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Managing Inflammation in Cancer Therapy: Effects of Inflammation Control on Metastasis and Treatment Response

Maryam Abbasi Saeidi [1,*], Mina Ekrami Noghabi[2]

[1]Department of Biology, Faculty of Basic Sciences, Science & Research Branch, Islamic Azad University, Tehran, Iran.

[2]Department of Pediatrics, Bohlool Hospital, Gonabad University of Medical Sciences, Gonabad, Iran.

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Corresponding author:
Maryam Abbasi Saeidi
Email: maryamabbasisaeidi@gmail.com.

ABSTRACT

Chronic inflammation plays a critical role in cancer development and progression. Moreover, it has long been recognized as essential for tumor development, survival, metastasis, and treatment resistance. This review intends to systematically discuss and explore complex interactions between cancer cells and inflammation, highlighting its importance in cancer development and its impact on treatment outcomes. Furthermore, we will discuss molecular mechanisms underlying inflammation-driven cancer development and explore its impact on metastasis, treatment sensitivity to therapies including chemotherapy, immunotherapy, and targeted therapies. Moreover, we will explore new emerging strategies to treat inflammation in cancer therapy, keeping in view its need for selective modulation to improve treatment efficiency and reduce adverse reactions, including immunosuppression and susceptibility to infections. Finally, concluding remarks for new research directions on improving anti-inflammatory strategies to optimize cancer treatment therapies are presented to explore new ways for innovative cancer therapies to emerge for improved patient survival rates and better patient prognosis.

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INTRODUCTION

Inflammation as a Driver of Cancer

Long-term irritation has to be one of the key instigators of cancerology (1). Although the exact molecular/cellular mechanisms whereby inflammation can give rise to tumors, become metastatic or resist therapies are not fully elucidated, a significant work has been done (2). We also discuss how inflammatory pathways can be manipulated to modulate responses to therapy and present an in-depth review on the complex interaction of tumors with inflammatory cells in tumor pathogenesis (3). This persistent infiltration of various immune system subtypes, particularly macrophages, neutrophils and myeloid derived suppressor cells (MDSCs), into the tumor microenvironment (TME) has been the hallmark of tumoral inflammation (4). The heterogenic population of these cells, along with the tumor microenvironment of macrophages, neutrophils and MDSCs, as well as the pro-inflammatory components of cytokine, chemokine and growth factor secretions they release play a major role in tumour cell growth control, survival advantages and immune evasion transport. As cancer cells manipulate components of the immune system to create a tumor-supporting microenvironment that enables them to survive and proliferate, the TME is critical in regulating inflammation of the tumors (5).

This inflammatory storm allows the malignant cells to grow at will, reject apoptotic markers and insidiously spread throughout local and remote matrices. The balance between pro-inflammatory and

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anti-inflammatory signals tilts, over time during the course of disease, to favor chronic inflammation that eventually governs the progression of the disease as well as resistance toward therapy. This has been described for numerous diseases, including cancer (7). Obesity has become one of the biggest public health challenges worldwide due to alarming increases in its prevalence (8). Certainly, a multitude of genetic, environmental and lifestyle factors underlie obesity, but the accumulating data pointing to the gut microbiome as one of the major determinants of body weight and fat distribution is currently attracting most attention (1- 3). Through the gut micro-biota, obesity phenotype is influenced by various mechanisms such as regulation of energy extraction from diet, host metabolism control and interaction with systemic hormonal and immune pathways (6).

Alterations in the abundance and composition of gut bacteria could affect nutrient utilization and conversion to available energy (4). Lines evidence a higher Firmicutes to Bacteroidetes ratio is positively associated with increased ability to ferment complex polysaccharides into harvestable calories that can be absorbed and therefore, explain enhanced energy utilisation and fat deposition, i.e., the phenotype often reported in patients afflicted by an obesity disorder. It alters the host lipid metabolism and lipid storage, resulting in the adiposity and redistribution of body fat (8). It is also an influence on the ecology of the gut microbiota. Besides providing energy, the gut microbiota influences bile acid metabolism influencing lipid digestion and absorption directly. Bacteria present in the gut are capable of converting primary to secondary bile acids, which act as signaling molecules via receptors including TGR5 and FXR. These receptors impact energy utilization, lipid metabolism and glucose homeostasis. A dysregulation of control signals for bile acids may cause Clev.CIN and can impact lipid metabolism and increase fat storage to mediate obesity (3).

There are many studies centering on these newly developed biological therapies trying in fact to target the microbiome, attempting to improve our problems with obesity. FMT has been most effective (1, 2, 5). It encompasses the transfer of gut bacteria from a healthy donor and the possibility for FMT to alter the microbiota composition of the recipient toward a more symbiotic and metabolically favorable ecology seems promising. Conclusion: The definitive evidence for long-term safety and efficacy of this approach is unknown, yet some data indicate the potential to improve certain obesity-related metabolic parameters and overall body fat (101). Further, the application of FMT, open prebiotics and probiotics helping to modulate microbiome are promising. Prebiotics, and especially those from inulin and fructooligosaccharide (FOS don't increase only the growth of good bacteria but are also short chain fatty acid producers with an anti-obesity importance that helps to control appetite and enhance fullness factor as well as energy expenditure (2).

Through changing inflammation, gut barrier function and metabolic signaling pathways live beneficial microorganisms including Lactobacillus and Bifidobacterium species (composing probiotics) have reported different degree of success to body weight reduction or metabolic health improvement. These microbiome-based therapies represent, as already mentioned, the good complement or substitutive solutions regarding classical chains for obesity control diets and physical activity (6, 7). These strategies could potentially reduce the risk associated with both the SBO-complications (e.g., type 2 diabetes, cardiovascular diseases and certain cancer types) as well as enhance weight loss (4).

Historical Perspective on the Link Between Inflammation and Cancer

There is a known association between inflammation and cancer since a long time. Earlier studies have demonstrated that people suffering from chronic inflammatory diseases are at a greater risk of having cancer. Moreover, middle of the last century was also a milestone for understanding the molecular mechanism behind this interaction (8). Identification of important inflammatory cytokines e.g. TNF-alpha, IL-1β and angiogenic factors, VEGF as well key signaling pathways like NF-κB or MAPK has made remarkable progress in understanding the role of inflammation in cancer initiation, progression and metastases. Such molecular mediators can be further employed for developing new therapies designed to halt tumor growth and mediate control of inflammation through their interaction. Potential benefits of the current drugs targeting pro-inflammatory pathways (immune checkpoint inhibitors, and customized anti-inflammatory drugs) have been demonstrated across multiple cancer types (10). Clinics are where these therapies are being tested right now.

Therapeutic Implications: Targeting Inflammation to Improve Cancer Therapy

Recent advances in cancer therapy have brought the microenvironment and its inflammatory actors to center stage for the disease (11). By enabling the precise targeting of neoplastic cells, drugs and immunotherapies including immune checkpoint inhibitors have utterly transformed cancer treatment (12). Prolonged inflammation in the tumour microenvironment may abrogate the action of these therapies via immunosuppression, acquisition of resistance to drugs and remodelling neovasculature for the tumor. Current cancer research primarily investigates remedies focused on the inflammatory nature of the TME, to address these issues. Manipulating the inflammatory pathways of tumors may lead to more efficacious treatments, better patient outcomes and fewer side effects (14).

Mechanisms of Inflammation in Cancer Progression

Key Molecular Pathways in Inflammation and Cancer

Cancer initiation due to inflammation is explained by several biological mechanisms. These pathways are involved in the cell survival, proliferation, migration, angiogenesis and immune evasion (15). The NF-κB pathway plays a key role in regulating pro-inflammatory cytokines, survival genes and genes associated with immune evasion (16). Upon activation by inflammatory cytokines (e.g., TNF-α and IL-1β) NF-κB translocates to the nucleus and initiates transcription of pro-survival and pro-inflammatory genes (17). This activation preserves a pro-inflammatory tumor microenvironment that facilitates tumor development.

The PI3K/AKT and MAPK pathways are also two other important signaling cascades which contribute to tumor formation during inflammation (18). These pathways play a critical role in determining tumor tone and metastatic likelihood and regulate cell proliferation, migration, resistance to death. Of these, perhaps most important in promoting tumor aggressiveness and therapy resistance is the activation of these sequences by inflammatory signals such as cytokines and growth factors (19). In addition, reactive oxygen species (20) as secondary signal molecules of developing inflammation caused by oxidative stress (20-21).

Tumor Microenvironment and Immune Cells

The tumor microenvironment (TME) is a dynamic network of tumour cells, immune cells, stromal cells and the extracellular matrix (ECM). Tumor microenvironment (TME) is shaped and rebalanced by recruitment and activation of different immune cells, including tumor-associated macrophage (TAM), neutrophil, myeloid-derived suppressor cell (MDSC), which are modulated by the signals from inflammation. Subsequently, these immune cells produce an array of cytokines, growth factors and proteolytic enzymes that are important in promoting survival, immune escape and metastatic dissemination of tumor cells (24).

Categorized into an M2 phenotype, the tumor-infiltrating macrophages (TAMs) switch to a state that significantly benefits tumor growth and inhibits antitumor immune responses (25). VEGF is important for tumor development because it offers the nutritional and oxygen conditions that facilitate the stimulation of their expansion; therefore, a pro-angiogen produced from M2 polarized TAMs provides growing (26). In addition, these macrophages suppress cytotoxic immune cells (CTL and NK) activity through secretion of immunosuppressive cytokines like IL-10 and TGF-β (27).

Even though their main function is in preventing infection, neutrophils also promote tumor growth by releasing cytokines, such as IL-8, that promote cancer cell motility and invasion (28). By targeting extracellular matrix (ECM) and further enhancing penetration of tumor cells in surrounding tissues, hidden matrix metalloproteinases (MMPs) under neutrophils together with other immune cells set up a feedback loop that exacerbates the inflammation and accelerates spreading of the tumors/growth (29).

Oxidative Stress and DNA Damage

The pro-inflammatory TME is characteristic for chronic inflammation and serves as a source of persistent reactive oxygen species (ROS) production (20), which possess multifaceted functions in the context of cancer formation and resistance against treatment. At moderate levels, ROS are signaling molecules that trigger pro-survival pathways resulting in tumor cell proliferation, immune evasion and adaptation to stress. However, when in excess, ROS result in oxidative damage of cellular components including lipids, proteins and especially DNA which will then lead to mutations, genomic instability and activation of pro-oncogenic genes (30). This genomic instability facilitates tumor growth and contributes to the more aggressive characteristic of cancer cells, including their ability to resist apoptosis (31).

Importantly ROS in this sense are also a factor of resistance to the conventional cancer therapies. Oxidative stress also promotes the survival of cancer stem cells (CSCs), a subtypethat is resistant to chemotherapy, radiotherapy and immunotherapy, resulting in tumor relapse and metastasis (32). Proinflammatory cytokines, such as IL-6 and TNF-α, sustain high levels of ROS, leading to a positive feedback loop that strengthens proliferative signaling immune suppression through attracting immunosuppressive cells (e.g., MDSCs and Tregs) and angiogenesis. The inflammation-induced fibrosis in the TME builds a physical barrier that prevents efficient delivery of chemotherapeutic drugs, also (33).

Collectively, these mechanisms describe how chronic inflammation and oxidative stress hamper treatment efforts by promoting cancer cell survival, creating an immunosuppressive environment, and hindering drug penetrance (34). Inhibition of ROS production and inflammation signaling, including NF-κB and STAT3, could be a potential strategy to overcome resistance to therapy and increase sensitivity of tumor cells (35).

Inflammation and Metastasis

Inflammation as a Driver of Metastasis

Metastasis, the spread of cancer cells from the primary tumor site to distant organs, is a leading cause of death due to cancer, responsible for most cancer deaths. Inflammation plays a critical role in promoting metastasis through increasing motility, invasion and survival of tumor cells in distant organs (36). Pro-inflammatory cytokines, IL-6 and TNF-a as well as chemokines like IL-8 are able to enhance the motility of tumor cells and increase their invasiveness through activation of signaling pathways that lead to epithelial-to-mesenchymal transition (EMT) (37). Epithelial-mesenchymal transition (EMT), a critical process by which the epithelial tumor cells acquire mesenchymal properties, causes these tumor cells to dissociate from the bulk of the tumor and, thus, increase their ability to invade adjacent tissues (38).

Additionally, inflammatory cytokines induce the production of matrix metalloproteinases (MMPs), enzymes that promote ECM degradation. Breakdown of the ECM allows tumor cells to breach the physical barriers in neighboring tissues and escape into the bloodstream, where they can reach distant organs (39). Once circulating, these CTCs can give rise to metastatic outgrowth at distant organ sites that permits process of commiseration. In addition, inflammation may also initiate angiogenesis, the production of new blood vessels, which is critical to sustain the blood supply of the growing tumor and supported further metastasis (40). Pro-inflammatory cytokines, such as VEGF (vascular endothelial growth factor), play a central role in the angiogenic process which ensures the tumor is well nourished and provided with oxygen to grow and spread (41).

Molecular Mechanisms of Inflammation-Induced Metastasis

The activation of inflammatory cytokines in the tumor surrounding stroma leads to extracellular matrix remodeling, an important step in metastasis. ECM degradation by tumor and immune-cell derived MMPs contributes to the development of an environment conducive for tumor cell motility and invasion (42). In addition, inflammation promotes angiogenesis through upregulated secretion of VEGF as well as other pro-angiogenic factors. This neovasculature not only drives tumor growth, but provides a route for cancer cells to enter the blood stream and thereby metastisize (43).

In conclusion, inflammation directly promotes the metastatic process through several mechanisms including EMT activation, ECM degradation or angiogenesis. These activities enhance the invasive potential of tumor cells to migrate to distant organs and create new lesions.

Impact of Inflammation on Treatment Response

Chemotherapy Resistance Induced by Inflammation

Chemotherapy is still one of the main modalities for cancer treatment, but its efficacy can be plagued by chronic inflammation that occurs in the tumor microenvironment (44). In addition, pro-inflammatory cytokines, including TNF-α, IL-6 and IL-1β, stimulate signaling pathways such as NF-kB and STAT3 that support cancer cell survival by blocking apoptosis and protect tumor cells from chemotherapy-induced cell death (45). These cytokines can also increase DNA repair, resulting in more resistance to DNA-damaging chemotherapeutic agents (46). Moreover, tumor microenvironment (TME) can cause inflammation-mediated fibrosis, forming a physical barrier and preventing penetration of drug as well as leading to decreased chemotherapy agents delivered to the tumor cells (47). In addition, the inflammatory milieu also favored the maintenance of cancer stem cells (CSCs), a subset with high chemoresistance linked to tumor recurrence and metastasis after treatment (48). Neoadjuvant chemotherapy combined with inhibitors of inflammatory pathways (e.g., NF-κB) or cytokine-neutralizing antibodies can inhibit inflammation-induced tumor progression and sensitize cancer cells to chemotherapeutic regimens, providing a tempting approach for overcoming resistance and increasing efficacy of treatment (1).

Immunotherapy Resistance

Immunotherapy has become a game-changer in the way of treating cancer, harnessing the immune system to detect and destroy tumor cells. Chronic inflammation in the cancer can act to suppress immunity and may therefore limit the effectiveness of immune therapies (49). Inflammation may induce the expression of immunologic checkpoints like PD-L1 [77], which immune response repressive through binding to T-cell-expressing PD-1 receptors, thus impeding their action in countering against cancer. Meanwhile, inflammatory cytokines such as IL-10 and TGF-β help recruit immunosuppressive cells like myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), weakening immune responses and promoting pathways for immune escape (50).

In addition to stimulating immunological checkpoints, inflammation can mediate TIL immune exhaustion. The effector function of T cells that are able to target tumor can be reduced by pro-inflammatory signals (51).

Paradoxically, acute inflammation may enhance anti-tumor immune response by allowing infiltration of immune cells such as CTLs and NK into the tumor (52). This implies that a systemic control of inflammation would increase the immunotherapy efficiency. Therefore, drugs targeting pro-inflammatory pathways alone in concert with promoting immune activation might improve the efficacy of immunotherapies (53).

Targeted Therapies and Inflammation

Targeted drugs aim at blocking specific signaling pathways which contribute to the cancer cell growth. The presence of inflammation in the TME may amend the response to these medications. These inflammatory cytokines, such as IL-6 and TNF-α can activate the PI3K/AKT pathway which is often associated with tumor cell survival, inhibition of apoptosis and metastasis 11. Such activation can render targeted drugs ineffective by eliminating therapeutic benefit of blockage (54). Also, the remodeling of extracellular matrix due to inflammation might modulate the efficacy of targeted treatment by altering tumor biomechanical properties. Furthermore, augmented stiffness in the extracellular matrix often due to inflammation makes it difficult for anticancer therapeutic payload to penetrate the tumor itself (55).

There may be a role for using targeted therapy in combination with anti-inflammatory treatments to maximize their effectiveness. Inhibitors of inflammatory cytokines or immune modulators applied together with targeted therapy might even pave the way for better drug delivery and overcome mechanisms of resistance(56).

Therapeutic Strategies for Targeting Inflammation in Cancer

Anti-Inflammatory Agents

Targeted drugs aim to block specific signaling pathways that drive the growth of cancer cells. The presence of inflammation within the TME may have an impact on the potential efficacy of these agents (57). Inflammatory cytokines, such as IL-6 and TNF-α can also activate the PI3K/AKT pathway which is commonly involved in tumor cell survival, resistance to apoptosis and metastasis. This activation may confer resistance to targeted drugs by negating the therapeutic effects of pathway blockade (58).

Moreover, inflammation-driven ECM remodeling may alter the physical characteristics of tumour which can in turn influence the effective of targeted therapy. Elevated stiffness in the extracellular matrix, often due to inflammation, may block targeted therapeutics from penetrating into the tumor. Combining targeted therapy with anti-inflammatory medications could help them work better. Entherapies that promote cytokine inhibition or immune modulation, combined with targeting therapy may provide a way to increase drug delivery and overcome resistance mechanisms (55).

Immunomodulatory Therapies

Immunomodulatory therapies are a promising avenue to combat inflammation in cancer. These immune-therapies aim to influence the body's defense system to create a preferable (ie, beneficial) inflammatory response which will improve anti-tumor immunity(59). One such approach is the use of immune checkpoint inhibitors that block inhibitory receptors expressed on immune cells, such as PD-1 and CTLA-4. By deactivating these receptors, checkpoint inhibitors release the "brakes" on the immune system and thus allow T cells or NK cells to attack tumor cells more efficiently (60).

Prolonged inflammation can cause immune cell loss and reduces sensitivity to immunotherapy, as a result, the research on regulation of inflammatory responses has become very important (61). Therapies that inhibit the recruitment of immunosuppressive cells including MDSCs or Tregs could potentially lead to an improved response to immune checkpoint inhibitors (62). Similarly, the use of agents regulating inflammatory cytokines within TME might increase effector immune cell infiltration and activation such as CTLs and NK cells (63).

Targeting Tumor-Associated Inflammatory Pathways

In addition to non-specific anti-inflammatory agents, treatments that specifically inhibit the inflammatory cascades involved in cancer progression would offer a more targeted strategy (64). The NF-κB signalling pathway is a major target for cancer therapy given its central role in inflammation and tumour formation. IKK inhibitors and other NF-κB signalling inhibitors have shown promise in preclinical studies, as they reduced tumor outgrowth and metastasis (65).

Other appealing targets include JAK/STAT and PI3K/AKT pathways which are often activated by inflammatory cytokines. Blocking these pathways can decrease inflammation and tumor progression (66). Developing personalized drugs that can specifically control inflammation in the tumor microenvironment is very attractive. Clinical trials are needed to demonstrate the safety and effectiveness of these treatments with conventional therapy for cancer (67).

Challenges and Future Directions

Specificity in Targeting Inflammation

Inflammatory targeting provides a strategy to improve the outcomes of cancer therapy, but with significant challenges for implementation. A major hurdle is to target the exact inflammatory routes promoting cancer development, and maintain the body's innate immune responses (68). Inflammation is essential for immunological surveillance, tissue repair, and immunoprotection. Overinhibition or non-specific inhibition of inflammation can compromise critical response to infection, autoimmunity, and inadequate repair (69).

To reduce or avoid these risks, drugs need to be specifically designed to inhibit pro-tumorigenic inflammatory mediators such as certain cytokines [e.g., (TNF-α and IL-6)] and signaling pathways that are elevated within the TME (70). At the same time, such therapies must preserve an antitumor immune response by retaining beneficial components of inflammation that contribute to immune activation such as those for tissue repair or attraction of cytotoxic immune cells (71). Achieving this balance requires a more detailed knowledge as to what specific roles the various inflammatory pathways play in differing types of cancer and the identification of novel, highly-target-selective, proinflammatory targets (72).

Clinical Trials and Biomarkers

An important challenge in anti-inflammatory cancer therapy is the lack of reliable biomarkers to identify patients who will respond. The inflammatory response is a complex dynamic process and varies significantly between individuals and types of tumors (73). While certain pro-inflammatory mediators, such as IL-6, TNF-α and IL-1β are known to support cancer growth, the specific inflammatory components associated with each patients disease may differ. This heterogeneity makes the prediction of patient responses to therapeutics targeting inflammation difficult (74).

To solve this problem, identifying and validating the accurate biomarkers that can reflect the inflammatory status of TME and predict therapeutic response are urgently needed. These biomarkers could include some cytokines/chemokines or signaling molecules which are increased in tumor microenvironment and being associated with poor prognosis (75). Liquid biopsy techniques such as circulating tumor DNA, RNA, and protein have the potential for non-invasive detection of these markers. In addition, IHC or gene expression profiling from tumor biopsies may help determine the inflammatory nature of some malignancies and guide personalized treatment plans (76).

The efficacy of anti-inflammation approaches will depend on clinical trials that fully evaluate their safety and effectiveness in combination with standard cancer treatments. Although the preclinical evidence suggests that anti-inflammatory drugs can enhance treatment efficiency of chemotherapy, immunotherapy, and target therapy, these findings are not easy to translate on real patients and so need a thorough test across a variety of demography before they are used in the clinic (77). Potential damaging consequences of the modulation of inflammatory responses must be considered by clinical trials, because insufficient tuning could entail unexpected consequences as immune depression or excessive local tissue damage (78).

Overcoming Therapy Resistance

Resistance to therapy is a major challenge in oncologic treatment and represents a critical barrier to successful patient management. Despite the remarkable achievements achieved in regards to chemotherapy, immunotherapy, and targeted therapeutic drugs, a number of the malignancies have delevoped resistance to drug treatments. This resistance frequently leads to relapse and metastasis, a challenging aspect in cancer treatment (79).

The inflammation is also the key stimulator for inducing this drug resistance, it up-regulate some survival signaling pathways and contributes to immune escape mechanisms exploited by cancer cells (80). The pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF)-α have the potential to activate multiple signaling pathways including NF-κB and STAT3. These pathways mediate the increased of tumor cells survival, magulating proliferation, inhibiting apoptosis and enhancing DNA repair. These activities together promote resistance to chemotherapy and radiotherapy (81, 82).

In order to successfully overcome the formidable obstacle of therapeutic resistance, a comprehensive treatment strategy is required that includes inflammation-modulating agents in combination with established treatments. This broad-ranged approach is expected to act on both the cancer cells and the inflammatory microenvironment, which interconnects with mechanisms of resistance (83). For instance, cytokine inhibitors or NF-κB antagonists, added to chemotherapy, could help reducing the inflammatory signals that protect cancer cells from the damaging processes activated by chemo (84). Likewise, a combination of inflammation-modifying interventions and immune-based approaches such as immune checkpoint inhibitors may potentiate the anti-tumour immune response by alleviating the immunosuppression that is frequently evident in locoregional tumour microenvironments (85).

In addition, the formidable challenge of overcoming resistance in cancer treatments requires accurate targeting of cells, such as CSCs- a specific subset of cells characterized by its remarkable capacities for self-renewal and its extraordinary resistance to classic therapeutic approaches in contrast to other cell types (86). It has been shown that inflammation is a crucial element in supporting the survival of these cancer stem cells, and therefore targeting those inflammatory pathways which maintain the support provided to these resistant population of cells could result into development of more potent therapeutic strategies (87). A rationally designed multi-targeted therapy targeting the CSC population and its pro-survival inflammatory factors offers an attractive approach for improving treatment efficacy leading to the potential of overcoming resistance against current therapies (88).

The development of combination drugs that effectively and cooperatively influence both the malignant tumor cells and the associated inflammatory processes within the tumor is a very appealing approach to dramatically enhance overall therapeutic efficacy of cancer therapy (89). Due to an ability to target the cancer cells and also against a surrounding inflammatory response, these new agents may dramatically improve on clinical outcomes in patient who have failed current treatment regimens (90). Further active investigation is warranted to determine the optimal combinations of anti-inflammatory agents with existing treatments as well as the clinical applicability and safety of these multi-faceted therapeutic approaches (91).

CONCLUSION

Inflammation is an important factor in cancer development, metastasis and resistance to therapy. The capacity to modulate inflammation, both alone, and in combination with traditional as well as novel anticancer agents holds substantial potential to enhance treatment responsiveness and improve patient outcomes. With a better appreciation for the intricate relationship between inflammatory response and tumor microenvironment, personalized and context-specific anti-inflammatory interventions are emerging as an absolute necessity. In the future years, research should focus on identification of reliable biomarkers to allow patient stratification, discovery of new and safer anti-inflammatory drugs and how they can be integrated into clinical management. PAVE'ing the way and bringing forward these efforts into properly-designed clinical trials will be essential to bridge novel preclinical findings into effective, real-life interventions that can help more patients with cancer.

Authors's Contribution

Maryam Abbasi Saeidi and Mina Ekrami Noghabi data curation; editing and review. The author read and confirmed the final manuscript.

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Conflict of Interest

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Consent for publication

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