenario. CTCs are cancer cells that have detached from the primary tumor and entered the bloodstream, where they can disseminate to distant organs, leading to metastasis. ctDNA, on the other hand, represents fragments of tumor DNA released into the bloodstream, often as a result of tumor cell death or active secretion. Both CTCs and ctDNA have emerged as critical biomarkers for assessing tumor burden, tracking disease progression, and evaluating treatment response in cancer patients. Their presence in the blood signifies advanced disease and is often associated with poorer outcomes.

In addition to inflammation and tumor markers, neurotransmitter imbalances play a pivotal role in the pathogenesis of metastatic NSCLC. Neurotransmitters such as melatonin, dopamine, serotonin, and stress-related hormones like cortisol and histamine are not only involved in regulating physiological processes but also interact with the immune system and tumor biology. Melatonin, for instance, is a hormone with potent antioxidant and anti-inflammatory properties, known to have oncostatic effects, particularly in the regulation of cancer cell proliferation and apoptosis. In patients with cancer, melatonin levels are often significantly reduced, particularly in those with advanced disease. The depletion of melatonin in cancer patients has been linked to the disruption of circadian rhythms, immune suppression, and the promotion of tumor growth (Table 1).

Similarly, dopamine, a neurotransmitter involved in reward and pleasure pathways, also exerts anti-tumor effects

through its ability to modulate immune responses and inhibit angiogenesis, the process by which new blood vessels form to supply nutrients to growing tumors. Reduced levels of dopamine in cancer patients are associated with increased tumor aggressiveness and immune dysfunction. In contrast, serotonin, adrenaline, noradrenaline, cortisol, and histamine are often elevated in cancer patients, reflecting the body's heightened stress response. These neurotransmitters, particularly cortisol and histamine, can promote tumor growth by suppressing anti-tumor immunity, enhancing inflammation, and supporting cancer cell survival and metastasis.

In the context of metastatic NSCLC, understanding the interplay between inflammation, neurotransmitters, and tumor markers is crucial for unraveling the complex pathogenesis of the disease. This study aims to investigate the differences in inflammatory markers, neurotransmitter levels, and tumor markers between patients with stage IV metastatic NSCLC (adenocarcinoma) and those with early-stage NSCLC. We hypothesize that metastatic NSCLC is associated with increased systemic inflammation, altered neurotransmitter levels, and higher concentrations of tumor markers, which together reflect the progression and severity of the disease.

Specifically, we aim to quantify the levels of inflammatory cytokines such as TNF-alpha, IL-6, and IL-1beta, as well as acute-phase reactants like CRP, ferritin, and SAA, in both advanced and early-stage NSCLC patients. Additionally, we will measure the blood levels of key neurotransmitters, including melatonin, dopamine, serotonin, adrenaline, noradrenaline, cortisol, and histamine, to explore their potential role in cancer progression. Tumor markers, including CYFRA, carcinoembryonic antigen (CEA), CTCs, and ctDNA, will also be evaluated to assess their correlation with disease stage and metastatic potential. By comparing these biomarkers between patients with metastatic and early-stage NSCLC, this study seeks to provide insights into the pathophysiological mechanisms driving cancer progression. Understanding these differences may offer new therapeutic targets for inhibiting tumor growth and improving outcomes in patients with advanced NSCLC.

Table 1: Biomarkers in Inflammation, Neurotransmission, and Cancer Processes

Marker Name	General Biological Role and Role in Cancer Processes	Normal Ranges in Blood Plasma
TNF-alpha	Pro-inflammatory cytokine, involved in systemic inflammation and cancer progression by promoting tumor cell proliferation and survival.	1-15 pg/mL
CRP	Acute phase protein, marker of inflammation, often elevated in cancer due to ongoing systemic inflammatory response.	0-10 mg/L
Ferritin	Iron storage protein, elevated in chronic inflammation and cancer, reflecting increased iron metabolism needed by rapidly proliferating tumor cells.	30-300 ng/mL (varies by age and gender)
IL-1beta	Pro-inflammatory cytokine, involved in immune responses and inflammation, promotes tumor growth and survival.	0-5 pg/mL
IL-6	Pro-inflammatory cytokine, involved in cancer-related inflammation, promotes tumor cell proliferation, invasion, and metastasis.	<4.4 pg/mL
SAA	Acute phase protein, elevated during inflammation, associated with cancer progression and metastasis.	0-10 mg/L
ERS	Rate of erythrocyte sedimentation, elevated in inflammation and often associated with cancer due to chronic inflammatory processes.	0-20 mm/hr
Leukocytes in CBC	White blood cells, elevated counts indicate infection or inflammation, often seen in advanced cancer due to immune response.	4.5-11.0 x10^9/L
Melatonin	Antioxidant hormone, regulates circadian rhythms and has oncostatic effects, often decreased in cancer.	10-70 pg/mL at night
Dopamine	Neurotransmitter, modulates immune responses, typically decreased in cancer patients, contributing to immune suppression.	0-30 pg/mL
Serotonin	Neurotransmitter, elevated in cancer, promotes growth via immune system modulation and tumor cell survival.	101-283 ng/mL
Adrenalin	Stress hormone, increases heart rate and blood flow, elevated in cancer due to stress-response activation.	20-200 pg/mL
Noradrenalin	Stress hormone, involved in fight-or-flight response, elevated in cancer due to chronic stress.	70-1700 pg/mL

Cortisol	Stress hormone, regulates metabolism and immune function, elevated in cancer patients reflecting chronic stress.	6-23 µg/dL
Histamine	Mediator of allergic reactions, elevated in cancer, contributes to tumor progression via inflammation.	0.1-1.0 ng/mL
CYFRA	Cytokeratin fragment, tumor marker used for monitoring lung cancer progression.	<3.3 ng/mL
CEA	Oncofetal glycoprotein, elevated in various cancers, used as a tumor marker for monitoring disease progression.	<5 ng/mL
CTCs	Circulating tumor cells, presence indicates metastatic spread, a marker of disease burden and poor prognosis.	< 5 cells in 7.5 ml blood
ctDNA	Fragments of tumor DNA in the bloodstream, indicative of tumor burden and metastasis, used for monitoring cancer progression.	N/A (presence indicates metastasis)

2. Material and Methods

This study was designed to compare the biological profiles of inflammatory markers, neurotransmitters, and tumor markers in two distinct groups of patients diagnosed with non-small cell lung cancer (NSCLC) adenocarcinoma at different stages of the disease. The research was conducted at a tertiary cancer center where patient selection, data collection, and laboratory analyses were rigorously managed to ensure the accuracy and relevance of the findings.

Patient Selection

The study cohort consisted of two groups of patients, each with 41 individuals. Group I, the research group, included patients with advanced-stage IV NSCLC (adenocarcinoma, G3-G4) who had multiple metastases (MTS) in the liver, bones, brain, and adrenal glands. All patients in Group I had detectable circulating tumor cells (CTCs) and cell-free DNA (ctDNA) in their blood. Group II, the control group, comprised patients diagnosed with early-stage NSCLC (adenocarcinoma, G1-G3), without the presence of CTCs or ctDNA in their bloodstream. The patients were selected based on strict inclusion and exclusion criteria. The inclusion criteria for both groups were as follows: confirmed diagnosis of NSCLC adenocarcinoma through histopathological evaluation, no prior history of other malignancies, and adequate organ function as determined by routine clinical laboratory tests. For Group I, patients were required to have evidence of metastasis confirmed via imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI), as well as the presence of CTCs and ctDNA detected in the blood. The control group (Group II) consisted of patients with early-stage disease, confirmed to be CTC- and ctDNA-free through peripheral blood testing.

Exclusion criteria for both groups included patients undergoing immunotherapy or chemotherapy at the time of blood collection, the presence of infectious diseases, autoimmune disorders, or other systemic conditions that could potentially alter inflammatory markers or neurotransmitter profiles. The aim was to ensure that the data obtained would specifically reflect cancer-related alterations and not be influenced by extraneous medical conditions.

All patients provided written informed consent, and the study protocol was approved by the institutional ethics committee.

Blood Sample Collection and Processing

Peripheral blood samples were collected from all patients after overnight fasting to avoid any potential confounding effects of food intake on biomarker levels. A total of 10 mL of venous blood was drawn into EDTA-coated tubes to prevent clotting, and samples were immediately transported to the laboratory for processing. Plasma was separated by centrifuging the blood samples at 3000 revolutions per minute (rpm) for 15 minutes at 4°C. The plasma was then aliquoted and stored at -80°C until further analysis. All analyses were conducted within six months of sample collection to ensure the stability of the biomarkers.

Measurement of Inflammatory Markers

Inflammatory markers were quantified using enzyme-linked immunosorbent assay (ELISA) kits, which are highly sensitive and specific for detecting cytokines and acute-phase proteins in plasma. The following markers were measured:

- **TNF-alpha:** This pro-inflammatory cytokine was measured using a commercially available ELISA kit. The kit had a detection range of 1-15 pg/mL. Plasma levels of TNF-alpha were compared between the research and control groups.
- **C-reactive protein (CRP):** CRP, a well-established marker of systemic inflammation, was also quantified using an ELISA kit. The assay had a detection range of 0-10 mg/L. Elevated CRP levels are associated with ongoing inflammatory processes in cancer.
- **Ferritin:** Ferritin, a protein that stores iron and is elevated during chronic inflammation, was measured with an ELISA kit with a detection range of 30-300 ng/mL, depending on age and gender. Ferritin serves as both a marker of inflammation and iron metabolism, which is often altered in cancer patients.
- **IL-1beta:** This cytokine, involved in pro-inflammatory and immune responses, was measured with a detection range of 0-5 pg/mL.
- **IL-6:** A key cytokine in cancer-related inflammation, IL-6 was measured using an ELISA kit with a detection range of <4.4 pg/mL. IL-6 is known to promote tumor proliferation and metastasis in various cancers, including NSCLC.
- **Serum amyloid A (SAA):** SAA, an acute-phase protein elevated in systemic inflammation, was quantified using an ELISA kit with a detection range of 0-10 mg/L. Increased levels of SAA are often seen in cancer patients, particularly

in those with advanced-stage disease.

• **Erythrocyte sedimentation rate (ERS):** ERS is a nonspecific marker of inflammation, measured by the rate at which red blood cells settle in a test tube over a given period. ERS was determined using the Westergren method, and results were reported as millimeters per hour (mm/hr).

• **Leukocyte Count:** Leukocyte (white blood cell) counts were determined using automated hematology analyzers, and the results were expressed as cells per microliter of blood. Elevated leukocyte counts are a hallmark of inflammation and are frequently observed in cancer patients, particularly those with metastatic disease.

Measurement of Neuromediators

Blood levels of key neurotransmitters were assessed using immunoassays, which allow for the precise quantification of hormones and neurochemicals involved in the stress response. The following neuromediators were measured:

• **Melatonin:** Plasma levels of melatonin, a hormone involved in regulating circadian rhythms and possessing oncostatic properties, were measured using a melatonin-specific immunoassay. The normal range of melatonin in plasma is 10-70 pg/mL at night. Melatonin levels are often reduced in cancer patients, and a significant decrease was expected in the research group.

• **Dopamine:** Dopamine, a neurotransmitter involved in reward and immune regulation, was measured with an immunoassay. The detection range was 0-30 pg/mL. Decreased dopamine levels are often seen in cancer patients and may reflect impaired immune function.

• **Serotonin:** Serotonin, a neurotransmitter that influences mood and has been implicated in tumor growth, was measured using an immunoassay. The normal range for serotonin in blood is 101-283 ng/ml. Elevated serotonin levels are associated with cancer progression.

• **Adrenalin and Noradrenalin:** Both adrenalin and noradrenalin are stress hormones involved in the fight-or-flight response. Their levels were measured using immunoassays, with adrenalin ranging from 20-200 pg/mL and noradrenalin from 70-1700 pg/mL in normal plasma.

• **Cortisol:** Cortisol, a glucocorticoid hormone that regulates metabolism and immune responses, was measured using an immunoassay with a detection range of 6-23 µg/dL. Cortisol levels are often elevated in cancer patients due to chronic stress and immune suppression.

• **Histamine:** Histamine, a mediator of allergic responses, was measured using a histamine-specific immunoassay. The detection range was 0.1-1.0 ng/mL. Elevated histamine levels in cancer patients have been associated with tumor promotion through inflammation.

Measurement of Tumor Markers

Tumor markers were quantified to assess the burden of cancer and the presence of metastatic disease

• ***CYFRA 21-1:*** CYFRA is a fragment of cytokeratin 19, commonly elevated in lung cancer, especially NSCLC. It was measured using an ELISA kit with a detection range of <3.3 ng/mL. Elevated CYFRA levels are indicative of tumor burden and disease progression.

• ***Carcinoembryonic antigen (CEA):*** CEA is an oncofetal glycoprotein used as a tumor marker in various cancers, including NSCLC. CEA levels were quantified using an immunoassay, with a normal range of <5 ng/mL. Elevated levels indicate tumor growth and metastasis.

• ***Circulating Tumor Cells (CTCs):*** CTCs were detected in blood samples using a PCR-based technique that targets epithelial markers specific to tumor cells. The presence of CTCs in the bloodstream is a key indicator of metastatic potential and tumor spread. CTC quantification was reported as the number of cells per 7.5 mL of blood.

• ***Cell-free DNA (ctDNA):*** ctDNA, representing fragments of tumor-derived DNA in the bloodstream, was quantified using PCR-based techniques. The presence of ctDNA in the blood correlates with tumor burden and is a marker of metastasis. ctDNA levels were reported as the proportion of tumor-derived DNA fragments in the total cell-free DNA pool.

Reagents and standards required for the study were provided by the Department of Biotechnology, Foconsci Chemical Industry, Shandong, China.

Statistical Analysis: All data were analyzed using statistical software (SPSS, GraphPad). Descriptive statistics, including means, standard deviations, and ranges, were calculated for each biomarker. The mean values of each marker in the research and control groups were compared using independent t-tests to determine whether the differences between the two groups were statistically significant. A p-value of less than 0.05 was considered statistically significant, indicating that the differences in biomarker levels between the advanced and early-stage NSCLC groups were unlikely to be due to chance.

In addition to the t-tests, correlation analyses were performed to explore potential relationships between different biomarkers, such as the association between inflammatory markers and tumor burden (as reflected by CTC and ctDNA levels). Linear regression models were also employed to assess the extent to which inflammatory markers and neuromediators could predict tumor marker levels in the research group. All analyses were conducted with a 95%

3. Results

The study aimed to compare inflammatory markers, neurotransmitter levels, and tumor markers between two groups of NSCLC adenocarcinoma patients at different stages of disease progression. Group I, representing the research group, consisted of 41 patients with stage IV NSCLC adenocarcinoma with multiple metastases. Group II, the control group, also consisted of 41 patients but represented those with early-stage NSCLC (stage I), without detectable metastases. The biomarkers analyzed in this study provided significant insights into the differences in inflammation, neuroendocrine dysregulation, and tumor activity between advanced and early-stage NSCLC patients.

Inflammatory Markers

A key finding of this study was the substantial elevation in inflammatory markers in patients with advanced-stage

NSCLC (Group I) compared to those in the control group (Group II). Chronic inflammation has long been associated with cancer progression, and the elevated levels of pro-inflammatory cytokines in Group I patients corroborate this association.

• **TNF-alpha:** The tumor necrosis factor-alpha (TNF-alpha) levels were significantly elevated in the research group, showing a 70% increase compared to the control group. This pro-inflammatory cytokine plays a pivotal role in the cancer microenvironment by promoting tumor cell proliferation and survival. TNF-alpha is also known to enhance immune evasion by tumor cells and support the development of a tumor-friendly microenvironment through its influence on other cytokines and signaling pathways.

• **C-reactive protein (CRP):** CRP levels were increased by 20% in the research group. As a marker of systemic inflammation, CRP is frequently elevated in cancer patients and is often used as an indicator of cancer-related inflammation. The modest increase in CRP compared to other inflammatory markers suggests a baseline elevation in chronic inflammation in metastatic NSCLC patients.

• **Ferritin:** Ferritin, a marker of iron metabolism and inflammation, was elevated by 11% in the research group. Increased ferritin levels are common in cancer patients, reflecting both the body's need for enhanced iron storage to support tumor growth and the inflammatory environment that frequently accompanies advanced cancer.

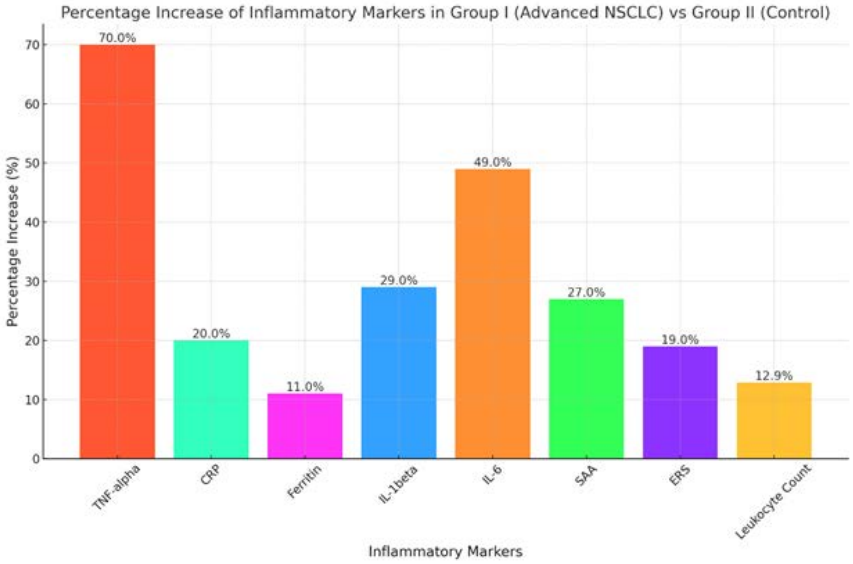
• **Interleukin-1beta (IL-1beta):** IL-1beta, a cytokine involved in regulating inflammatory and immune responses, was elevated by 29% in Group I. IL-1beta is known to promote tumor growth by fostering an inflammatory tumor microenvironment, which aids in tumor cell proliferation, invasion, and metastasis. The elevated levels of IL-1beta in the research group suggest a more aggressive tumor phenotype, driven by inflammatory signaling.

• **Interleukin-6 (IL-6):** IL-6 levels were significantly higher in the research group, with a 49% increase compared to the control group. IL-6 is a well-established pro-inflammatory cytokine that contributes to cancer-related inflammation, and its elevation is associated with poorer outcomes in NSCLC patients. IL-6 not only promotes tumor growth but also plays a role in immune evasion by cancer cells, making it a key factor in the progression of metastatic NSCLC.

• **Serum Amyloid A (SAA):** SAA levels were elevated by 27% in Group I. As an acute-phase protein, SAA is produced in response to inflammatory stimuli and is often elevated in patients with advanced cancer. The increase in SAA levels aligns with the general inflammatory state observed in metastatic NSCLC patients, further highlighting the role of chronic inflammation in tumor progression.

• **Erythrocyte Sedimentation Rate (ERS):** The erythrocyte sedimentation rate (ERS), a nonspecific marker of inflammation, was increased by 19% in the research group compared to the control group. ERS is often elevated in patients with chronic inflammatory conditions, including cancer, and its elevation in advanced NSCLC patients supports the notion that systemic inflammation is a hallmark of metastatic disease.

• **Leukocyte Count:** The total leukocyte count was elevated by 12.9% in the research group. An increase in leukocytes, particularly neutrophils, is a common feature of advanced cancer and reflects the body's response to the chronic inflammatory state induced by the tumor. Elevated leukocyte levels are often associated with poor prognosis in cancer patients, as they indicate an ongoing inflammatory response that may contribute to tumor progression (Figure 1).



The figure titled "Percentage Increase of Inflammatory Markers in Group I (Advanced NSCLC) vs Group II (Control)" visually represents the comparison of inflammatory marker levels between patients with advanced non-small cell lung cancer (NSCLC) (Group I) and those with early-stage NSCLC (Group II). Each bar corresponds to a specific inflammatory marker, with the height of the bar reflecting the percentage increase in that marker in the advanced-stage group compared to the control group. The chart shows that

• TNF-alpha had the highest increase (70%) in Group I, indicating a strong pro-inflammatory response.

• IL-6 also showed a significant increase (49%), reinforcing the role of inflammation in metastatic cancer progression.

• Other markers such as IL-1beta (29%), SAA (27%), and

Citation: Tavartkiladze, A., Gabadadze, S., Simonia, G., Lou, R., Kasradze, D., et al. (2024). The Role of Systemic Inflammation, Neurotransmitter Dysregulation, and Tumor Markers in the Progression of Metastatic NSCLC: Pathophysiological Insights and Therapeutic Implications. *J Cancer Rec, 2*(1), 1-22.

ERS (19%) exhibited moderate increases, while CRP (20%) and Ferritin (11%) showed more modest increases.

• The Leukocyte Count saw a smaller rise (12.9%) but still indicated elevated systemic inflammation in Group I.

• This chart underscores the profound differences in inflammatory activity between early and advanced NSCLC, highlighting the role of inflammation in cancer progression. The various colors used for the bars help distinguish between different markers, with the percentage increase clearly labeled above each bar for easy interpretation.

• This visualization helps convey how chronic inflammation is much more pronounced in patients with advanced NSCLC, contributing to tumor survival, proliferation, and metastasis.

Neuromediators

Neuromediators, or neurotransmitters, play a crucial role in regulating the body's stress response and immune function. Alterations in these chemicals have been associated with cancer progression, particularly in the context of stress-related hormones. The comparison between the two groups revealed significant dysregulation in neuromediator levels, particularly in patients with metastatic NSCLC.

• ***Melatonin:*** Melatonin levels were dramatically reduced in the research group, showing a 90% decrease compared to the control group. Melatonin is a hormone that regulates circadian rhythms and possesses oncostatic properties, meaning it can inhibit tumor growth and induce apoptosis (programmed cell death) in cancer cells. The marked reduction in melatonin levels in metastatic NSCLC patients suggests that the protective effects of this hormone are significantly diminished in advanced disease, contributing to unchecked tumor growth and progression.

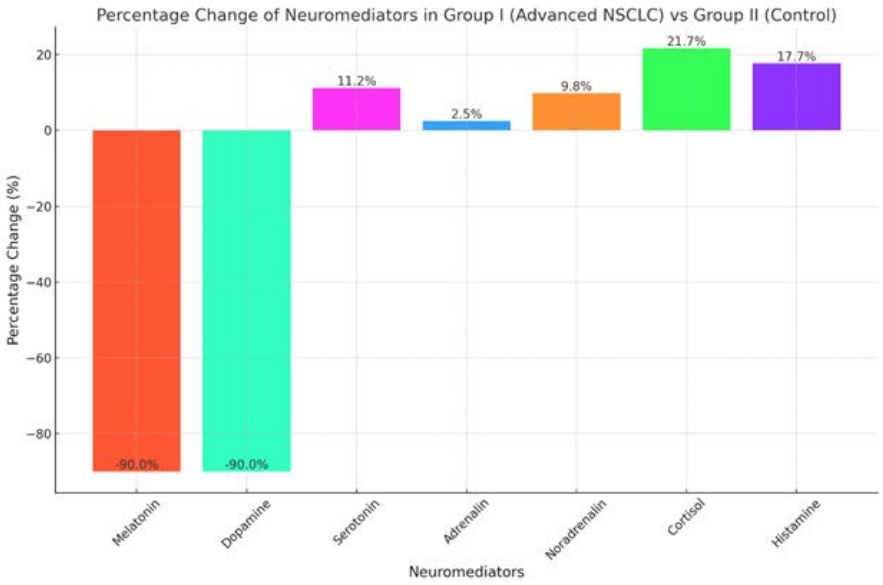
• ***Dopamine:*** Similarly, dopamine levels were reduced by 90% in the research group. Dopamine plays an important role in immune regulation and has been shown to inhibit angiogenesis (the formation of new blood vessels that feed tumors). The significant decrease in dopamine levels may reflect an impaired immune response in metastatic NSCLC patients, allowing tumors to grow and metastasize more easily.

• ***Serotonin:*** Serotonin levels were elevated by 11.2% in the research group. While serotonin is primarily known for its role in regulating mood, it also plays a role in modulating immune responses. Elevated serotonin levels have been linked to cancer progression, and the increase observed in this study suggests that serotonin may contribute to the aggressive behavior of metastatic NSCLC by influencing tumor survival and immune evasion.

Adrenalin and Noradrenalin: Both adrenalin and noradrenalin levels were elevated in the research group, with increases of 2.5% and 9.8%, respectively. These stress-related hormones are part of the body's fight-or-flight response and are often elevated in cancer patients due to chronic stress. The modest increases in adrenalin and noradrenalin in metastatic NSCLC patients suggest that the stress response is more pronounced in advanced disease, potentially contributing to tumor progression through immune suppression and enhanced angiogenesis.

• **Cortisol:** Cortisol levels were significantly elevated in the research group, with a 21.7% increase compared to the control group. Cortisol is a glucocorticoid hormone that regulates immune function and metabolism, and its chronic elevation in cancer patients is associated with immune suppression and poorer outcomes. The increase in cortisol levels in metastatic NSCLC patients may reflect the body's attempt to manage the stress of advanced disease, but it also likely contributes to immune dysfunction and tumor survival.

• **Histamine:** Histamine levels were elevated by 17.7% in the research group. Histamine is a mediator of allergic responses and inflammation, and its role in cancer is increasingly being recognized. Elevated histamine levels in metastatic NSCLC patients may contribute to tumor progression by promoting angiogenesis and immune evasion, as well as exacerbating the chronic inflammatory state observed in these patients (Figure #2).



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The figure titled "Percentage Change of Neuromediators in Group I (Advanced NSCLC) vs Group II (Control)" visually represents the differences in neuromediator levels between patients with advanced-stage NSCLC (Group I) and those with early-stage NSCLC (Group II).

***Key points from the* chart:** Melatonin and Dopamine levels were dramatically reduced, showing a 90% decrease in the advanced NSCLC group compared to the control. This reflects significant impairment in immune regulation and circadian rhythm control, contributing to cancer progression.

Serotonin levels increased by 11.2%, suggesting that this neuromediator, known for its role in mood regulation, also contributes to tumor survival and immune evasion. Adrenalin and Noradrenalin, both stress-related hormones, increased by 2.5% and 9.8%, respectively, highlighting the body's enhanced stress response in metastatic cancer. Cortisol levels saw a notable increase of 21.7%, indicating chronic stress and immune suppression in advanced NSCLC. Histamine levels rose by 17.7%, supporting its role in promoting tumor progression via inflammation and angiogenesis. This chart emphasizes the profound neuromediator dysregulation seen in advanced cancer patients, linking stress hormones to tumor progression.

Histamine elevation in cancer can be influenced by several factors, all of which are associated with the body's immune response, inflammation, and the tumor microenvironment. Here are the key mechanisms and influences that lead to increased histamine levels in cancer

Tumor-Induced Inflammation: Cancer often creates a pro-inflammatory environment to support its growth and survival. Histamine is a key mediator of inflammation, produced primarily by **mast cells, basophils,** and **macrophages** in response to inflammatory stimuli. Tumors stimulate these immune cells to release histamine, which in turn contributes to sustaining chronic inflammation, a hallmark of cancer progression.

Mast Cell Activation: Mast cells are a primary source of histamine in the body. In many cancers, especially solid tumors like lung cancer and breast cancer, the tumor microenvironment leads to mast cell recruitment and activation. These cells then release histamine, which can promote tumor angiogenesis (formation of new blood vessels), providing the tumor with necessary nutrients and oxygen for growth.

Immune Modulation: Histamine plays a complex role in the immune response. It can suppress the activity of certain immune cells, such as **cytotoxic T cells** and **natural killer (NK) cells,** which are responsible for identifying and killing cancer cells. By elevating histamine levels, tumors may create an immunosuppressive environment that allows them to evade immune detection and destruction. This immune evasion contributes to cancer progression and metastasis.

Histamine Receptors on Cancer Cells: Cancer cells may express histamine receptors (H1, H2, H3, and H4 receptors), which when activated by histamine can promote various cellular processes that are beneficial to tumor growth. For example:

- **H1 and H2 receptors** are associated with increased proliferation of cancer cells.
- **H4 receptors** are implicated in immune modulation and further promote tumor tolerance by reducing the anti-tumor immune response.

Angiogenesis and Tumor Growth: Histamine contributes to the process of **angiogenesis** (the formation of new blood vessels) within the tumor microenvironment. This occurs through its effects on **vascular endothelial growth factor (VEGF)** and other angiogenic factors, which are key in supplying the tumor with nutrients and oxygen. Elevated histamine levels can thus support faster tumor growth and metastasis by increasing blood flow to the cancerous tissues.

Hypoxia in Tumor Microenvironment: Cancerous tissues often exist in a state of **hypoxia** (low oxygen levels), which can stimulate the production of histamine. Hypoxia triggers the activation of hypoxia-inducible factors (HIFs) that induce angiogenesis and support tumor survival in low-oxygen conditions. Histamine, through its involvement in vasodilation and increased permeability, assists in resolving hypoxia by promoting blood vessel growth.

Histamine and Estrogen in Hormone-Responsive Cancers: In hormone-responsive cancers like **breast cancer,** histamine levels may be influenced by **estrogen**. Estrogen can increase mast cell activity, leading to higher histamine release. This interaction may help explain why elevated histamine is often observed in estrogen-driven tumors.

Chronic Allergic Conditions and Cancer: There is some evidence that patients with chronic allergic conditions, where histamine levels are frequently elevated due to constant immune stimulation, may have a higher risk of developing certain types of cancers. Chronic inflammation caused by long-term histamine release could promote a tumor-supportive environment in such individuals.

Histidine Decarboxylase (HDC) Overexpression:
Histamine is synthesized from the amino acid **histidine** by the enzyme **histidine decarboxylase (HDC).** Some cancers show overexpression of this enzyme, leading to increased histamine production within the tumor microenvironment. This heightened histamine production is associated with more aggressive cancer behavior and poorer patient outcomes. Histamine elevation in cancer is primarily driven by tumor-induced inflammation, mast cell activation, and immune modulation, all of which contribute to tumor growth, immune evasion, and angiogenesis. Understanding the role of histamine in cancer progression has led to research on potential therapeutic strategies, such as **histamine receptor blockers,** to mitigate its pro-tumor effects and improve cancer outcomes.

Histamine promotes angiogenesis, the process of new blood vessel formation, through several key mechanisms that involve its interaction with various cells in the tumor microenvironment, signaling molecules, and histamine receptors. Angiogenesis is crucial for tumors to grow and metastasize, as it provides the tumor with essential nutrients and oxygen. Here's how histamine contributes to this process:

Activation of Histamine Receptors: Histamine exerts its effects through binding to four types of histamine receptors: **H1, H2, H3,** and **H4** receptors. Of these, **H1** and **H2** receptors are primarily involved in promoting angiogenesis. These receptors are present on endothelial cells (which line blood vessels), immune cells, and various other cells within the tumor microenvironment.

- **H1 receptors** are located on endothelial cells and, when activated by histamine, lead to increased vascular permeability, dilation of blood vessels, and endothelial cell proliferation.
- **H2 receptors** play a role in the proliferation and migration of endothelial cells, essential steps in angiogenesis.

Increase in Vascular Permeability: Histamine is well-known for its ability to increase **vascular permeability**, which allows proteins and other molecules to leak from the bloodstream into surrounding tissues. This leakage creates a more favorable environment for angiogenesis by enabling the migration of endothelial cells into the tumor microenvironment. Histamine-induced permeability also allows the diffusion of nutrients and pro-angiogenic factors like **vascular endothelial growth factor (VEGF)** into the area around the tumor.

Stimulation of Pro-Angiogenic Factors: Histamine influences the release of various **pro-angiogenic factors**, particularly **VEGF** (vascular endothelial growth factor), which is one of the most important mediators of angiogenesis. Through the activation of histamine receptors on endothelial cells and other immune cells, histamine increases the production and release of VEGF in the tumor microenvironment. VEGF then acts on endothelial cells to promote their proliferation, migration, and the formation of new blood vessels.

Additionally, histamine stimulates the release of other pro-angiogenic molecules, such as:

- **Basic fibroblast growth factor (bFGF),** which also promotes the proliferation and migration of endothelial cells.
- **Interleukin-8 (IL-8),** a cytokine known to facilitate angiogenesis by attracting and activating endothelial cells.

Endothelial Cell Proliferation and Migration: Histamine directly promotes the **proliferation and migration of endothelial cells,** which are critical steps in angiogenesis. By binding to H1 and H2 receptors on endothelial cells, histamine activates signaling pathways such as the **phosphoinositide 3-kinase (PI3K)/Akt** pathway and the **extracellular signal-regulated kinase (ERK)** pathway, both of which are known to enhance cell survival, migration, and proliferation.

- **Proliferation:** Endothelial cells multiply in response to histamine, contributing to the expansion of the blood vessel network around the tumor.
- **Migration:** Histamine induces the movement of endothelial cells toward areas of low oxygen (hypoxia) and high concentrations of angiogenic factors, which are often found in tumors.

Interaction with Hypoxia-Inducible Factors (HIFs): Tumors are frequently **hypoxic** (low in oxygen), which triggers the stabilization and activation of **hypoxia-inducible factors (HIFs),** particularly HIF-1alpha. **HIFs play** a central role in promoting angiogenesis by inducing the expression of VEGF and other angiogenic factors. Histamine can enhance the activity of HIFs, particularly in hypoxic tumor environments, further boosting the production of pro-angiogenic factors and facilitating blood vessel formation.

Modulation of the Immune System: Histamine's effects on the immune system also indirectly promote angiogenesis. Histamine can modulate the activity of immune cells like **macrophages, mast cells,** and **basophils**, encouraging them to release pro-angiogenic factors. Tumor-associated macrophages (TAMs), for instance, are known to secrete VEGF and other growth factors that stimulate angiogenesis. By interacting with histamine receptors on these immune cells, histamine promotes the secretion of VEGF and other cytokines that contribute to the angiogenic process.

Promotion of Extracellular Matrix Remodeling: For angiogenesis to occur, endothelial cells must degrade and move through the **extracellular matrix (ECM).** Histamine can upregulate enzymes called **matrix metalloproteinases (MMPs),** which break down the ECM, creating space for new blood vessels to form. This remodeling of the ECM is essential for the migration of endothelial cells and the establishment of new blood vessels in the tumor microenvironment.

Histamine's Synergy with Other Angiogenic Pathways: Histamine often works in synergy with other angiogenic factors and signaling pathways. For example, histamine enhances the angiogenic response initiated by VEGF and bFGF. It can also act in concert with inflammatory cytokines like **tumor necrosis factor-alpha (TNF-alpha)** and **interleukin-6 (IL-6),** which are frequently elevated in the tumor microenvironment and contribute to both inflammation and angiogenesis. Histamine promotes angiogenesis in cancer through multiple mechanisms, including increasing vascular permeability, stimulating the release of VEGF and other pro-angiogenic factors, activating endothelial cell proliferation and migration, and enhancing extracellular matrix remodeling. By fostering a pro-angiogenic environment, histamine facilitates tumor growth, survival, and metastasis, making it a key player in the progression of many cancers. These effects underscore the potential therapeutic interest in targeting histamine receptors or histamine signaling pathways to inhibit angiogenesis and slow down cancer progression. Histamine has a complex role in modulating tumor immunity,

influencing both pro- and anti-tumor immune responses. Its effects on immune cells depend on the context of the tumor microenvironment, the types of histamine receptors involved, and the concentration of histamine. Here are the main ways in which histamine affects tumor immunity

Modulation of Immune Cell Activity: Histamine interacts with various immune cells, including **macrophages, dendritic cells (DCs), natural killer (NK) cells, T cells,** and **myeloid-derived suppressor cells (MDSCs**), which can either promote or inhibit the immune response against tumors. The four types of histamine receptors (H1, H2, H3, and H4) found on immune cells mediate these effects.

Macrophages

Histamine can polarize macrophages toward different phenotypes, affecting their tumoricidal (anti-tumor) or tumor-promoting roles.

• **M1 macrophages** (pro-inflammatory, tumoricidal) are stimulated by histamine to release inflammatory cytokines like **TNF-alpha** and **interleukin-1 (IL-1)**, which can help kill tumor cells.

• **M2 macrophages** (pro-tumor, immunosuppressive) are also influenced by histamine, which can promote the M2 phenotype in certain contexts. M2 macrophages release factors like **IL-10** and **VEGF** that suppress immune responses and promote tumor growth and angiogenesis.

Natural Killer (NK) Cells

NK cells are critical for detecting and destroying tumor cells, but histamine can suppress their activity. By binding to **H2 receptors** on NK cells, histamine reduces their ability to secrete cytotoxic factors like **interferon-gamma (IFN-γ)** and **granzyme B,** weakening their capacity to kill tumor cells. This leads to a reduced anti-tumor immune response, aiding tumor evasion.

Dendritic Cells (DCs)

Histamine affects the ability of DCs to activate T cells:

• Through **H1 receptor activation**, histamine can promote the maturation and antigen-presenting activity of DCs, enhancing T cell-mediated immune responses.

• However, activation of **H2 receptors** can suppress DC function, leading to decreased T cell activation and impaired anti-tumor immunity. This dual effect depends on the balance of receptor activation.

• **T Cell Regulation** - Histamine has differential effects on T cells depending on the type of receptor activated and the type of T cell involved:

• **H1 receptor activation** can enhance the proliferation and activation of **Th1 cells,** which promote anti-tumor immunity by releasing pro-inflammatory cytokines such as **IFN-γ** and **IL-2.**

• **H2 receptor activation**, on the other hand, tends to inhibit **Th1** responses and favors the development of **Th2 cells**, which produce anti-inflammatory cytokines like **IL-4** and **IL-10.** This shift toward a Th2-dominated response suppresses effective anti-tumor immunity.

• Histamine can also promote **regulatory T cells (Tregs)** through **H2 receptor** activation, which contributes to immune suppression in the tumor microenvironment. Tregs inhibit effector T cells, dampening the immune response against the tumor and promoting immune evasion.

Myeloid-Derived Suppressor Cells (MDSCs): Histamine can enhance the recruitment and activation of **MDSCs**, a population of immune cells that suppress the immune system and promote tumor progression. MDSCs inhibit the activity of T cells and NK cells, allowing tumors to evade immune surveillance. By binding to **H2 receptors** on MDSCs, histamine increases their immunosuppressive functions, which include producing **arginase** and **nitric oxide** to dampen the immune response.

Tumor-Associated Mast Cells: Mast cells are major producers of histamine, especially in the tumor microenvironment. When activated, mast cells release histamine along with other factors that modulate the immune response

In some contexts, mast cells can promote tumor immunity by releasing **pro-inflammatory** cytokines and recruiting immune cells like T cells and NK cells. However, more commonly, mast cells contribute to **tumor-promoting inflammation**. By releasing histamine and **IL-10,** they create an immunosuppressive environment that fosters tumor growth and angiogenesis while dampening the anti-tumor immune response. **Histamine and Tumor Immune Evasion** - Histamine helps tumors evade immune destruction by creating an immunosuppressive microenvironment

• By suppressing the cytotoxic functions of NK cells and T cells through **H2 receptor** activation, histamine reduces the body's ability to recognize and kill tumor cells.

• Histamine also promotes the expansion and activity of immunosuppressive cells such as Tregs and MDSCs, both of which inhibit effective anti-tumor immune responses.

• Additionally, by enhancing **angiogenesis**, histamine supports the growth of the tumor's blood supply, which can also contribute to immune evasion by shielding the tumor from immune surveillance.

Histamine's Role in Tumor Tolerance: Histamine promotes **tumor tolerance**, a state in which the immune system becomes less responsive to the tumor

• Through chronic activation of **H2 receptors** on immune cells, histamine continuously dampens the anti-tumor response.

• This leads to a **tolerogenic environment** where immune cells, particularly T cells, are less likely to attack tumor cells, allowing the tumor to grow unchecked.

• **Histamine's Dual Role** - Interestingly, histamine's effect on tumor immunity can be **dualistic**, meaning it can either enhance or suppress immune responses depending on the concentration and the specific receptors involved:

• At **low concentrations**, histamine may promote immune activation through **H1 receptor** stimulation, enhancing inflammatory and anti-tumor responses.

• At **high concentrations,** typically seen in the tumor microenvironment, histamine predominantly activates **H2 receptors**, which suppress immune responses and support tumor growth.

Histamine plays a multifaceted role in regulating tumor immunity. It can both enhance and suppress immune responses, but in the tumor microenvironment, histamine tends to favor immunosuppression and immune evasion, contributing to cancer progression. This is mainly achieved through **H2 receptor-mediated** inhibition of NK cells, T cells, and the promotion of immunosuppressive cells like MDSCs and Tregs. Understanding the dual nature of histamine's role in tumor immunity has led to interest in targeting histamine signaling, particularly **H2 receptor antagonists**, as potential therapies to improve immune responses in cancer treatment.

Can histamine inhibitors slow tumor growth? Yes, histamine inhibitors, particularly **histamine receptor antagonists,** have the potential to slow tumor growth by targeting the immunosuppressive and pro-tumorigenic effects of histamine in the tumor microenvironment. This therapeutic approach is based on the understanding that histamine can promote tumor growth, angiogenesis, and immune evasion, and that inhibiting histamine activity could mitigate these effects. Here's how histamine inhibitors can slow tumor growth.

Histamine Receptor Antagonists: Histamine exerts its effects through four histamine receptors: **H1, H2, H3,** and **H4**. The two most commonly targeted receptors in cancer therapy are **H1** and **H2**, as they are involved in promoting inflammation, immune suppression, and angiogenesis in tumors.

H2 Receptor Antagonists

H2 receptor antagonists (also known as **H2 blockers**) such as **cimetidine** and **ranitidine** are primarily used to reduce stomach acid production in conditions like ulcers. However, several studies suggest that H2 blockers can also have anti-cancer effects by reducing the pro-tumor effects of histamine.

• ***Immune Modulation:*** H2 blockers can enhance anti-tumor immunity by preventing the immunosuppressive effects of histamine. By blocking the H2 receptor, these antagonists may reduce the recruitment and activity of **myeloid-derived suppressor cells (MDSCs)** and **regulatory T cells (Tregs)**, both of which suppress the immune response against tumors. This can lead to increased activation of **cytotoxic T cells** and **natural killer (NK) cells**, allowing the immune system to better recognize and destroy cancer cells.

• ***Inhibition of Angiogenesis:*** H2 receptor antagonists can reduce tumor-associated angiogenesis by blocking the histamine-induced release of pro-angiogenic factors like **vascular endothelial growth factor (VEGF).** By inhibiting the formation of new blood vessels that supply the tumor with nutrients and oxygen, H2 blockers can help slow tumor growth and metastasis.

• ***Clinical Studies:*** Several studies have suggested that H2 receptor antagonists, particularly **cimetidine**, can improve outcomes in cancer patients. For example, some research has shown that cimetidine treatment in colorectal cancer patients can improve survival by enhancing immune responses and reducing tumor growth. Other studies have demonstrated similar effects in cancers such as gastric, lung, and melanoma.

H1 Receptor Antagonists

H1 receptor antagonists (commonly known as **antihistamines**) like **diphenhydramine** and **loratadine** are widely used to treat allergic reactions. H1 receptor antagonists also have potential anti-tumor effects, although their role is less studied compared to H2 blockers.

• **Reduction of Inflammation:** H1 receptor antagonists can reduce the inflammatory environment in tumors by blocking histamine's action on H1 receptors. This can lower the production of inflammatory cytokines like **TNF-alpha** and **IL-6,** which contribute to tumor growth and metastasis.

• **Anti-Angiogenic Effects:** Like H2 blockers, H1 receptor antagonists can inhibit histamine-induced angiogenesis, potentially slowing tumor growth by cutting off the tumor's blood supply.

Inhibition of Mast Cells: Mast cells are a primary source of histamine in the tumor microenvironment. By stabilizing mast cells or inhibiting their degranulation, histamine release can be reduced. Certain drugs, like **cromolyn sodium,** are known as **mast cell stabilizers** and can prevent the release of histamine and other inflammatory mediators from mast cells. By inhibiting histamine release, mast cell stabilizers could help slow tumor progression by reducing the pro-tumor effects of histamine, including angiogenesis and immune suppression.

Blocking Histamine Synthesis: Histamine is synthesized from the amino acid histidine by the enzyme **histidine decarboxylase (HDC).** Some cancers overexpress HDC, leading to increased histamine production within the tumor microenvironment. Inhibiting HDC activity can reduce histamine levels and potentially limit its tumor-promoting effects. Experimental drugs that inhibit HDC are under investigation for their potential to slow tumor growth.

Enhancing Immunotherapy: Histamine inhibitors, particularly H2 receptor antagonists, may enhance the efficacy of immunotherapies by improving the body's natural anti-tumor immune response. Immunotherapies, such as **checkpoint inhibitors** and **CAR-T cell therapy**, rely on a robust immune response to eliminate cancer cells. Since histamine can suppress immune activity, blocking its effects may improve the outcomes of immunotherapy by reducing immune suppression within the tumor microenvironment.

Evidence from Preclinical and Clinical Studies: Several studies support the idea that histamine inhibition can slow tumor growth:

• **Preclinical Studies:** Animal models of cancer have shown that H2 blockers can reduce tumor growth and metastasis. In mouse models of **melanoma** and **colorectal cancer,** cimetidine treatment was associated with reduced tumor growth, lower levels of immunosuppressive cells, and increased survival rates.

• **Clinical Evidence:** Some retrospective clinical studies have suggested that patients taking H2 blockers like cimetidine for non-cancer conditions may have a lower risk of cancer

progression or recurrence. For example, in a study of **colorectal cancer** patients, those who received cimetidine alongside standard treatment had improved survival rates compared to those who did not receive the H2 blocker.

Histamine inhibitors, particularly **H2 receptor antagonists** like cimetidine, have shown potential to slow tumor growth by reducing histamine's pro-tumor effects, including immune suppression, inflammation, and angiogenesis. While more research is needed to fully understand the mechanisms and potential of histamine inhibitors in cancer therapy, existing evidence suggests that these drugs could serve as adjuncts to traditional cancer treatments and immunotherapies to improve patient outcomes.

Can histamine Inhibitors Be Used Alongside Immunotherapy?

Yes, **histamine inhibitors,** particularly **H2 receptor antagonists** like **cimetidine**, can potentially be used alongside immunotherapy to enhance its effectiveness. The rationale for combining histamine inhibitors with immunotherapy stems from their ability to counteract the immunosuppressive effects of histamine within the tumor microenvironment, which may improve the body's natural immune response to cancer. Here's how histamine inhibitors can complement immunotherapy

Reducing Immune Suppression: Histamine plays a significant role in suppressing the immune system in the tumor microenvironment, particularly through **H2 receptor activation** on immune cells. By blocking H2 receptors, histamine inhibitors can:

• ***Reduce the activity of regulatory T cells (Tregs):*** Tregs suppress the immune system's ability to attack tumor cells. H2 receptor antagonists can reduce the recruitment and suppressive function of Tregs, allowing the immune system to mount a stronger anti-tumor response.

• ***Inhibit Myeloid-Derived Suppressor Cells (MDSCs):*** MDSCs are another population of immune cells that suppress T cell and NK cell activity in the tumor. H2 receptor antagonists can reduce the presence and activity of MDSCs, enhancing the effectiveness of immunotherapies like **checkpoint inhibitors**. By alleviating immune suppression, histamine inhibitors may help boost the effects of immunotherapies that rely on the activation of cytotoxic T cells and NK cells to target and kill cancer cells.

Enhancing Checkpoint Inhibitor Therapy - **Checkpoint inhibitors,** such as **PD-1/PD-L1 inhibitors** (e.g., pembrolizumab, nivolumab) and **CTLA-4 inhibitors** (e.g., ipilimumab), work by releasing the "brakes" on the immune system, allowing T cells to attack cancer cells more effectively. However, the success of checkpoint inhibitors can be limited by the immunosuppressive tumor microenvironment. Histamine inhibitors may enhance the efficacy of checkpoint inhibitors by

• ***Restoring T Cell Activity:*** By blocking H2 receptor-mediated suppression of T cells, histamine inhibitors can improve T cell function, making checkpoint inhibitors more effective in activating the immune response against tumors.

• ***Reducing Tumor-Promoting Inflammation:*** Histamine's role in promoting tumor-associated inflammation can be diminished by H2 blockers, thereby creating a more favorable environment for checkpoint inhibitors to work.

Synergy with CAR-T Cell Therapy - CAR-T cell therapy is a type of immunotherapy where a patient's T cells are genetically modified to express chimeric antigen receptors (CARs) that allow them to specifically target cancer cells. One of the challenges with CAR-T cell therapy is the immunosuppressive tumor microenvironment, which can limit the effectiveness of the CAR-T cells.

Histamine Inhibition: could help reduce the suppressive signals within the tumor microenvironment, allowing CAR-T cells to function more efficiently and persist longer in attacking the cancer.

Inhibition of Angiogenesis - Histamine contributes to **angiogenesis** (the formation of new blood vessels) in tumors, which supports tumor growth and protects the tumor from immune attack by creating physical barriers. H2 blockers can reduce histamine-induced angiogenesis, potentially improving the ability of immune cells, including those activated by immunotherapy, to access and penetrate the tumor.

Reduction of Tumor-Associated Mast Cells - Mast Cells: are a major source of histamine in the tumor microenvironment and are often involved in promoting tumor growth and immune evasion. Histamine inhibitors can reduce mast cell activity, thereby reducing the release of histamine and other immunosuppressive factors. This reduction in mast cell-driven immunosuppression could allow immunotherapies to work more effectively.

Histamine Inhibitors and Combination Immunotherapy Approaches: In some cancers, combining immunotherapies has shown significant success. Histamine inhibitors could be integrated into these combination approaches

• **Checkpoint inhibitors + histamine inhibitors:** Histamine inhibitors could be used alongside PD-1/PD-L1 or CTLA-4 inhibitors to improve immune activation in the tumor microenvironment.

• **Cancer vaccines + histamine inhibitors:** Cancer vaccines aim to stimulate the immune system to recognize and attack cancer cells. By reducing histamine-induced immune suppression, histamine inhibitors could help enhance the immune response generated by cancer vaccines.

Potential Use of H1 Receptor Antagonists - While **H2 receptor antagonists** are the most studied in cancer, **H1 receptor antagonists** (e.g., antihistamines like loratadine and diphenhydramine) might also have a role in combination with immunotherapy. H1 blockers can reduce inflammation and histamine-induced angiogenesis, which may also support the immune system's ability to attack tumors.

Clinical Studies and Evidence: There is growing clinical and preclinical evidence supporting the use of histamine

inhibitors alongside immunotherapy:

• **Cimetidine** has been investigated in combination with cancer vaccines and other immunotherapies. Some studies have shown that cimetidine can enhance the anti-tumor effects of these therapies, particularly in cancers such as colorectal cancer, melanoma, and gastric cancer.

• **Preclinical studies** using mouse models of cancer have demonstrated that blocking histamine receptors can enhance the efficacy of immunotherapy, leading to better tumor control and prolonged survival.

Challenges and Considerations

While the combination of histamine inhibitors and immunotherapy is promising, there are several challenges and considerations

• **Tumor heterogeneity:** Different tumors may respond differently to histamine inhibitors depending on their microenvironment, histamine receptor expression, and immune cell composition.

• **Optimal timing and dosing:** The timing and dosage of histamine inhibitors in combination with immunotherapy are critical. Researchers need to determine the best protocols to maximize immune activation without causing adverse effects.

• **Clinical trials:** More clinical trials are needed to validate the benefits of combining histamine inhibitors with immunotherapy across different cancer types.

Histamine inhibitors, especially **H2 receptor antagonists**, hold promise as an adjunct to immunotherapy. By reducing immune suppression, promoting T cell activation, and limiting tumor-promoting angiogenesis, histamine inhibitors could enhance the effectiveness of immunotherapies such as checkpoint inhibitors and CAR-T cell therapy. While more research is needed to fully establish their role in combination cancer therapies, histamine inhibitors represent a potential strategy to improve patient outcomes in cancers where the immune system plays a central role in tumor control.

Tumor Markers

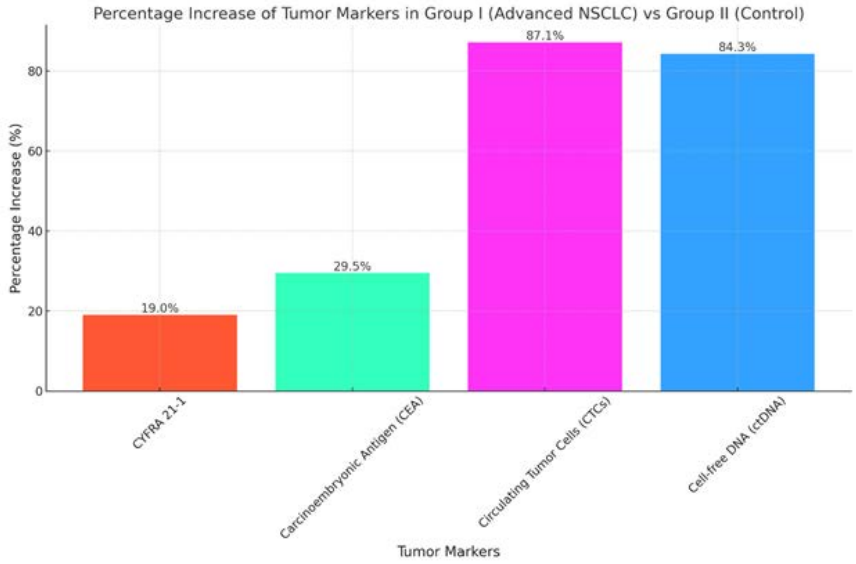
Tumor markers are proteins or other molecules produced by cancer cells that can be detected in the blood and are often used to assess tumor burden and progression. The comparison between the two groups revealed significant differences in tumor marker levels, with patients in the research group showing markedly higher levels of all measured markers.

• ***CYFRA 21-1:*** CYFRA, a fragment of cytokeratin 19, was elevated by 19% in the research group. CYFRA is commonly used as a tumor marker in NSCLC, particularly in patients with advanced disease. The increase in CYFRA levels in metastatic NSCLC patients reflects the higher tumor burden and greater degree of tumor cell proliferation in these individuals.

• ***Carcinoembryonic Antigen (CEA):*** CEA levels were significantly elevated in the research group, with a 29.5% increase compared to the control group. CEA is a glycoprotein that is often elevated in various cancers, including NSCLC, and is used as a marker of tumor progression. The substantial increase in CEA levels in metastatic NSCLC patients highlights the aggressive nature of advanced disease and the extensive tumor burden in these patients.

• ***Circulating Tumor Cells (CTCs):*** The presence of CTCs in the blood is a key indicator of metastatic potential, and CTC levels were elevated by 87.1% in the research group. CTCs are shed by the primary tumor into the bloodstream, where they can travel to distant organs and establish metastases. The significant increase in CTC levels in metastatic NSCLC patients indicates a high degree of tumor shedding and a greater likelihood of metastatic spread.

• ***Cell-free DNA (ctDNA):*** Similar to CTCs, ctDNA represents fragments of tumor-derived DNA in the bloodstream. ctDNA levels were elevated by 84.3% in the research group, reflecting the higher tumor burden and increased tumor cell turnover in metastatic NSCLC patients. The presence of ctDNA in the blood is a marker of advanced disease and is often associated with poorer outcomes (Figure 3).



Citation: Tavartkiladze, A., Gabadadze, S., Simonia, G., Lou, R., Kasradze, D., et al. (2024). The Role of Systemic Inflammation, Neurotransmitter Dysregulation, and Tumor Markers in the Progression of Metastatic NSCLC: Pathophysiological Insights and Therapeutic Implications. *J Cancer Rec, 2*(1), 1-22.

The figure titled "Percentage Increase of Tumor Markers in Group I (Advanced NSCLC) vs Group II (Control)" illustrates the significant differences in tumor marker levels between patients with advanced-stage NSCLC and those with early-stage disease.

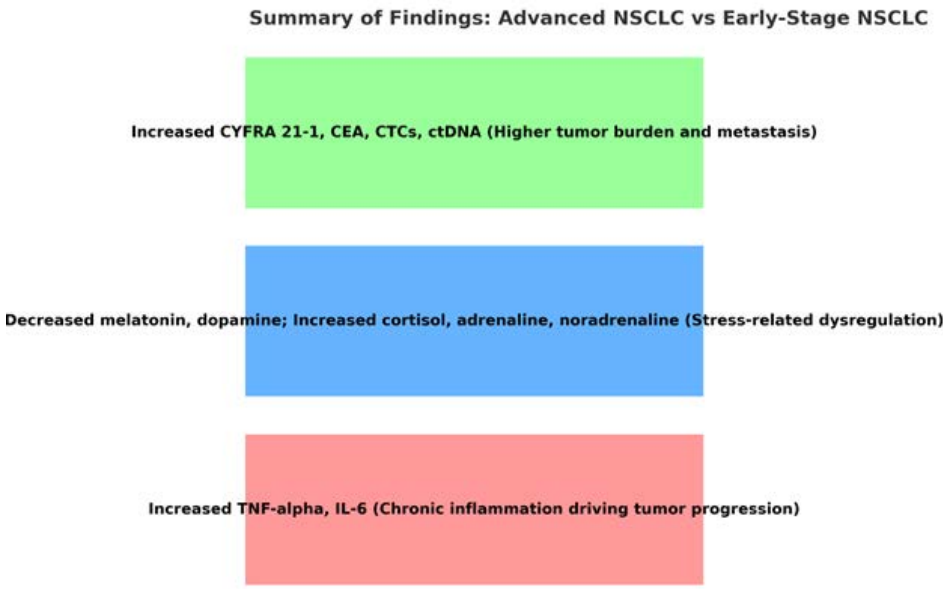
Key Points from the Chart

• CYFRA 21-1 levels increased by 19%, indicating higher tumor cell proliferation in advanced NSCLC.
• Carcinoembryonic Antigen (CEA) levels rose by 29.5%, highlighting the aggressive nature of metastatic NSCLC.
• Circulating Tumor Cells (CTCs) showed the highest increase at 87.1%, suggesting substantial tumor shedding and metastatic potential in Group I.
• Cell-free DNA (ctDNA) levels increased by 84.3%, reflecting the high tumor burden and cell turnover in metastatic patients.
• This chart underscores the elevated tumor activity and burden in advanced NSCLC, emphasizing the role of tumor markers in assessing disease progression and metastatic potential.

Summary of Findings

The results of this study demonstrate that patients with advanced NSCLC (adenocarcinoma) exhibit significantly higher levels of inflammatory markers, neuromediator dysregulation, and tumor markers compared to patients with early-stage NSCLC. The pronounced elevation in pro-inflammatory cytokines, such as TNF-alpha and IL-6, underscores the role of chronic inflammation in tumor progression and metastasis. In parallel, the marked decrease in protective neuromediators like melatonin and dopamine, coupled with the increase in stress-related hormones such as cortisol, adrenaline, and noradrenaline, highlights the dysregulation of the stress response in advanced NSCLC. This imbalance in neuromediator levels suggests that chronic stress and the disruption of circadian rhythms play a role in weakening the immune system and promoting tumor growth.

Moreover, the significant increase in tumor markers like CYFRA 21-1, CEA, circulating tumor cells (CTCs), and cell-free DNA (ctDNA) in the research group reflects the higher tumor burden and greater metastatic potential in advanced NSCLC patients. The presence of CTCs and ctDNA in particular is indicative of active tumor cell dissemination and suggests that these patients have a greater likelihood of developing distant metastases. The combination of heightened inflammatory activity, immune suppression via altered neuromediator levels, and elevated tumor markers creates a tumor-supportive environment that facilitates cancer progression. This multi-faceted disruption, involving both the immune and endocrine systems, highlights the complexity of cancer's influence on the body and the importance of targeting multiple pathways in treatment strategies. These findings support the idea that therapies aimed at reducing systemic inflammation, restoring neurotransmitter balance, and targeting circulating tumor biomarkers could be beneficial in managing advanced NSCLC and potentially improving patient outcomes (Figure 4)



This figure (scheme) highlights the key areas of inflammatory markers, neuromediator dysregulation, and tumor markers, showing how they differ in advanced NSCLC compared to early-stage NSCLC.

4. Discussion

The findings of this study demonstrate a significant association between elevated inflammatory markers, neuromediator imbalances, and increased tumor marker levels in patients with advanced-stage non-small cell lung cancer (NSCLC), particularly those with metastatic adenocarcinoma. The clear differences between these patients and those in the control group with early-stage NSCLC highlight the multifaceted role that systemic inflammation, chronic stress, and neurotransmitter dysregulation play in tumor progression and metastasis.

Inflammatory Markers and Tumor Progression

The markedly elevated levels of pro-inflammatory cytokines such as **TNF-alpha, IL-6, CRP,** and **IL-1beta** observed in patients with stage IV NSCLC underscore the critical role that systemic inflammation plays in cancer progression. These cytokines are known to support tumor growth through several mechanisms, including enhancing the tumor microenvironment, promoting angiogenesis, and enabling immune evasion. **TNF-alpha** and **IL-6** are particularly significant in cancer-related inflammation, as they contribute to both the local and systemic environments that allow cancer to thrive. TNF-alpha, for instance, can promote tumor cell proliferation, resist apoptosis, and enhance the metastatic potential of cancer cells through various pathways, including the nuclear factor-kappa B (NF-κB) signaling pathway.

IL-6, another key cytokine elevated in advanced NSCLC, not only facilitates tumor progression by promoting angiogenesis and immune evasion but also acts as a prognostic marker for poor outcomes in cancer patients. Elevated **CRP** and **ferritin** levels reflect the body's response to chronic inflammation, both of which are indicative of ongoing systemic inflammatory activity. **CRP** is an acute-phase protein that is elevated during systemic inflammation and often correlates with the degree of tumor burden. Similarly, increased **ferritin** levels, which are common in cancer patients, can be attributed to the altered iron metabolism seen in cancer, where tumors often hijack iron for their growth and proliferation.

The rise in **serum amyloid A (SAA)** and **erythrocyte sedimentation rate (ERS)** further supports the notion that metastatic NSCLC is accompanied by a chronic inflammatory state. **SAA** is another acute-phase protein elevated in response to inflammatory signals, and its increase in advanced cancer patients is consistent with the elevated pro-inflammatory cytokines observed. The heightened **ERS**, a nonspecific marker of inflammation, further illustrates the widespread systemic inflammation present in these patients.

Neuromediator Dysregulation and Stress Response

One of the most striking findings in this study is the significant imbalance in neuromediator levels in patients with advanced NSCLC. The profound reduction in **melatonin** and **dopamine** levels suggests a dysregulation of the body's circadian and stress-response systems. **Melatonin**, a hormone produced by the pineal gland, is not only involved in regulating circadian rhythms but also possesses powerful anti-cancer properties, including antioxidant, anti-inflammatory, and anti-proliferative effects. The sharp decrease in melatonin observed in stage IV NSCLC patients likely reflects the disrupted circadian rhythms commonly seen in advanced cancer and may also indicate a loss of melatonin's protective oncostatic effects, which could otherwise help suppress tumor growth and enhance the body's immune response.

Dopamine, another neuromodulator with critical immune-regulating properties, was also significantly decreased in advanced NSCLC patients. Dopamine plays a role in modulating the immune system by inhibiting angiogenesis and enhancing immune cell activity. Its depletion in advanced cancer may contribute to the immune dysfunction observed in these patients, particularly in relation to tumor immune evasion. The reduction of both melatonin and dopamine, two keys protective neuromediators, suggests that patients with advanced NSCLC are experiencing significant disruptions in both their circadian and immune-regulatory systems, leading to a diminished capacity to mount effective immune responses against tumor cells.

Conversely, the elevated levels of **serotonin, adrenalin, noradrenalin, cortisol**, and **histamine** in patients with advanced NSCLC point to an overactive stress-response system. These neurotransmitters and hormones are associated with the body's response to chronic stress, and their increased levels can have several detrimental effects on tumor progression. **Cortisol**, the primary stress hormone, is known to suppress immune function, particularly by reducing the activity of cytotoxic T cells and natural killer (NK) cells, which are crucial for identifying and destroying cancer cells. Chronic cortisol elevation has been linked to poorer cancer outcomes, as it weakens the body's anti-tumor immunity.

The increase in **adrenaline** and **noradrenaline**, both part of the sympathetic nervous system's fight-or-flight response, may also contribute to tumor progression through their effects on promoting angiogenesis, increasing tumor cell motility, and enhancing tumor cell survival. **Histamine**, a mediator of inflammation and immune modulation, is elevated in advanced cancer patients and plays a role in promoting tumor-associated angiogenesis and facilitating immune evasion. The combination of these stress-related hormones and mediators suggests that chronic stress exacerbates tumor growth and metastasis by weakening the body's natural defenses against cancer.

Tumor Markers and Metastatic Activity

The significant increases in tumor markers such as **CYFRA 21-1, carcinoembryonic antigen (CEA), circulating tumor cells (CTCs),** and **cell-free DNA (ctDNA)** observed in the research group validate the aggressive nature of metastatic NSCLC. **CYFRA 21-1,** a fragment of cytokeratin 19, is a well-established tumor marker in NSCLC and is often elevated in patients with advanced disease. Its rise in stage IV patients reflects the increased tumor burden and cell turnover associated with metastatic cancer.

Similarly, **CEA**, a glycoprotein that is elevated in various cancers, including NSCLC, serves as an indicator of tumor burden and metastasis. The detection of **CTCs** and **ctDNA** in the blood of all advanced NSCLC patients underscores the extensive tumor shedding and dissemination that characterize metastatic cancer. These markers not only indicate the presence of circulating tumor material but also suggest that the cancer has a higher likelihood of spreading to distant organs. The presence of **CTCs** and **ctDNA** is particularly concerning because they represent the ability of the tumor to metastasize, which is a key factor in the poor prognosis associated with stage IV NSCLC. Moreover, the elevated levels of tumor markers in conjunction with the

inflammatory and neuromediator changes observed in these patients suggest that metastatic NSCLC is a highly dynamic and aggressive disease that affects multiple systems within the body.

Can restoring neurotransmitter balance improve outcomes?

Restoring neurotransmitter balance in cancer patients, particularly those with **advanced non-small cell lung cancer (NSCLC),** may potentially improve outcomes by addressing the dysregulation of the **stress response, immune function,** and **tumor microenvironment.** Neurotransmitters like **melatonin, dopamine, serotonin, adrenaline,** and **noradrenaline** play key roles in modulating these processes, and their imbalance can contribute to tumor progression, immune suppression, and cancer-related symptoms like fatigue and depression. Here's how restoring neurotransmitter balance might help

Reduction of Chronic Stress and Tumor Growth: The stress hormones **adrenaline** and **noradrenaline** are often elevated in cancer patients, particularly in advanced stages. These hormones, part of the body's "fight-or-flight" response, can promote tumor progression by Enhancing **angiogenesis** (the formation of new blood vessels to support tumor growth). Increasing **tumor cell migration** and **invasion**, leading to metastasis. Suppressing immune responses, particularly through effects on **natural killer (NK) cells** and **T cells**. By restoring the balance of these stress-related neurotransmitters, it may be possible to reduce the pro-tumor effects of chronic stress. Interventions like **beta-blockers** (which inhibit the effects of adrenaline and noradrenaline) are being studied for their potential to slow cancer progression by reducing stress-mediated pathways.

Melatonin and Immune Modulation: - **Melatonin**, a hormone and neurotransmitter produced primarily by the pineal gland, regulates **circadian rhythms** and has potent **antioxidant** and **anti-inflammatory** properties. In cancer, melatonin levels are often significantly reduced, especially in advanced disease. Melatonin has demonstrated several anti-cancer effects, including:

Enhancing immune responses: Melatonin can stimulate the production of **cytokines** and increase the activity of NK cells and T cells, improving the body's ability to fight cancer.

Inhibiting tumor growth: Melatonin has been shown to reduce the proliferation of tumor cells, induce apoptosis (programmed cell death), and inhibit **angiogenesis**.

Improving quality of life: Restoring melatonin levels can help regulate sleep patterns, reduce fatigue, and improve overall well-being in cancer patients.

Clinical studies have suggested that **melatonin supplementation** alongside conventional cancer therapies, such as chemotherapy or immunotherapy, may improve patient outcomes by boosting immune function, reducing tumor growth, and enhancing patients' quality of life.

Dopamine and Anti-Angiogenesis: **Dopamine** is a neurotransmitter involved in regulating mood, reward, and the immune system. In cancer, dopamine levels are often suppressed, and this can contribute to Increased **angiogenesis**, as dopamine normally inhibits the growth of new blood vessels by suppressing **vascular endothelial growth factor (VEGF)** production. Reduced **immune surveillance**, as dopamine has been shown to enhance the activity of NK cells and inhibit the formation of **immunosuppressive cells** such as **myeloid-derived suppressor cells (MDSCs).** Restoring dopamine levels, or using dopamine agonists, could help reduce tumor-induced angiogenesis and improve immune responses, thereby slowing tumor growth and metastasis.

Serotonin Modulation and Symptom Management – Serotonin: is another key neurotransmitter that is often dysregulated in cancer patients, with both elevated and reduced levels observed depending on the individual and the type of cancer. While serotonin is essential for mood regulation, excessive serotonin can sometimes contribute to tumor progression by:

Promoting **tumor cell survival** and resistance to apoptosis.
Enhancing **inflammation** in the tumor microenvironment.

Restoring serotonin balance through **serotonin-modulating therapies** could help manage symptoms like depression, anxiety, and cancer-related fatigue, which are common in cancer patients. Additionally, controlling excessive serotonin levels may help prevent its pro-tumor effects in certain cancers.

Reducing Immune Suppression: Chronic stress, along with imbalances in neurotransmitters like adrenaline and cortisol, can suppress immune function, reducing the body's ability to fight cancer. Neurotransmitter dysregulation can

Decrease NK cell activity, which is essential for killing cancer cells.
Reduce T cell responses, weakening the adaptive immune response.
Increase the levels of **immunosuppressive cells,** such as MDSCs and **regulatory T cells (Tregs),** which allow tumors to evade immune detection.

By restoring neurotransmitter balance, particularly through the reduction of stress hormones, it may be possible to restore immune function and improve the effectiveness of **immunotherapies** and **chemotherapy**.

Combination with Conventional Therapies: Restoring neurotransmitter balance may also enhance the efficacy of conventional cancer therapies, including chemotherapy, targeted therapies, and immunotherapy. For instance:

Melatonin: has been shown to increase the sensitivity of tumor cells to chemotherapy and radiotherapy, potentially improving treatment outcomes.

Beta-blockers: (which reduce the effects of adrenaline and noradrenaline) have been investigated for their potential to improve survival in cancer patients by slowing tumor growth and reducing metastasis.

Potential Interventions to Restore Neurotransmitter Balance

Melatonin supplementation: May enhance immune responses, reduce tumor growth, and improve sleep and quality of life.

Dopamine Agonists: Could inhibit angiogenesis and boost immune function, slowing cancer progression.

Beta-Blockers: Medications like **propranolol** can reduce the effects of stress hormones on tumor growth and metastasis.

Antidepressants (SSRIs): Selective serotonin reuptake inhibitors (SSRIs) can help manage depression and anxiety in cancer patients, improving their quality of life and possibly influencing cancer progression.

Restoring neurotransmitter balance holds potential as a strategy to improve outcomes in cancer patients, particularly those with advanced NSCLC. By targeting the dysregulation of stress-related hormones, enhancing immune responses, and reducing tumor-promoting factors like angiogenesis, this approach may complement existing cancer treatments. Further research and clinical trials are needed to determine the best methods for restoring neurotransmitter balance and integrating these therapies into personalized cancer care.

Can neuromodulators be combined with immunotherapy?

Yes, **neuromodulators** can potentially be combined with **immunotherapy** to enhance the overall efficacy of cancer treatment, including in advanced non-small cell lung cancer (NSCLC). Neuromodulators such as **melatonin**, **dopamine**, and **beta-blockers** (which target stress-related hormones like adrenaline and noradrenaline) play significant roles in modulating the immune system and the tumor microenvironment. By restoring the balance of these neurotransmitters and hormones, neuromodulators may complement immunotherapy and help improve patient outcomes. Here's how neuromodulators can be combined with immunotherapy

Melatonin as an Immune Enhancer - Melatonin, commonly known for its role in regulating sleep, has powerful **immunomodulatory** and **anti-cancer** properties. It has been shown to enhance immune responses by boosting the activity of **cytotoxic T cells** and **natural killer (NK) cells,** which are critical for the immune system to attack and eliminate cancer cells. Melatonin also reduces chronic inflammation, which can suppress the immune system and promote tumor growth.

Potential Benefits of Combining Melatonin with Immunotherapy

Synergistic Effect with Checkpoint Inhibitors: Melatonin could improve the efficacy of immune checkpoint inhibitors (such as **PD-1/PD-L1 inhibitors** and **CTLA-4 inhibitors**) by enhancing T cell activity. Immune checkpoint inhibitors work by reactivating T cells that have been suppressed by the tumor, and melatonin may boost this effect by promoting T cell activation and reducing immune suppression in the tumor microenvironment.

Reduction of Immunotherapy-Related Side Effects: Immunotherapy can sometimes cause severe side effects, including inflammation and autoimmunity. Melatonin's **anti-inflammatory** properties could help mitigate some of these adverse effects, allowing patients to tolerate immunotherapy better.

Clinical Evidence: Some studies have suggested that melatonin, when combined with standard cancer treatments, improves survival rates and quality of life in cancer patients. Combining melatonin with immunotherapy could potentially lead to improved outcomes by enhancing the immune system's ability to target and destroy cancer cells.

Dopamine Agonists to Reduce Immunosuppression - Dopamine: is another neuromodulator that plays a key role in regulating the immune system. It has been shown to inhibit **angiogenesis** (the formation of new blood vessels that feed the tumor) and to enhance the function of immune cells, including T cells and NK cells. **Dopamine agonists** (drugs that increase dopamine levels or mimic its effects) could therefore be useful in cancer treatment by reducing the immunosuppressive environment within tumors.

Potential Benefits of Combining Dopamine Agonists with Immunotherapy

Enhanced Immune Function: Dopamine agonists can potentially boost the effects of immunotherapies by improving the activity of immune cells. For example, dopamine helps to suppress **myeloid-derived suppressor cells (MDSCs)** and **regulatory T cells (Tregs),** both of which are immunosuppressive and allow tumors to evade immune detection. By reducing the number of these cells, dopamine agonists may improve the immune system's ability to respond to immunotherapy.

Inhibition of Tumor Angiogenesis: Dopamine is known to inhibit angiogenesis by downregulating **vascular endothelial growth factor (VEGF),** a key molecule involved in blood vessel formation. Immunotherapies like checkpoint inhibitors are more effective when the tumor is deprived of its blood supply, and dopamine agonists may enhance this effect.

Beta-Blockers to Counteract Stress-Related Immunosuppression: **Beta-blockers** (such as propranolol) are commonly used to treat cardiovascular conditions by blocking the effects of stress hormones like **adrenaline** and **noradrenaline**. These hormones, when elevated chronically due to stress, can promote tumor growth by increasing angiogenesis, cell migration, and immune suppression. Beta-blockers may help counteract these effects, particularly in

patients with high levels of stress-related hormones.

Potential Benefits of Combining Beta-Blockers with Immunotherapy

• ***Reduction of Tumor-Induced Stress Response:*** Beta-blockers can help reduce the influence of chronic stress on the tumor microenvironment. By blocking the effects of adrenaline and noradrenaline, beta-blockers may decrease **angiogenesis, tumor cell migration**, and immune suppression, making immunotherapies more effective.

• ***Synergy with Immune Checkpoint Inhibitors:*** Beta-blockers may enhance the efficacy of **PD-1/PD-L1 inhibitors** by reducing the pro-tumor effects of stress hormones. Chronic stress can impair the function of immune cells, including T cells, and beta-blockers may help restore proper immune function, allowing checkpoint inhibitors to work more effectively.

• ***Clinical Evidence:*** Some retrospective studies have shown that cancer patients who are taking beta-blockers for other conditions tend to have better outcomes. This suggests that beta-blockers may have a beneficial effect on the immune system's ability to fight cancer and combining them with immunotherapy could enhance this effect.

Serotonin Modulation

Serotonin plays a complex role in cancer, and its effects vary depending on the type of cancer and its levels in the body. In some cancers, elevated serotonin levels are associated with tumor progression, while in others, serotonin helps modulate the immune response. **Selective serotonin reuptake inhibitors (SSRIs),** commonly used to treat depression, may have a role in cancer treatment by improving mood and reducing cancer-related stress, which could support better immune function.

Potential Benefits of Combining SSRIs with Immunotherapy

• ***Improved Quality of Life:*** SSRIs can help reduce depression and anxiety in cancer patients, which may indirectly improve immune function by reducing chronic stress. A more balanced psychological state can enhance the body's natural immune defenses and improve the response to immunotherapy.

• ***Potential Anti-Cancer Effects:*** Some studies have suggested that SSRIs may have direct anti-tumor effects, although more research is needed in this area. If SSRIs can modulate the immune system or reduce tumor-promoting serotonin levels, they could be a valuable addition to immunotherapy regimens.

Challenges and Considerations

While combining neuromodulators with immunotherapy offers promise, there are several challenges and considerations

• ***Individual Variation:*** The effects of neuromodulators on cancer and the immune system may vary from patient to patient, depending on the type of cancer, the tumor microenvironment, and the patient's overall health.

• ***Optimal Dosing and Timing:*** Determining the best timing and dosage for combining neuromodulators with immunotherapy is essential to maximize the potential benefits and minimize adverse effects.

• ***Potential Side Effects:*** Neuromodulators like melatonin and dopamine agonists can have side effects, and their interactions with immunotherapy agents need to be carefully monitored.

Combining **neuromodulators** with **immunotherapy** holds great promise for enhancing the immune response and improving outcomes in cancer patients. Neuromodulators like melatonin, dopamine agonists, beta-blockers, and even SSRIs can potentially reduce immune suppression, inhibit angiogenesis, and restore proper immune function, making immunotherapies like checkpoint inhibitors more effective. Further research and clinical trials are needed to fully understand the benefits and challenges of these combinations, but they represent a promising avenue for personalized cancer therapy, particularly for patients with advanced diseases like NSCLC.

Can dopamine agonists help lung cancer?

Dopamine agonists: may offer potential therapeutic benefits in lung cancer, particularly in **non-small cell lung cancer (NSCLC)**, by targeting several pathways involved in tumor growth, immune modulation, and angiogenesis. While research in this area is still emerging, dopamine agonists are being explored for their potential to inhibit tumor progression and enhance the effectiveness of existing cancer treatments. Here's how dopamine agonists could help in lung cancer management

Inhibition of Angiogenesis

One of the critical way's dopamine agonists may help in lung cancer is through the **inhibition of angiogenesis**, which is the formation of new blood vessels that tumors need to grow and spread. Dopamine plays a natural role in suppressing angiogenesis by

• **Blocking vascular endothelial growth factor (VEGF):** Dopamine reduces the production of VEGF, a key molecule that stimulates blood vessel formation in tumors. By inhibiting VEGF, dopamine agonists can starve tumors of the oxygen and nutrients they need to grow.

• **Inhibiting endothelial cell migration:** Dopamine agonists can inhibit the migration and proliferation of endothelial cells (the cells that line blood vessels), further preventing the development of new blood vessels.

• By limiting angiogenesis, dopamine agonists may slow tumor growth and metastasis in lung cancer, particularly in advanced stages when angiogenesis plays a crucial role in tumor progression.

Immune System Modulation

Dopamine has a profound impact on the **immune system**, and dopamine agonists could enhance the body's ability to fight lung cancer by improving immune responses. Dopamine affects several immune cells that are critical in controlling tumor growth

• ***Inhibition of Myeloid-Derived Suppressor Cells (MDSCs):*** MDSCs are a population of immune cells that suppress the activity of **T cells** and **natural killer (NK) cells,** allowing tumors to evade immune detection. Dopamine agonists

can reduce the recruitment and function of MDSCs, thereby restoring immune surveillance and improving the effectiveness of **immunotherapy** or the body's natural immune response against lung cancer cells.

• ***Activation of Cytotoxic T Cells and NK Cells:*** Dopamine agonists may enhance the activity of cytotoxic T cells and NK cells, which are crucial for identifying and killing cancer cells. By boosting these cells' activity, dopamine agonists may enhance the overall anti-tumor immune response.

This immune-modulating effect makes dopamine agonists a potential adjunctive therapy to **immunotherapy**, which has become a cornerstone in the treatment of advanced NSCLC. **Direct Anti-Tumor Effects** - Emerging research suggests that dopamine and its receptors (specifically the D2 dopamine receptor) may have direct anti-tumor effects. Dopamine agonists can activate dopamine receptors expressed on cancer cells, leading to

• ***Inhibition of cancer cell proliferation:*** Studies have shown that dopamine agonists can reduce the growth rate of cancer cells by interacting with dopamine receptors on the surface of these cells. This interaction may induce apoptosis (programmed cell death) or slow down the cancer cell cycle.

• **Prevention of metastasis:** Dopamine agonists may inhibit cancer cell migration and invasion, key processes in metastasis, by modulating signaling pathways involved in cell movement.

• While research on direct anti-tumor effects of dopamine agonists in lung cancer is still in early stages, these findings suggest that dopamine receptor signaling plays a role in lung cancer cell biology.

Potential Synergy with Chemotherapy and Immunotherapy: Dopamine agonists could potentially **enhance the efficacy of standard lung cancer treatments**, such as chemotherapy and immunotherapy

• ***Chemotherapy:*** Dopamine agonists, by reducing angiogenesis and modulating the immune response, may improve the delivery of chemotherapy drugs to the tumor and enhance their effectiveness. They may also help reduce some of the side effects of chemotherapy by improving the overall immune response.

• ***Immunotherapy:*** The ability of dopamine agonists to inhibit MDSCs and enhance T cell activity could make them synergistic with **immune checkpoint inhibitors like PD-1/PD-L1 inhibitors** (e.g., pembrolizumab, nivolumab). By reducing the immunosuppressive environment in the tumor, dopamine agonists may improve the efficacy of these immunotherapies.

Potential Role in Reducing Cancer-Related Fatigue: Lung cancer patients, especially those undergoing treatment, often experience severe fatigue and depression, which can impact their quality of life. Since dopamine is a neurotransmitter involved in regulating mood and energy levels, dopamine agonists might help alleviate cancer-related **fatigue** and **depression** by boosting dopamine levels in the brain. This could improve the overall well-being of lung cancer patients, allowing them to better tolerate and respond to cancer treatments.

Preclinical and Clinical Research: Most of the evidence supporting the role of dopamine agonists in lung cancer comes from **preclinical studies** (studies done in cell cultures or animal models). Some key findings from this research include:

• **Inhibition of angiogenesis and metastasis:** Animal studies have demonstrated that dopamine agonists can inhibit the growth and spread of lung tumors by reducing blood vessel formation and preventing cancer cell migration.

• **Immune modulation:** Dopamine agonists have been shown to reduce the suppressive activity of MDSCs in lung cancer models, leading to enhanced T cell responses and reduced tumor growth.

While these findings are promising, more **clinical trials** are needed to determine the safety and effectiveness of dopamine agonists in lung cancer patients. Clinical trials would provide a clearer understanding of how these drugs interact with standard cancer treatments and whether they improve patient outcomes.

Examples of Dopamine Agonists Being Studied

• **Cabergoline:** This dopamine agonist, commonly used to treat conditions like Parkinson's disease and hyperprolactinemia, has been studied for its anti-angiogenic and anti-tumor effects. Preclinical studies have shown that cabergoline can inhibit tumor growth and reduce blood vessel formation in cancer models, including lung cancer.

• **Bromocriptine:** Another dopamine agonist primarily used for Parkinson's disease, bromocriptine has also demonstrated anti-angiogenic effects in cancer models. Its potential to reduce tumor growth and metastasis is being investigated in preclinical studies.

While dopamine agonists are not yet widely used as a standard treatment for lung cancer, there is growing evidence that they may have potential as adjunct therapies. By inhibiting angiogenesis, modulating the immune system, and potentially enhancing the effects of chemotherapy and immunotherapy, dopamine agonists offer a promising area of research for improving lung cancer treatment outcomes. However, more clinical studies are needed to fully understand the therapeutic benefits and safety of dopamine agonists in lung cancer patients. In summary, the findings of this study highlight the complex interplay between inflammation, stress-response dysregulation, and tumor burden in advanced NSCLC. The significant increases in inflammatory markers, coupled with neuromediator imbalances and elevated tumor markers, create a tumor-supportive environment that promotes cancer progression and metastasis. These results emphasize the importance of addressing not only the tumor itself but also the broader systemic disruptions that contribute to cancer progression. Therapeutic strategies aimed at reducing systemic inflammation, restoring neurotransmitter balance, and targeting circulating tumor biomarkers may offer new avenues for managing advanced NSCLC and improving patient outcomes.

5. Conclusion

This study sheds light on the intricate biological mechanisms

that underlie the progression of **metastatic non-small cell lung cancer (NSCLC),** particularly adenocarcinoma, by demonstrating significant elevations in inflammatory markers, tumor markers, and disruptions in the balance of critical neurotransmitters. These findings underscore the critical role that **chronic inflammation, tumor burden**, and **stress-related neuromodulation** play in facilitating tumor growth and metastasis in advanced-stage NSCLC. By examining these pathways in depth, this research opens up potential avenues for therapeutic interventions aimed at mitigating the detrimental effects of systemic inflammation and restoring the neuroendocrine balance in cancer patients.

Role of Systemic Inflammation in Metastatic NSCLC

The elevation of inflammatory markers such as **TNF-alpha, IL-6, CRP,** and **IL-1beta** in patients with metastatic NSCLC highlights the importance of chronic inflammation as a driver of tumor progression. Chronic inflammation creates a pro-tumor environment by promoting angiogenesis, enhancing immune evasion, and facilitating metastatic potential. **TNF-alpha** and **IL-6,** in particular, are well-documented in their roles as pro-inflammatory cytokines that not only contribute to inflammation but also actively enhance tumor growth. The increased levels of these cytokines in advanced-stage NSCLC suggest that targeting systemic inflammation could help slow disease progression by modulating the tumor microenvironment.

CRP and **ferritin** elevations in the study further indicate an overall heightened inflammatory response in metastatic NSCLC. CRP is commonly used as a marker of systemic inflammation, and its elevated levels in cancer patients often reflect the severity of disease and tumor burden. Ferritin, associated with altered iron metabolism in cancer, also points to the tumor's ability to manipulate systemic processes for its own survival and proliferation. The role of **serum amyloid A (SAA)** and **erythrocyte sedimentation rate (ERS)** in reflecting heightened inflammatory states in advanced NSCLC patients also provides evidence that systemic inflammation plays a pivotal role in the disease's progression.

Neuromodulator Dysregulation in Metastatic NSCLC

One of the most significant findings of this study is the **neuromodulator imbalance** observed in patients with metastatic NSCLC, which strongly suggests that disruptions in the body's stress-response system exacerbate tumor progression. The marked decrease in **melatonin** and **dopamine** levels in these patients provides insights into the broader consequences of neuroendocrine disruption in advanced cancer. Melatonin, a hormone with both **antioxidant** and **anti-tumor** properties, plays a protective role by suppressing tumor growth and enhancing immune responses. Its reduction in metastatic NSCLC patients reflects the loss of these protective effects and may contribute to the aggressiveness of the disease. The correlation between low melatonin levels and increased tumor burden highlights the potential therapeutic value of melatonin supplementation in restoring circadian rhythms and modulating immune function in cancer patients. Melatonin could potentially serve as an adjunct therapy in combination with standard treatments like chemotherapy and immunotherapy, offering a means to reduce tumor growth and improve patient outcomes.

Dopamine, another critical neuromodulator, also plays a significant role in regulating immune responses and inhibiting **angiogenesis**. Its depletion in metastatic NSCLC patients suggests that tumors actively disrupt dopamine signaling to enhance their survival. The reduction of dopamine likely contributes to immune suppression, further enabling the tumor to evade detection and destruction by the body's immune system. The implications of these findings are profound, as restoring dopamine balance could help re-activate immune cells, such as **natural killer (NK) cells** and **cytotoxic T cells,** which are critical in the fight against cancer.

Impact of Stress Hormones on Tumor Progression

The increased levels of stress-related hormones, including **cortisol, adrenaline, noradrenaline**, and **histamine**, observed in the study, point to the role of chronic stress in worsening cancer outcomes. Chronic stress has long been associated with poor immune function and enhanced tumor progression, and these findings further confirm the negative impact of stress hormones on the body's ability to combat cancer.

Cortisol, the primary stress hormone, suppresses the immune system's anti-tumor response by inhibiting **T cell activity** and promoting **regulatory T cells (Tregs),** which protect tumors from immune attack. The increase in cortisol levels in metastatic NSCLC patients supports the idea that chronic stress not only weakens the immune response but also promotes an environment conducive to tumor survival and metastasis. Targeting the stress-response system through the use of **beta-blockers** or **cortisol-lowering therapies** could present new therapeutic strategies to slow tumor growth and improve overall outcomes.

Similarly, **adrenaline** and **noradrenaline**, which are released during the body's "fight-or-flight" response, promote tumor angiogenesis and enhance the spread of cancer cells to distant sites. These stress hormones can also impair the effectiveness of cancer therapies by reducing the immune system's ability to recognize and destroy cancer cells. By targeting stress pathways through pharmacological interventions that block the effects of these hormones, such as **beta-adrenergic blockers**, patients may experience improved responses to standard cancer treatments like chemotherapy and immunotherapy

Elevation of Tumor Markers and Metastatic Potential

The significant increase in **tumor markers**—including **CYFRA 21-1, CEA, CTCs,** and **ctDNA**—in patients with metastatic NSCLC underscores the aggressive nature of the disease and the extensive metastatic activity occurring in these patients. These markers are commonly associated with high tumor burden and poor prognosis, and their elevation in this study indicates active tumor cell dissemination and

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an increased likelihood of metastasis. The presence of **circulating tumor cells (CTCs)** and **cell-free DNA (ctDNA)** in the blood of all stage IV patients further validates the notion that metastatic NSCLC is characterized by widespread tumor shedding. These markers are increasingly being used as **liquid biopsies** to monitor tumor progression and response to treatment in real-time. They provide clinicians with valuable insights into the extent of metastatic disease and the effectiveness of therapeutic interventions. Targeting circulating tumor cells and ctDNA may present new opportunities for precision medicine approaches, particularly in developing therapies that aim to prevent the spread of cancer to distant organs.

Therapeutic Implications and Future Directions

The findings of this study suggest that **targeting systemic inflammation, restoring neuromodulator balance**, and **modulating the stress-response system** may offer new avenues for therapeutic intervention in metastatic NSCLC. By addressing the underlying biological processes that contribute to tumor progression and metastasis, clinicians may be able to develop more effective treatment strategies that go beyond traditional chemotherapy and immunotherapy.

The complexities of metastatic NSCLC are deeply rooted in the interactions between chronic inflammation, neurotransmitter imbalances, and the body's response to stress. Addressing these pathways could potentially improve outcomes for patients with advanced lung cancer. Future research should focus on exploring therapeutic interventions that reduce systemic inflammation, restore neurotransmitter balance, and mitigate the effects of chronic stress to improve survival rates and quality of life for patients with metastatic NSCLC [1-42].

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