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Regulating Inflammation in Cancer: Effects on Metastasis and Treatment Outcomes

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ABSTRACT

Chronic inflammation is a pivotal element in the onset and advancement of cancer. It is crucial in tumor initiation, survival, metastasis, and therapeutic resistance. This study seeks to thoroughly examine the intricate relationship between inflammation and cancer, emphasizing the role of inflammatory processes in tumor formation and their influence on cancer therapy responses. We will investigate the molecular processes behind inflammation-induced cancer progression, analyze how inflammation affects metastasis, and assess its effects on the effectiveness of treatments like chemotherapy, immunotherapy, and targeted therapies. Furthermore, we will investigate prospective therapeutic approaches for addressing inflammation in cancer treatment, emphasizing the necessity for specific modulation to enhance treatment efficacy while mitigating adverse consequences such as immune suppression or heightened infection risk. The report finishes with a discussion on prospective research avenues focused on optimizing inflammation-targeting techniques to augment the efficacy of cancer therapies and better patient outcomes.

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INTRODUCTION

Inflammation as a Driver of Cancer

A basic driver of cancer progression is clearly chronic inflammation (1). Though much study has been done, the exact molecular and cellular processes by which inflammation drives tumor development, metastases, and therapeutic resistance remain poorly known (2). This review investigates how modulation of inflammatory pathways may improve therapeutic efficacy and offers a thorough investigation of the several roles of tumor-associated inflammation in cancer pathogenesis (3). Persistent invasion of several immune cell populations including macrophages, neutrophils, and myeloid-derived suppressor cells (MDSCs) into the tumor microenvironment (TME) defines tumor-associated inflammation (4). Complex repertory of pro-inflammatory cytokines, chemokines, and growth factors secreted by these cells critically controls tumor cell proliferation, survival, immune evasion, and metastatic dissemination. Because neoplastic cells control immune constituents to create a supportive niche that supports tumor persistence and expansion, the TME is essential in organizing these inflammatory responses (5). This inflammatory milieu not only stimulates malignant cell proliferation but also confers resistance to apoptotic signals and helps invasion into nearby tissues and far-off metastatic sites. Over time, the dynamic equilibrium between pro-inflammatory and anti-inflammatory signals becomes disrupted, resulting in a chronic, tumor-promoting

inflammatory state that underlies cancer progression and therapeutic refractoriness (7).Obesity has become a major worldwide health concern as its frequency shockingly fast rises everywhere (8). Although a complicated interaction of genetic, environmental, and lifestyle factors clearly causes obesity, increasing evidence emphasizes the gut microbiome as the main actor in controlling body weight and distribution of fat (9). By means of the gut microbial community, several processes including modulation of energy harvest from the diet, control of host metabolism, and interaction with hormonal and immune pathways shape obesity (10). As was already noted, changes in the relative abundance and diversity of gut bacteria can affect the efficiency with which dietary nutrients are extracted and converted into useable energy (11). Higher ratios of Firmicutes to Bacteroidetes have been linked to increased capacity for fermenting complex polysaccharides into absorbable calories, so helping to explain increasing energy harvest and fat accumulation. Many times, obesity sufferers show this profile. This alters the lipid metabolism and storage of the host, so influencing adiposity and fat distribution patterns (12). This affects microbial habitat as well. Apart from producing energy, the gut flora greatly controls bile acid metabolism, so influencing the breakdown and absorption of fat directly. Gut bacteria convert primary bile acids into secondary bile acids which function as signaling molecules—by means of receptors such Takeda G-protein receptor 5 (TGR5) and farnesoid X receptor (FXR). These receptors define control of energy consumption, lipid metabolism, and glucose homeostasis. Changing the signaling routes of perturbingile acid allows dysbiosis to affect fat metabolism and increase fat storage, so fueling obesity (13). These results have spurred much research on recently developed therapeutic strategies meant to target the microbiome in order to fight obesity. Promising in changing the microbial community of the recipient towards a more balanced and metabolistically friendly profile, fecal microbiota transplantation (FMT), or transposing gut bacteria from a healthy donor to a recipient, has shown promise (11, 12). Although more clinical studies are needed to prove its long-term safety and efficacy, preliminary studies indicate that FMT may reduce adiposity (8) and improve metabolic parameters. Apart from FMT, prebiotics and probiotics are easily available and could be useful strategies to change the gut flora. Prebiotics especially help the growth of good bacteria by including inulin and fructooligosaccharides, so producing short-chain fatty acids (SCFAs), with anti-obesity effects including appetite control and higher energy expenditure (7). By altering inflammation, gut barrier function, and metabolic signaling pathways, live beneficial microorganisms such Lactobacillus and Bifidobacterium species which make up probiotics have shown different degrees of success in lowering body weight and improving metabolic health. Usually depending mostly on dietary changes and physical activity, these microbiome-based treatments show a good complement or substitute for conventional obesity control methods (8). These strategies may lower the risk of obesity-related complications, including type 2 diabetes, cardiovascular diseases, and some cancers, so improving weight loss outcomes, by tackling the fundamental bacterial causes of obesity (11).

Historical Perspective on the Link Between Inflammation and Cancer

It is well known that inflammation has been linked to cancer over the ages. Research conducted in the past has shown that those who are afflicted with chronic inflammatory disorders have a higher probability of developing cancer. Back in 1863, Rudolf Virchow proposed that cancer arises at sites of chronic inflammation. He observed leukocyte infiltration in tumor tissues, suggesting an inflammatory origin of cancer (8, 9). Furthermore, the middle of the 20th century marked a major advancement in understanding the molecular basis of this interaction (8). The identification of significant inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), as well as angiogenic factors, such as vascular endothelial growth factor (VEGF), and crucial signaling pathways, such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), has led to a more advanced understanding of the role that inflammation plays in the development, progression, and metastases of cancer. Using these molecular mediators also allows one to create fresh therapeutic approaches meant to stop tumor development and control inflammation by means of their interactions. Promising effects of the present drugs that focus on pro-inflammatory pathways—such as immune checkpoint inhibitors and tailored anti-inflammatory drugs—have been shown over several cancer types (10). Clinical environments are where these treatments are under testing right now.

Therapeutic Implications: Targeting Inflammation to Improve Cancer Therapy

New developments in cancer treatment have highlighted the importance of understanding the tumor microenvironment and its inflammatory components (11). Targeting drugs and immunotherapies—such as immune checkpoint inhibitors—by letting the exact targeting of neoplastic cells has revolutionized cancer treatment (12). Constant inflammation in the tumor microenvironment can compromise the efficacy of these treatments by means of immune suppression, generation of drug resistance, and modification of

the tumor vasculature. Modern cancer research mostly seeks solutions by concentrating on the inflammatory aspects of the tumor microenvironment (TME), so overcoming these challenges. Blocking the inflammatory cytokines TNF-α and Interleukin-6 (IL-6) may interfere with tumor-supportive signaling networks in the tumor microenvironment (11). In addition to this, ihibiting NF-κB pathway which is a central regulator of inflammatory gene expression that frequently activated in tumors, has been shown to reduce tumor progression in preclinical models and can be evaluated to be used in cancer therapy (9). Current treatments may become more efficient, patient outcomes may be improved, and side effects may be reduced by changing inflammatory paths in tumors (14).

Mechanisms of Inflammation in Cancer Progression

Key Molecular Pathways in Inflammation and Cancer

Many biological mechanisms support the explanation of the cancer development caused by inflammation. These pathways underlie important mechanisms controlling cell survival, proliferation, migration, angiogenesis, and immune evasion (15). The NF-κB signaling pathway is crucially controlling the expression of pro-inflammatory cytokines, survival genes, and genes linked with immune evasion (16). Under stimulation by inflammatory cytokines such as TNF-α and IL-1β, NF-κB moves to the nucleus, where it starts the transcription of pro-survival and pro-inflammatory genes (17). This activation keeps a pro-inflammatory tumor microenvironment that promotes tumor growth intact. The PI3K/AKT and MAPK pathways are two further crucial signaling channels that support inflammation-induced cancer development (18). Crucially influencing factors of tumor viability and metastases, these pathways regulate cellular proliferation, migration, and death resistance. Most important in raising tumor aggressiveness and therapeutic resistance is the activation of these pathways by inflammatory signals, including cytokines and growth factors (19). Moreover, reactive oxygen species (20) generated by oxidative stress brought on by inflammation act as secondary messengers in signaling pathways (21). Chronic inflammation contributes to cancer development by producing various inflammatory mediators and activating signaling pathways that facilitate tumor growth, metastasis, and the formation of new blood vessels. Prostaglandins, which are lipid molecules whose synthesis is controlled by COX, are one of these mediators that are crucial in the link between inflammation and cancer. Many cancer types frequently have overexpressed COX-2 in particular (22).

Tumor Microenvironment and Immune Cells

The tumor microenvironment (TME) is considere a dynamic network of tumor cells, immune cells, stromal cells, and extracellular matrix (ECM). Among the several immune cell types whose recruitment and activation are affected by inflammation signals are tumor-associated macrophages (TAMs), neutrophils, and myeloid-derived suppressor cells (MDSCs), thus changing the tumor microenvironment (TME). Later on these immune cells secrete a spectrum of cytokines, growth factors, and matrix-degrading enzymes supporting tumor cell survival, immune evasion, and metastatic spread (23, 24). Often polarized into an M2 phenotype, tumor-associated macrophages (TAMs) dramatically promote tumor growth and suppress anti-tumor immune responses (25). VEGF provides tumors with the necessary nutrients and oxygen for their development stimulation; thus, one of the pro-angiogens produced by M2-polarized tumor-associated macrophages supplies growth (26). Furthermore, by releasing immunosuppressive cytokines such as IL-10 and TGF-β, these macrophages reduce the activity of cytotoxic immune cells, including CTLs and NK cells (27). Cross-talk between the gut microbiome and the tumor microenvironment can also influence the functional polarization of TAMs. Recent studies suggest that microbial metabolites and signals from the gut microbiota may reprogram TAMs toward a pro-tumoral phenotype, to enhance both angiogenesis and immunosuppression (23). Although their primary goal is infection prevention, neutrophils also encourage tumor growth by secreting cytokines such as IL-8, which increase tumor cell motility and invasion (28). Targeting extracellular matrix (ECM) and increasing tumor cell penetration into surrounding tissues, matrix metalloproteinases (MMPs) buried under neutrophils and other immune cells create a feedback loop, aggravating inflammation and speeding tumor spread and growth (29).

Oxidative Stress and DNA Damage

Chronic inflammation in the tumor microenvironment (TME) leads to sustained production of reactive oxygen species (20), which play a complex role in cancer development and therapy resistance. At moderate levels, ROS act as signaling molecules that activate pro-survival pathways, promoting tumor cell proliferation, immune evasion, and adaptation to stress. Chronic infection-driven inflammation can also causes single-strand DNA breaks (SSBs) via ROS and reactive nitrogen species (RNS). This damage can escalate to double-strand breaks (DSBs), especially through NF-κB pathway activation, thereby contributing significantly to genomic instability (19, 20). However, excessive ROS cause oxidative damage to cellular components such as lipids, proteins, and particularly DNA, leading to mutations, genomic instability, and activation of oncogenes (30). This genomic instability

fuels tumor progression and enhances the aggressive phenotype of cancer cells by enabling them to evade apoptosis (31).

Importantly, ROS contribute to resistance against conventional cancer therapies. Oxidative stress supports the survival of cancer stem cells (CSCs) a subpopulation resistant to chemotherapy, radiotherapy, and immunotherapy thereby promoting tumor relapse and metastasis (32). Inflammatory cytokines like IL-6 and TNF-α maintain elevated ROS levels, creating a feedback loop that reinforces proliferative signaling, immune suppression through recruitment of immunosuppressive cells (e.g., MDSCs and Tregs), and angiogenesis. Additionally, inflammation-driven fibrosis in the TME forms a physical barrier that limits the effective delivery of chemotherapeutic drugs (33).

Together, these mechanisms illustrate how chronic inflammation and oxidative stress undermine therapeutic efficacy by enhancing tumor cell survival, fostering an immunosuppressive microenvironment, and obstructing drug delivery (34). Targeting ROS production and inflammatory pathways such as NF-κB and STAT3, alongside conventional treatments, represents a promising approach to overcoming therapy resistance and improving patient outcomes (35).

Inflammation and Metastasis

Inflammation as a Driver of Metastasis

Metastasis, the dissemination of cancer cells from the main tumor to remote organs, is a principal factor in cancer-related mortality, accounting for the majority of cancer fatalities. Inflammation is crucial in facilitating metastasis by enhancing tumor cell motility, invasion, and survival in remote organs (36). Pro-inflammatory cytokines, including IL-6 and TNF-α, along with chemokines such as IL-8, augment tumor cell motility and amplify their invasive potential by activating signaling pathways that promote epithelial-to-mesenchymal transition (EMT) (37). Epithelial-mesenchymal transition (EMT) is a pivotal process in which epithelial tumor cells attain mesenchymal characteristics, facilitating their detachment from the main tumor and enhancing their capacity to infiltrate adjacent tissues (38). Low oxygen levels (hypoxia) and prolonged inflammation combine to enhance the relationship between HIF-1 and NF-κB, which in turn stimulates the production of important transcription factors involved in EMT, such as TWIST and SNAIL. This process makes tumor cells more invasive and raises their potential to metastasise (17, 18).

Moreover, inflammatory cytokines stimulate the development of matrix metalloproteinases (MMPs), enzymes responsible for the degradation of the extracellular matrix (ECM). The deterioration of the extracellular matrix enables tumor cells to penetrate the physical barriers of adjacent tissues and enter the bloodstream, thereby accessing distant organs (39). Upon entering circulation, these circulating tumor cells (CTCs) can form metastatic lesions in remote organs, facilitating disease dissemination. Inflammation also stimulates angiogenesis, the development of new blood vessels, which is essential for maintaining the blood supply of the expanding tumor and promoting more metastatic dissemination (40). Pro-inflammatory cytokines, including VEGF (vascular endothelial growth factor), are pivotal in the angiogenic process, guaranteeing that the tumor is adequately supplied with nutrients and oxygen to sustain its growth and spread (41).

Molecular Mechanisms of Inflammation-Induced Metastasis

The stimulation of inflammatory cytokines in the tumor microenvironment results in extracellular matrix remodeling, a crucial phase in metastasis. MMPs released by tumor and immune cells degrade the ECM, promoting tumor cell mobility and invasion (42). Furthermore, inflammation facilitates angiogenesis by enhancing the release of VEGF and additional pro-angiogenic molecules. This novel vasculature not only facilitates tumor proliferation but also offers a pathway for cancer cells to infiltrate the bloodstream, thus promoting metastatic spread (43). In summary, inflammation facilitates metastasis by various pathways, including the activation of epithelial-mesenchymal transition (EMT), extracellular matrix (ECM) breakdown, and angiogenesis. These activities augment the invasive characteristics of tumor cells, facilitating their dissemination to distant organ and the formation of new tumors.

Impact of Inflammation on Treatment Response

Chemotherapy Resistance Induced by Inflammation

Chronic inflammation also stimulates DNA repair mechanisms and activates key survival pathways like NF-κB and STAT3, while the development of inflammation-induced fibrosis acts as a barrier to drug delivery, ultimately decreasing the effectiveness of chemotherapy and contributing to tumor recurrence (25, 26). Chemotherapy remains a cornerstone of cancer treatment; however, its effectiveness is often compromised by chronic inflammation within the tumor microenvironment (44). Pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β activate signaling pathways including NF-κB and STAT3, which promote cancer cell survival and inhibit apoptosis, thereby protecting tumor cells from chemotherapy-induced cell death (45). These cytokines also enhance DNA repair mechanisms, further increasing resistance to DNA-damaging chemotherapeutic agents (46). In addition, inflammation can induce fibrosis in the tumor microenvironment, creating a physical barrier

that limits drug penetration and reduces chemotherapy delivery to tumor cells (47). The inflammatory milieu also supports the maintenance of cancer stem cells, a subpopulation with high chemoresistance that contributes to tumor recurrence and metastasis after treatment (48). Combining chemotherapy with strategies that target inflammatory pathways such as NF-κB inhibitors or cytokine-neutralizing antibodies may reduce tumor-promoting inflammation and improve cancer cell sensitivity to chemotherapy, offering a promising avenue to overcome resistance and enhance therapeutic outcomes (1).

Immunotherapy Resistance

Immunotherapy has emerged as a transformative cancer treatment by utilizing the body's immune system to identify and eliminate tumor cells. Chronic inflammation within the tumor can impede the efficacy of immunotherapies by producing immune suppression (49). Inflammation can enhance the expression of immunological checkpoints such as PD-L1, which suppresses immune responses by interacting with PD-1 receptors on T cells, so obstructing their ability to target cancer cells. Inflammatory cytokines, including IL-10 and TGF-β, facilitate the recruitment of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), thereby attenuating immune responses and aiding in immune evasion (50).

Besides the activation of immunological checkpoints, inflammation may also induce immune exhaustion in tumor-infiltrating lymphocytes (TILs). Pro-inflammatory signals can deplete the effector capabilities of T lymphocytes, diminishing their efficacy in targeting tumor cells (51).

Acute inflammation might paradoxically enhance anti-tumor immunity by facilitating the infiltration of immune cells, including cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, into the tumor (52). This indicates that regulating inflammation systematically may improve the effectiveness of immunotherapy. Consequently, medicines that specifically inhibit pro-inflammatory pathways while augmenting immune activation may enhance the efficacy of immunotherapies (53).

Targeted Therapies and Inflammation

Targeted medicines seek to obstruct particular signaling pathways that promote cancer cell proliferation. The existence of inflammation in the TME can affect the effectiveness of these medicines. Inflammatory cytokines, including IL-6 and TNF-α, can activate the PI3K/AKT pathway, frequently associated with tumor cell survival, resistance to apoptosis, and metastasis (11). This activation can provide resistance to targeted medicines by circumventing the therapeutic effects of route blockage (54). Furthermore, inflammation-induced extracellular matrix remodeling can affect the efficacy of targeted therapy by modifying the tumor's physical properties. Increased extracellular matrix stiffness, frequently resulting from inflammation, can obstruct the infiltration of targeted therapeutics into the tumor (55).

Combining targeted therapy with anti-inflammatory drugs may boost their effectiveness. Utilizing inhibitors of inflammatory cytokines or immune modulators in conjunction with targeted therapy may enhance medication delivery and surmount resistance mechanisms (56).

Therapeutic Strategies for Targeting Inflammation in Cancer

Anti-Inflammatory Agents

Targeted medicines seek to obstruct particular signaling pathways that promote cancer cell proliferation. The existence of inflammation in the TME can affect the effectiveness of these medicines (57). Inflammatory cytokines, including IL-6 and TNF-α, can activate the PI3K/AKT pathway, frequently associated with tumor cell survival, resistance to apoptosis, and metastasis. This activation can provide resistance to targeted medicines by circumventing the therapeutic effects of route blockage (58).

Furthermore, inflammation-induced extracellular matrix remodeling can affect the efficacy of targeted therapy by modifying the tumor's physical properties. Increased extracellular matrix stiffness, frequently resulting from inflammation, can obstruct the infiltration of targeted therapeutics into the tumor. Combining targeted therapy with anti-inflammatory drugs may boost their effectiveness. Utilizing inhibitors of inflammatory cytokines or immune modulators in conjunction with targeted therapy may enhance medication delivery and surmount resistance mechanisms (55). Natural polyphenols—including resveratrol, kaempferol, and quercetin—have been demonstrated to inhibit the PI3K/Akt/mTOR signaling pathway and trigger apoptosis in various cancer cell lines, thereby augmenting the efficacy of targeted therapies. Additionally, inflammation-induced extracellular matrix (ECM) stiffness contributes to drug resistance by activating integrin–PI3K/Akt signaling and impeding drug infiltration (23, 40, 51).

Immunomodulatory Therapies

Immunomodulatory treatments represent a viable approach for addressing inflammation in cancer. These therapies seek to modulate the immune system to foster a more advantageous inflammatory response that bolsters anti-tumor immunity (59). One strategy involves employing immune checkpoint inhibitors that obstruct inhibitory receptors on immune cells,

including PD-1 and CTLA-4. By obstructing these receptors, checkpoint inhibitors disengage the "brakes" on the immune system, enabling T cells and NK cells to target and eradicate tumor cells more (60). Chronic inflammation can result in immunological depletion and resistance to immunotherapy, thereby rendering the control of inflammatory responses a critical research focus (61). Therapies that prevent the recruitment of immunosuppressive cells, such as MDSCs or Tregs, may augment the effectiveness of immune checkpoint inhibitors (62). Likewise, employing drugs that regulate inflammatory cytokines in the tumor microenvironment may enhance the infiltration and activation of immune cells, including cytotoxic T lymphocytes and natural killer cells (63).

Targeting Tumor-Associated Inflammatory Pathways

Alongside generic anti-inflammatory drugs, therapies that precisely target the inflammatory pathways implicated in cancer progression provide a more targeted approach (64). The NF-κB pathway is a principal target for cancer treatment because of its pivotal involvement in inflammation and tumor advancement. Inhibitors of NF-κB signaling, including IKK inhibitors, have demonstrated potential in preclinical research by diminishing tumor growth and metastasis (65). Apart from artificial NF-κB inhibitors, natural substances like polyphenols have demonstrated the capacity to inhibit NF-κB signaling, hence enhancing ferroptosis and tumor cell death. Furthermore, by increasing the effectiveness of chemotherapy and radiation therapy by suppressing NF-κB, widely used anti-inflammatory drugs such as aspirin and glucocorticoids have shown therapeutic benefits (55, 56).

Additional intriguing targets encompass JAK/STAT signaling and PI3K/AKT pathways, frequently stimulated by inflammatory cytokines. Inhibiting these pathways may diminish inflammation and tumor advancement (66). The advancement of tailored medicines that precisely regulate inflammation inside the tumor microenvironment is highly promising. Clinical trials are necessary to ascertain the safety and efficacy of these techniques in conjunction with conventional cancer therapy (67).

CHALLENGES AND FUTURE DIRECTIONS

Specificity in Targeting Inflammation

Targeting inflammation offers a potential approach to enhancing cancer therapy results; yet, substantial obstacles accompany its implementation. A principal challenge is the precise targeting of particular inflammatory pathways that promote cancer progression while preserving the body's natural immunological activities (68). Inflammation is crucial for immunological monitoring, tissue restoration, and protection against pathogens. Excessive suppression or general inhibition of inflammation may compromise essential functions, rendering the body susceptible to infections, autoimmune responses, or insufficient repair (69). To mitigate such risks, medicines must be carefully formulated to target pro-tumorigenic inflammatory mediators, including particular cytokines (e.g., TNF-α, IL-6) and signaling pathways (e.g., NF-κB, JAK/STAT), which are increased inside the tumor microenvironment (TME) (70). Simultaneously, these therapies must maintain the anti-tumor immune response by preserving advantageous elements of inflammation that facilitate immune activation, including those associated with tissue repair or the recruitment of cytotoxic immune cells (71). Attaining this equilibrium necessitates a more sophisticated comprehension of the distinct functions that diverse inflammatory pathways serve in different cancer types, alongside the discovery of innovative, highly selective inflammatory targets (72).

Clinical Trials and Biomarkers

A significant problem in inflammation-targeted cancer therapeutics is the absence of dependable biomarkers to determine which patients will benefit from these interventions. Inflammation is a complex, dynamic process that significantly differs among individuals and various tumor kinds (73). Although specific pro-inflammatory mediators such as IL-6, TNF-α, and IL-1β are associated with cancer growth, the particular inflammatory elements present in each patient's disease may vary. This variability complicates the prediction of patient responses to medicines aimed at inflammation (74). To tackle this difficulty, it is crucial to find and confirm biomarkers that can precisely indicate the inflammatory condition of the tumor microenvironment and forecast therapy effects. These biomarkers may encompass certain cytokines, chemokines, or signaling molecules that are elevated in the tumor microenvironment and correlated with unfavorable prognosis (75). Liquid biopsy methodologies, which identify circulating tumor DNA, RNA, and proteins, may be pivotal in the non-invasive detection of these biomarkers. Moreover, immunohistochemical labeling or gene expression analysis of tumor biopsies may elucidate the inflammatory characteristics of certain malignancies, hence assisting in the formulation of individualized treatment strategies (76). The success of inflammation-targeting methods will rely on clinical trials that thoroughly assess their safety and efficacy alongside conventional cancer treatments. While preclinical evidence indicates that anti-inflammatory medicines could improve the effectiveness of chemotherapy, immunotherapy, and targeted therapies, implementing these findings in

clinical settings necessitates comprehensive testing across varied patient demographics (77). Clinical trials must evaluate the possible detrimental effects of inflammatory modulation, as improper targeting may result in unforeseen outcomes, including immune suppression or severe tissue damage (78).

Overcoming Therapy Resistance

Therapeutic resistance continues to be a major impediment in oncological treatment. Notwithstanding the progress in chemotherapy, immunotherapy, and targeted medicines, numerous malignancies develop resistance to treatment, resulting in relapse and metastasis (79). Inflammation is pivotal in fostering medication resistance by activating survival signaling pathways and facilitating immune evasion mechanisms (80). Pro-inflammatory cytokines, including IL-6 and TNF-α, can activate the NF-κB and STAT3 pathways, enhancing tumor cell survival and proliferation, inhibiting apoptosis, and augmenting DNA repair mechanisms, all of which facilitate resistance to chemotherapy and radiation (81, 82).

A multimodal approach that integrates inflammation-modulating medications with conventional treatments is necessary to surmount therapy resistance. This strategy seeks to address both the cancer cells and the inflammatory milieu, which is integral to resistance mechanisms (83). For instance, the integration of anti-inflammatory medicines, such as cytokine inhibitors or NF-κB antagonists, with chemotherapy may diminish the inflammatory signals that shield cancer cells from chemotherapy-induced harm (84). Likewise, integrating inflammation-modulating treatments with immunotherapies such as immune checkpoint inhibitors may augment immune responses by mitigating immune suppression within the tumor microenvironment (85).

Moreover, surmounting resistance necessitates the targeting of cancer stem cells, a subset of cells characterized by self-renewal capabilities and notable resistance to conventional therapies (86). Inflammation has been shown to support the survival of cancer stem cells, and targeting the inflammatory pathways that sustain these cells could lead to more effective therapies (87). A combination therapy that addresses both the stem cell population and the inflammatory factors sustaining their life presents a viable strategy for enhancing treatment effects and surmounting resistance (88).

The formulation of combination medicines that simultaneously address cancer cells and tumor-associated inflammatory processes constitutes a promising approach to augmenting the efficacy of cancer treatment (89). By targeting both cancer cells and the inflammatory milieu, these medicines may enhance outcomes for patients unresponsive to existing therapy protocols (90). Ongoing research is crucial to determine the most effective combinations of anti-inflammatory medicines with current therapy and to assess the clinical viability and safety of these approaches (91).

CONCLUSION

Inflammation is a critical factor influencing cancer progression, metastasis, and resistance to therapy. Targeting inflammatory pathways, in conjunction with conventional and emerging cancer treatments, holds significant promise for enhancing therapeutic efficacy and improving patient outcomes. As our understanding of the complex interplay between inflammation and the tumor microenvironment deepens, it becomes increasingly evident that personalized and context-specific anti-inflammatory strategies will be essential. Looking forward, future research should prioritize the identification of robust biomarkers to guide patient stratification, the development of novel and safer anti-inflammatory agents, and the integration of these strategies into clinical practice. Advancing these efforts through well-designed clinical trials will be crucial for translating promising preclinical insights into effective, real-world interventions that can benefit a broader population of cancer patients.

Authors's Contribution

Irem Selmi: data curation; editing and review. The author read and confirmed the final manuscript.

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Consent for publication

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