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CONNECTION BETWEEN CANCER AND INFLAMMATION: COMPREHENSIVE REVIEW

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ABSTRACT

Inflammation is often associated with the development and progression of cancer. The cells responsible for cancer-associated inflammation are genetically stable and thus are not subjected to rapid emergence of drug resistance; therefore, the targeting of inflammation represents an attractive strategy both for cancer prevention and for cancer therapy. Tumor-extrinsic inflammation is caused by many factors, including bacterial and viral infections, autoimmune diseases, obesity, tobacco smoking, asbestos exposure, and excessive alcohol consumption, all of which increase cancer risk and stimulate malignant progression. In contrast, cancer-intrinsic or cancer-elicited inflammation can be triggered by cancer-initiating mutations and can contribute to malignant progression through the recruitment and activation of inflammatory cells. Both extrinsic and intrinsic inflammations can result in immune suppression, thereby providing a preferred background for tumor development. The current review provides a link between inflammation and cancer development. Inflammation that promotes cancers is one of the hallmarks of cancer. Research has demonstrated that inflammation, both acute and chronic, has a significant impact on the development of cancer. Advances in the study of inflammation have demonstrated a link between inflammatory processes and tumor growth, neoplastic transformation, and the production

of metastases and recurrences. Furthermore, the invasive procedures for tumors (biopsy and surgery) impact the residual tumor cells by promoting their migration, proliferation, and survival. In this review, we concentrate on the state of our understanding on inflammation and how inflammatory processes may induce cancer.

Keywords: Inflammation, cancer, cell signalling, immunotherapy's, cyclooxygenase-2

INTRODUCTION

An essential component of the innate immune system's reaction to infection or tissue damage is inflammation, which also makes it easier for circulating immune cells and antibodies to bind to the injured tissue and initiate the adaptive immunological response. Certain cancers can be caused by chronic inflammation, and solid tumors can cause and sustain local inflammatory processes that promote tumor growth and metastasis. Damaged tissues emit substances like prostaglandins and histamines, which trigger an inflammatory response. White blood cells react by moving to the injured tissues and producing chemicals that encourage cell division and growth in order to restore the tissue. Once the injury has healed, the inflammatory phase is over. However, issues might develop when inflammation happens unintentionally or persists over an extended period of time.

As a result, efforts to restore injured tissues have focused on inflammatory pathways, a topic of ongoing active inquiry. Furthermore, there are significant differences in both systems' responses to cancer, which develops from "self" cells that change into cancerous ones. In the clinic, immunotherapies that stimulate adaptive immunity have recently demonstrated previously unheard-of potential, leading to long-lasting responses and significantly raising the survival rate of patients with advanced stage melanoma. As a result, the connection between inflammation and cancer is once again in the forefront of clinical oncology **[1]**.

Rudolf Virchow's discovery in the 19th century of leukocytes within tumors offered the first clue as to a potential connection between inflammation and cancer. However, it has only become evident for the last ten years that inflammation is a major factor in the development of tumors **[2]**.

However, inflammation can be dangerous and even cause disease if it persists for an extended period of time or becomes chronic. Chronic inflammation has been associated with pro-inflammatory cytokines, chemokines, adhesion molecules, and inflammatory enzymes **[3]**.

Several illnesses such as autoimmune diseases, cancer, diabetes, lung conditions, Alzheimer's disease, arthritis, and cardiovascular problems have all been linked to chronic inflammation **[4]**.

According to Virchow, carcinogenesis is associated with "lymphoreticular infiltration" in the inflammatory tissue, and the vascularization of the tumor is necessary for the continued "infection" (dissemination of cancer cells). According to what is now known and the majority of recent research, inflammation and carcinogenesis are directly causally related. According to current estimates, inflammatory response may account for up to 20% of deaths due to cancer **[5]**.

Chronic inflammatory illnesses (such liver cancer and hepatitis), infections, or inflammations brought on by exposure to chemicals in the environment (like asbestos) raise the risk of getting cancer. Further supporting the involvement of inflammation in neoplastic transformation is the association between the administration of non-steroidal anti-inflammatory medicines and a lowered risk of acquiring various tumors as well as a decreased mortality rate.

In 2011, Hanahan and Weinberg identified tumor-promoting inflammation as one of the cancer's enabling characteristics, along with other characteristics. Even though inflammation is a crucial pro-tumorigenic component, tumors without inflammatory origins frequently have it in their microenvironment. Mantovani separated the two paths that contribute to inflammation associated with cancer **[6]**. The extrinsic pathway defines the inflammatory conditions that promote carcinogenesis, while the intrinsic pathway is linked to genetic processes that cause inflammation and neoplastic transformation.

The diagnosis and treatment of cancer linked to inflammation may be improved by more investigation into the pathways underpinning these processes. In this review, we concentrate on the most recent findings regarding the inflammatory process' role in carcinogenesis and the encouragement of cancer growth.

Somatic mutations and environmental variables cause nearly 90% of cancer cases, with germline mutations affecting just a small fraction of cancer cases. Some kind of chronic inflammation is linked to numerous environmental cancer causes and risk factors **[7]**. Thirty percent of cancer cases are related to inhaled pollutants (including asbestos and silica) and tobacco use, whereas twenty percent of cancer cases are associated to chronic infections. Fifteen percent of cancer cases are related to dietary variables **[8]**.

New research has revealed the cellular and molecular pathways that connect inflammation and cancer. Two pathways have been schematically identified: in the extrinsic pathway, inflammatory conditions promote the development of cancer, and in the intrinsic pathway, genetic events leading to neoplasia start the expression of programs related to inflammation that direct the creation of an inflammatory microenvironment.

Chronic inflammation can be caused by autoimmune diseases (e.g., inflammatory bowel disease for colon cancer), inflammatory conditions of uncertain origin (e.g., prostatitis for prostate cancer), and infections (e.g., Helicobacter pylori for gastric cancer and mucosal lymphoma; papilloma virus and hepatitis viruses for cervical and liver carcinomas, respectively). Inflammation associated with cancer, the eighth hallmark of cancer, is linked to genetic instability **[9]**.

Rudolf Virchow first identified leukocytes in neoplastic tissues in 1863, marking the beginning of the link between inflammation and cancer. He proposed that the origin of cancer at sites of persistent inflammation was reflected in the "lymphoreticular infiltrate." Virchow's concept has been strengthened over the past ten years by our understanding of the inflammatory environment of malignant tissues, and the connections between inflammation and cancer are beginning to have implications for therapy and prevention **[10]**.

Causes of Inflammation [11]

The body's reaction to tissue damage caused on by trauma, infection, ischemia injury, physical harm, or exposure to toxins is inflammation. The inflammatory response of the body triggers immunological reactions and cellular alterations that lead to tissue healing and cellular proliferation (growth) at the site of injury. If the underlying cause of the inflammation does not go away or if some of the control systems that are supposed to stop the process do not work, the inflammation may turn chronic. Chronic inflammatory responses can lead to cell mutation and proliferation, which frequently fosters an environment that is favorable for the growth of cancer.

Cancer sufferers confront an extremely difficult situation known as the "perfect storm." This holds true for when cancer first appears, but it's much more crucial for when the illness progresses. In order to activate these internal mutations, different signaling pathways play a crucial role in generating epigenetic modifications on the exterior of the cell. Treating the inflammatory causes is therefore always crucial.

Several stages of carcinogenesis, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis, have been connected to chronic inflammation.

There are several causes of chronic inflammation. These are a few things specialists have found to appear to increase the risk of specific cancers.

- **Infections that don't go away:** In the world, 20% of cancer cases are linked to infections. Certain infections have the ability to create inflammation, which alters the body's surrounding cells and may ultimately result in cancer. For example, *Helicobacter pylori (H. pylori)* infection has been associated with certain stomach malignancies.
- **Abnormal immune response:** Colon cancer risk is raised by autoimmune diseases such as Crohn's disease and ulcerative colitis, which can induce persistent inflammation in the gastrointestinal tract.
- **Obesity:** New blood vessels are created as a result of the production of new fat tissue. That may promote persistent inflammation and raise the chance of developing cancer.
- **Diet:** Consuming large amounts of alcohol, processed foods, red meat, or saturated fat can increase the risk of gastrointestinal malignancies and cause chronic inflammation. Dietary factors frequently contribute to acid reflux, which can harm throat tissue and increase the risk of esophageal cancer.
- **Other factors.** Chronic inflammation can be influenced by lifestyle choices like stress reduction and the quality of one's sleep.

Cancer development:

Malignant neoplasms that exhibit metastatic growth are classified as cancer. Due to a multitude of etiologic causes, including environmental stress and genetic instability, it can arise in nearly every organ and tissue **[12]**. Nonetheless, it is still acknowledged that the genesis of cancer is a multi-step process in which particular sorts of growth advantages are conferred by genetic mutations, which in turn propels the ongoing transformation of normal cells into malignant cancer cells. The self-sufficiency of growth signals, insensitivity to antigrowth signals, escape from apoptosis, unregulated proliferative potential, accelerated angiogenesis, and metastasis are some of the major alterations that define malignant growth. These changes are all intricate and require the cooperation of several signaling mechanisms. We will learn that inflammation may play a role in the

development of various cancer characteristics in a later section **[13]**.

Mechanism for the association between inflammation and cancer

The hallmarks of chronic inflammation are persistent tissue damage, cellular proliferation brought on by damage, and tissue regeneration. In this situation, cell proliferation is typically associated with "metaplasia," a reversible alteration in the kind of cell. Since "dysplasia," a disturbance of cellular proliferation that results in the formation of abnormal cells, is typically detected next to the site of neoplasm, it is thought to have preceded cancer **[14]**.

Mutagenic potential for inflammation

Macrophages dominate the chronic inflammatory microenvironment. In order to combat infection, these macrophages and other leukocytes produce large amounts of reactive oxygen and nitrogen species **[15]**. However, the continued presence of these infection-fighting chemicals is harmful in an environment where tissue damage and cellular proliferation are ongoing. They could also produce mutagenic substances like peroxynitrite, which combines with DNA to alter growing stroma and epithelial cells. To worsen DNA damage, macrophages and T-lymphocytes may release macrophage migration inhibitory factor and tumor necrosis factor-alpha (TNF-α) **[16]**.

By reducing p53-dependent preventive responses, migration inhibitory factor contributes to the build-up of carcinogenic mutations. Migration inhibitory factor disrupts the Rb-E2F pathway, which also plays a role in carcinogenesis.

Helicobacter pylori and cancer risk

It is well recognized that the bacteria *H. pylori* can colonize the human stomach and cause intestinal metaplasia, gastric cancer, and chronic atrophic gastritis. The development of stomach cancer, one of the most difficult malignant diseases in the world with few effective treatments, is significantly increased by *H. pylori* infection **[17]**.

The Correa sequence, which describes the sequential progression to gastric cancer defined by various histological alterations, best illustrates the multistep pathophysiology of gastric cancer. According to this hypothesis, an *H. pylori* infection sets off an inflammatory response that leads to chronic gastritis and eventually atrophic gastritis. Intestinal metaplasia, which can be further divided into full and partial subtypes, comes next. Some patients will later progress from this stage of dysplasia to the intermediate stage of gastric cancer **[Figure 1] [18]**.

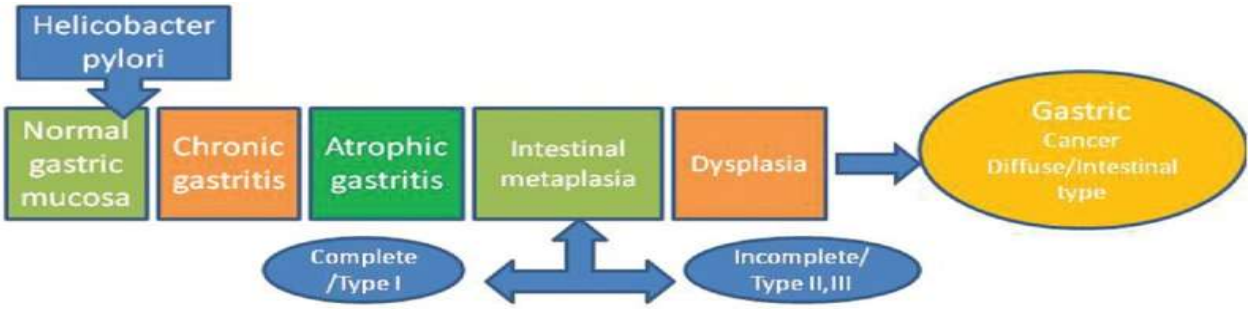

Figure 1: Stage of gastric ulcer

Eradication of *H. pylori* may improve or eliminate intestinal metaplasia and atrophy, which may prevent the development of stomach cancer. It is important to highlight that even with effective eradication therapy, stomach cancer can still arise. Not all precancerous lesions resolve once *H. pylori* is eradicated; this may depend on the severity and duration of preneoplastic alterations at the time of eradication.

Inflammatory cells and microenvironment:

Host leukocytes are found in both the tumor and the supportive stroma, which defines the inflammatory microenvironment of malignancies. Tumor-infiltrating lymphocytes may have a role in the development and spread of cancer as well as the immune system suppression linked to malignant illness **[19]**.

Macrophages

Most cancers, if not all of them, include a significant infiltration of tumor-associated macrophages (TAM). TAM is transported into the tumor by chemoattractant cytokines known as chemokines, which are derived from circulating monocytic progenitors. Colony-stimulating factors are cytokines that are produced by a large number of tumor cells that extend the survival of TAM. TAM has the ability to eradicate tumor cells when it is activated correctly or cause tissue-damaging reactions that target the vascular endothelium. Protease enzymes, which break down the extracellular matrix, are also produced by TAM along with growth and angiogenic factors. As a result, TAM can encourage the growth of tumor cells, angiogenesis, invasion, and metastasis **[20]**.

Dendritic cells

As a bridge between innate and adaptive immunity, dendritic cells are essential for the maintenance of tolerance as well as the activation of antigen-specific response. Generally speaking, tumor-associated dendritic cells (TADCs) exhibit an immature phenotype and a reduced capacity to activate T-cells **[21]**.

In contrast to TAM, which is uniformly distributed throughout tumor tissue, TADC has a distinct distribution. The ineffective maturation signals, the rapid migration of mature cells to lymph nodes, or the existence of maturation inhibitors could all be contributing factors to TADC's immaturity. It is likely that tumor antigens will not effectively elicit responses from TADC.

Lymphocytes

In the tumor microenvironment, natural killer cells are rare. There is a "memory" phenotype in the majority T-cell population. These tumor-infiltrating T-cells have an unknown cytokine profile, however in certain cancers (including Hodgkin's disease, bronchial carcinoma, cervical carcinoma, and Kaposi's sarcoma), they mostly generate interleukins (ILs) 4 and 5, not interferon. Interferon is linked to Th1 responses, while cytokines like IL-4 and 5 are connected to T-helper type 2 (Th2) cells **[22–24]**.

Chronic Inflammation in Cancer Development

Inductor	Inflammation	Cancer
Gut pathogens	Inflammatory bowel disease	Colorectal cancer
Tobacco smoke	Bronchitis	Bronchial lung cancer
Helicobacter pylori	Gastritis	Gastric cancer
Human papilloma virus	Cervicitis	Cervical cancer
Hepatitic B/C virus	Hepatitis	Hepatocellular carcinoma
Bacteria, gall bladder stones	Cholecystitis	Gall bladder cancer
Tobacco, genetics, alcohol	Pancreatitis	Pancreatic cancer
Epstein-Barr virus	Mononucleosis	Burkitt's lymphoma
Ultraviolet light	Sunburn	Melanoma
Asbestos fibers	Asbestosis	Mesothelioma
Gram-uropathogens	Schistosomiasis (Bilharzia)	Bladder cancer
Gastric acid, alcohol, tobacco	Esophagitis	Esophageal adenocarcinoma

Inflammatory Cell in Tumor Development:

- More genetic and epigenetic steps are needed to transform started cells into malignant tumors rather than just one mutation. It is also discovered that a few of these incidents are connected to long-term inflammation.
- For example, fibrosis, psoriasis, and rheumatoid arthritis are conditions associated with chronic inflammation, and angiogenesis is a crucial component in the growth of tumors. Furthermore, the basement membrane must rupture in order for tumor cells to

invade and migrate, and this can be aided by the inflammatory environment around the tumor **[25–26]**.

- A diverse range of immune cells, including leukocytes, penetrate the growing tumor site to create the inflammatory microenvironment surrounding the tumor. It has also been discovered that lymphocytes, neutrophils, eosinophils, dendritic cells, mast cells, and macrophages are important elements in cancers that develop from the epithelium.
- Immune cell infiltration into tumors may inhibit tumor growth. The idea that inflammatory cells in tumors linked to inflammation enhance tumor growth, however, is a growing source of concern. Dysregulation of the development and migration of epithelial cells is caused by accumulated mutations. Leukocyte recruitment signals may also be sent by these dysregulated epithelial cells **[27]**.
- Tumor cells may also release chemokines and cytokines to draw in immune cells and promote the growth of malignancy. Increased tumor-associated macrophages (TAM) density was linked to a worse prognosis in clinical investigations, but due to inconsistent results, research on the involvement of other immune cells, such as mast cells, neutrophils, and dendritic cells, in the formation of tumors, is currently ongoing **[28–30]**.

KEY MOLECULAR PLAYERS IN LINKING INFLAMMATION TO CANCER

To address the details of transition from inflammation to cancers and the further development of inflammation-associated cancers, it is necessary to investigate specific roles of key regulatory molecules involved in this process.

Investigations into the precise functions of important regulatory molecules engaged in this process are required to address the specifics of the shift from inflammation to malignancies as well as the continued development of cancers associated with inflammation.

Pro-inflammatory cytokines

Many common cancers have a cytokine network that is abundant in growth factors, chemokines, and inflammatory cytokines but often deficient in cytokines implicated in targeted and long-lasting immune responses.

There is now indication that tumor-associated leukocytes, platelets, and/or tumor cells can create inflammatory cytokines and chemokines, which may directly aid in the development of cancer. Hypoxia can induce a variety of cytokines and chemokines, which is a significant physiological distinction between tumor and healthy tissue. TNF, IL-1 and 6, and chemokines are a few examples. Cytokines released by both tumor and host stromal cells make up the immunological response to malignancies. Tumor-derived cytokines, including transforming growth factor-h, VEGF, and Fas ligand, may make it easier to suppress the immune system's reaction to malignancies. Furthermore, it has been documented that inflammatory cytokines promote the spectrum of tumor development.

Tumor necrosis factor

TNF is a multipurpose cytokine that affects many various aspects of biological processes, including differentiation, proliferation, survival, and death of cells. TNF is a pro-inflammatory cytokine released by inflammatory cells that may play a role in the carcinogenesis of inflammation. TNF activates various signaling pathways, including c-Jun N-terminal kinase (JNK) and nuclear factor-κB (NF-κB), to carry out its biological actions. A key antiapoptotic signal for cell survival is NF-κB, but persistent JNK activation is a factor in cell death. The way that NF-κB and JNK interact with one another affects how cells react to TNF. TNF has two opposing effects: it may be pro- or antitumorigenic.

Because TNF promotes the development, proliferation, invasion, and metastasis of cancer cells as well as tumor angiogenesis, it is possible that TNF functions as an endogenous tumor promoter. However, TNF may be a carcinogen. TNF is a possible cancer treatment because of its ability to cause cancer cell death.

TNF is frequently found in conjunction with ILs-1 and 6 and macrophage colony-stimulating factor in human ovarian, breast, prostate, bladder, and colorectal cancers, lymphomas, and leukemias. TNF can also be found in malignant and/or stromal cells in these conditions.

Interleukins 1 and 6 in cancer regulation

The pleiotropic cytokine IL-6 is involved in inflammation, hematopoiesis, and the immunological response. In addition to being produced by a range of healthy cells, such as macrophages and monocytes, it is also expressed by several tumor tissue types, including colorectal, ovarian, breast, and prostate cancer. In addition, IL-6 might be crucial for a number of tumor-related processes, such as angiogenesis, metastasis,

apoptosis, tumor development cell proliferation, migration, and invasion.

IL-10, originally known as "cytokine synthesis inhibitor" or "cytokine inhibitory factor," is produced by nearly all leukocytes and a variety of human tumor cells, including those from the breast, kidney, colon, pancreas, malignant melanomas, and neuroblastomas. It inhibits the production of cytokines by T helper cells. In order to inhibit the mediators of inflammation that promote tumor growth and metastasis, IL-10 is necessary. In particular, TAMs generate IL-10 and are linked to immunosuppression within tumors, creating an environment that is favorable for the development of cancer.

Treatment with an IL-1 receptor antagonist, which blocks IL-1's activity, significantly lowered the growth of tumors in mice models of metastasis, indicating that metastasis is aided by local IL-1 production. Furthermore, mice lacking IL-1 showed resistance against the growth of experimental metastases.

Chemokines

Leukocyte recruitment to inflammatory areas is mostly dependent on a class of chemoattractant cytokines known as chemokines, which are primarily induced by inflammatory cytokines. The two main families of chemokines, α (or CXC) and β, are produced by most malignancies. While CC chemokines function on a variety of leukocyte subsets, including monocytes, eosinophils, dendritic cells, lymphocytes, and natural killer cells, but not on neutrophils, CXC chemokines are generally active on both neutrophils and lymphocytes. CXC chemokines like IL-8 are also commonly secreted by tumors in humans and mice. Despite the fact that neutrophils are scarce in tumors, these chemokines are strong neutrophil attractants. Nevertheless, melanoma cell migration and proliferation are induced by both IL-8 and a similar chemokine known as "gro."

Cancer-promoting inflammation:

- It has been established that inflammation has a significant role in the initiation and advancement of cancer. It has been documented that immune cells and molecular communication pathways cause chronic inflammation, which increases the body's vulnerability to different types of cancer.
- Research indicates that chronic inflammatory illnesses may be associated with up to 25% of cancer cases; the precise mechanism underlying this association is still unknown.

- In clinical terminology, certain chronic inflammatory disorders have been identified as precancerous lesions of tumors. As an example, inflammatory bowel disease (IBD) is widely recognized as a precancerous lesion of colorectal cancer (CRC).
- Clinical observations have demonstrated that, over the course of several years to decades, IBD may develop into malignant tumors. Moreover, it is well recognized that one traditional technique for inducing CRC in mice is chemical stimulation of IBD.
- The DNA methylation level of colon cancer linked to IBD differs from that of colon cancers that occur randomly. Furthermore, a study employing human CRC single-cell multiomics sequencing has demonstrated the significant regulatory role that epigenetic inheritance plays in the onset and progression of CRC.

Inflammation in cancer recurrence:

Apart from initiating neoplastic transformation or stimulating tumor growth, inflammation can also be a significant factor in the post-treatment recurrence phase. Surgery is the gold standard for treating breast cancer; nevertheless, surgery causes an inflammatory response that may hinder the spread of cancer cells. Animal models supported these observations. After the mice's main tumor was removed, their serum became more abundant in growth factors, which accelerated the growth of the cancer cells.

Additionally, surgical wound fluids obtained from individuals with breast cancer following breast-conserving therapy have been used to test this hypothesis. In vitro, surgical wound fluids stimulated the growth, migration, and invasiveness of cancer cells. Interestingly, intraoperative radiation treatment reversed this effect, demonstrating that therapy selection may have a major influence on wound healing and inflammatory response after promoting stemness and tumor-initiating properties in breast cancer cells via STAT3 signaling.

Researchers also looked at the makeup of surgical wound fluids, and they found that patients receiving neoadjuvant chemotherapy had higher concentrations of inflammatory cytokines in their wound fluids. Higher quantities of cytokines were found in the inflammatory factors TNF and IL-6 discussed before.

Additional in vitro research demonstrated that even at distal anatomical locations, the systemic effects of surgery can stimulate the proliferation of tumor cells. They discovered

that tumor growth brought on by surgery was linked to both a local and systemic inflammatory response, which was characterized by the production of cytokines and the movement of myeloid cells into the mice's bloodstream. A notable portion of patients treated for cervical cancer have also shown signs of inflammation after radiation therapy.

CONCLUSION:

In conclusion, our comprehensive exploration of the intricate connection between cancer and inflammation underscores the pivotal role that chronic inflammatory processes play in the initiation, promotion, and progression of various types of cancer. Through an extensive review of scientific literature and empirical evidence, we have illuminated the multifaceted interplay between inflammatory responses and the development of malignancies, revealing key cellular and molecular mechanisms that contribute to tumor growth and evasion of the immune system.

The identified links between chronic inflammatory conditions, such as infections and autoimmune diseases, and an elevated risk of specific cancers emphasize the importance of understanding the dynamic relationship between the body's immune response and oncogenesis. Our project has highlighted the significance of inflammatory mediators, signaling pathways, and the immune system in shaping the tumor microenvironment, fostering angiogenesis, and providing crucial survival signals to cancer cells.

Moreover, the exploration of therapeutic implications underscores the potential for targeted interventions aimed at modulating inflammatory pathways to disrupt the favorable conditions for tumor growth. The development of anti-inflammatory drugs and immunotherapies emerges as a promising avenue in the quest for effective cancer prevention and treatment strate.

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