Article

Chronic Inflammation and Blood Cancer

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Abstract

Chronic inflammation may have a detrimental impact on human health as it tends to result in cancer. In addition, it is often linked to different steps that participate in tumorigenesis, including cellular transformation, survival, promotion, invasion, proliferation, angiogenesis, and metastasis. Hence, inflammation predisposes cancer development and plays a vital role in promoting all tumorigenesis stages. Inflammation is caused by many factors, such as bacterial and viral infections, tobacco smoking, autoimmune diseases, obesity[21], asbestos exposure, and many others, increasing cancer risk. Moreover, cancer can be enhanced by mutations that proceed to cancer progression. Consequently, it leads to immunosuppression and provides a favorable background for tumor development. Although many studies address the question of relationships between inflammation and cancer development, little attention is paid to the link between inflammation and blood cancer. Therefore, the current study reviews the role of inflammation in cancer development, particularly in blood cancer. A meta-analysis research approach meets the research objective and answers the research question. The review results indicate that chronic inflammation directly relates to the development of many cancer types, blood cancer in particular.

Keywords: blood cancer; chronic inflammation; inflammation; mutation; tumor

 doi:10.20944/preprints202211.0365.v2

INTRODUCTION

Inflammation is a normal physiological response of an injured tissue that needs healing [13]. An inflammatory process begins when a damaged tissue releases chemicals [2]. As a result, white blood cells produce substances that make cells divide and grow, aiming at rebuilding the tissue and repairing it. As soon as the wound is healed, the process of inflammation begins to approach its end [13]. However, in chronic inflammation, the inflammatory process tends to set up even when there is no injury [5]. It means that the process does not end due to the nature of inflammation. It is not always evident why the inflammation occurs and proceeds, but it may be provoked by abnormal immune reactions to normal tissues, infections, and obesity [13] [20]. Over time, chronic inflammation may lead to DNA damage and cancer. According to Hassuneh, Nagarkatti, and Nagarkatti (2013), chronic inflammation is linked to different steps that participate in tumorigeneses, such as cellular transformation, survival, promotion, invasion, proliferation, angiogenesis, and metastasis. Therefore, inflammation predisposes cancer development and promotes all tumorigenesis stages [5]. Many articles address the impact of inflammation on the onset and progression of certain cancer types. However, there is little scientific attention to the link between inflammation and the positivity of developing blood cancer. It remains one of the most common issues that affects people irrespective of age, personal characteristics, and status. Therefore, the current study reviews the role of inflammation in cancer development, particularly in blood cancer.

There is an idea that only some cancer types are caused by germline mutations [17]. Therefore, nearly 90% of cancers are linked to environmental factors and somatic mutations [22]. Chronic inflammation is one of the many environmental causes of cancer, as it significantly contributes to the risk factors. Research implies that chronic infections cause almost 20% of cancers, 30% occur due to inhaled pollutants and tobacco smoking, and up to 35% of cancer cases develop because of dietary factors [15]. The question of the immune system and inflammation and their role in cancer development and progression has attracted scientific attention [10]. Nowadays, cancer biology unis undergoing significant development. Studies indicate that inflammation impacts the composition of the tumor microenvironment (TME), particularly the tumor and stromal cell plasticity [23]. Therefore, it is necessary to view inflammatory processes in the immune system during carcinogenesis with the consideration of the anti-tumorigenic function of immunity exerts immunosurveillance and immunological tumor heterogeneity sculpting [23].

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Cancer is a disease that affects all people worldwide and is among the leading mortality causes as it is blamed for nearly 13% of all deaths worldwide [23]. As it is a sell-intrinsic genetic disease, most treatment options aim at destroying tumor cells with multidrug cancer cell resistance [17]. Research indicates that inflammation closely relates to all stages of development and malignant progression of most cancer types and with the anti-cancer therapy efficacy[2; 19]. It means that chronic inflammation participates in the process of immunosuppression and ensures a preferred microenvironment for tumorigenesis, tumor development, and metastasis [17]. However, there is not a sufficient amount of studies that directly address the impact of inflammation on blood cancer. Therefore, the link between inflammation and the possibility of developing blood cancer requires investigation. Thus, the study is developed to answer the question: Is there any relationship between inflammation and blood cancer development?

METHODS

Evidence-based medicine is a systematic and quantitative approach that aims at getting medical information [18]. Therefore, meta-analysis is a formal and quantitative research approach designed to systematically assess prior research to derive conclusions about the topic of interest [2]. It integrates and evaluates the results of studies and plays a vital role in evidence-based medicine [2]. Meta-analysis takes the top position in the evidence hierarchy, where clinical evidence is ranked in accordance with the strength of the freedom from various biases [18]. The main purpose of such research is to determine the presence of an effect in a study and identify whether this effect is positive or negative. Hence, meta-analysis aims at examining the primary strengths of the results of a study [17]. It assists in determining whether there is substantial evidence to support the research findings [12]. Also, this research approach is designed to analyze the results achieved in previously published studies to detect common trends and discrepancies.

Meta-analysis outcomes may include a more precise estimate of the effect of the disease risk factor, in the case of the current study, inflammation as a risk factor for blood cancer development. The use of meta-analysis is associated with some benefits, including a strong and quantitative review of large and complex data that may be conflicting [12]. However, it is necessary to highlight that a failure to identify most existing studies may result in making unreliable and ineffective conclusions [2]. A thoroughly conducted meta-analysis is considered to be a valuable tool in evidence-based medicine [18]. The need for integrating prior research findings ensures that a meta-analytic study is desirable and feasible.

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Meta-analyses are a constituent of systematic review [12]. A systematic review seeks to contrast empirical evidence that fits certain eligibility criteria with the aim of answering a research question [2]. A systematic review presupposes the use of precisely stated objectives to identify the studies that meet the eligibility criteria [18]. It is beneficial in reducing bias and providing reliable, effective, and valuable findings from conclusions drawn by other scientists. Studies for a meta-analysis are chosen with the consideration of inclusion criteria. Hence, the inclusion criteria for the current study are as follows: the publication of the study not earlier than 2012, the presence of at least two keywords; access to a full article; articles published only in English. These inclusion criteria were defined at the initial study development stage.

The steps of a systematic review or meta-analysis include developing a research question, identifying a search strategy, database search, evaluating the received results, and producing relevant conclusions [2]. Hence, the articles for the current review were taken from Google Scholar. All of them are published in reliable journals, and the reliability of the provided results cannot be doubted. The initial search in the database showed 19600 articles. However, most of them were no considered as they addressed different cancer types, did not contain at least two keywords, or provided only abstracts of the studies.

RESULTS

Chronic inflammation has been found to mediate many diseases, including arthritis, cardiovascular diseases, pulmonary diseases, Alzheimer's disease, autoimmune diseases, and cancer [3]. Chronic inflammation triggers increase cancer risk and cancer progression. The deconstruction of the roles and mechanisms of action of both cancer and inflammation is necessary to get a good understanding of how inflammation in cancer is induced and maintained. According to Green and Grivennikov (2016), up to 20% of all cancer cases occur due to chronic inflammation, infection, or autoimmunity at the same organ site or tissue. Cancer-promoting inflammation is induced and exists long before the formation of a tumor.

It has been found that a number of environmental factors incline to and promote cancer development. Considering the host, these factors may be site and organ-specific or systemic [7]. For instance, fine particle inhalation primarily causes lung and airway inflammation and initiates lung cancer and mesothelioma [3]. Also, low-grade inflammation induced by hyperglycemia, obesity[20], and excessive lipid accumulation is systematic in nature and can increase cancer risk, including colon, breast, pancreatic, liver, and other malig-

 doi:10.20944/preprints202211.0365.v2

nancies [3]. Systematic inflammation action can occur even during the late tumor development stages, activating neutrophils and the function of their extracellular trap to promote breast cancer metastasis [6]. Recent research has shed light on the pathways that link inflammation and cancer, including intrinsic and extrinsic pathways. Hence, intrinsic pathways are genetic events that cause the expression of inflammation-related programs that guide the inflammatory microenvironment construction, while the extrinsic pathway relates to the inflammatory conditions that enhance cancer development [1].

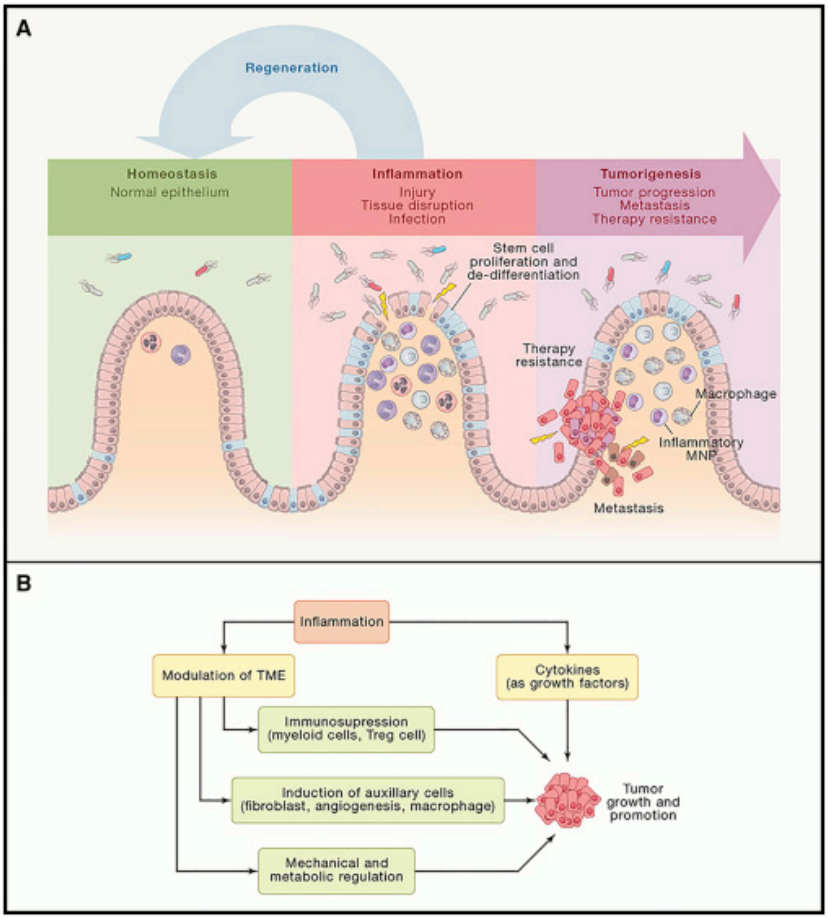
The analysis of relevant literature sources indicates that the tumor may be successfully initiated by two independent events. One of them leads to mutation accumulation and epigenetic gene alterations and signaling pathways included in tumor suppression and oncogenic pathways [1]. Traditionally, these mechanisms have been primarily linked to environmental factors and inherent errors in DNA repair and replication; inflammatory responses initiate powerful mechanisms that result in the accumulation of mutation and a number of epigenetic changes in adjacent epithelial cells [14]. Neutrophils and macrophages are potent nitrogen species and reactive oxygen producers, inducing mutations. Hence, inflammation induction can result in increased mutagenesis, predisposing to mutation accumulation in normal tissue [5]. Chronic intestinal inflammation leads to mutation accumulation in cancer-related genes in intestinal epithelial cells and can trigger tumor formation without additional extrinsic mutagens.

The inflammation potential to induce mutations and DNA damage is accounted for by evolution as inflammatory cytokines can enhance the expression of DNA damage response genes to counteract potential genotoxic insult induced caused by inflammation [6]. In addition, signaling by cytokines produced by inflammatory cells activates epithelial cell epigenetic machineries such as histone modifications, DNA components, microRNA, tumor suppressors, and others [5]. The net outcome of these epigenetic changes is suggested to be similar to inactivating mutations in tumor suppressors and activating mutations in oncogenes [5]. Stem cells are the proposed “cells of origin” for cancer, and inflammatory processes can initiate the dedifferentiation of post-mitotic epithelia into tumor-initiating cells similar to stem cells (see Figure 1). Tissue damage triggered by chronic inflammation can lessen the barrier function and expose the stem cell niche to environmental carcinogens. Also, it may move stem cells very close to active inflammatory cells, enhancing the production of genotoxic compounds [5]. Moreover, in microbial-rich cancer, enhanced inflammation can

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 24 November 2022 doi:10.20944/preprints202211.0365.v2

shape the qualitative characteristics of epithelial-adhesive microbiota, enriching the specie content accumulating genotoxic gene products, and inflicting mutations in host cells [5].

Figure 1: Pro-tumorigenic actions of inflammation [5]



Another independent event that initiates tumor development is the creation of transformed and/or cancerous clones [16]. However, it is necessary to highlight that it should be followed by their growth into a frank tumor, which is referred to as a process to which inflammatory mechanisms usually contribute [5]. For

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example, cytokine receptor signaling in mutated cells might converge at the pro-survival pathway induction, mediated by NF-κB, STAT, three, or other signaling types [5]. Therefore, it enhances proliferation or increases the survival transformed clone probability. There is a need for such an early inflammatory signaling contribution as tumor cells in limited numbers fail to establish a full-scale TME with auxiliary stromal cells, which can produce the proper amount of tumor-supporting growth factors [5]. Inflammation-driven cell survival is also the center of interest in cancer immunosurveillance and the tumor elimination phase of stresses and mutated cells [16]. Also, studies indicate that inflammatory signals can increase fitness and reduce the expression of “stress ligands” on cancer cells [5]. Lam et al. (2014) find that this is needed for proper recognition. Injury and inflammation initiate cell turnover in tissues, creating space for malignant clone growth [5]. This is visible in skin and liver cancer, as in these cancer types, normal cell death is required for compensatory proliferation of neighboring transformed clones. As a result, it creates a scenario where the tissue injury endued by inflammation and cell death is necessary for tumor growth [16]. In cases when the inflammatory cytokine is needed for tumor initiation, cytokines collaborate with tissue damage and regeneration induced by inflammation [5].

Greten and Grivennikov (2016) suggest that identical genetic changes can be characterized by the possession of different propensities that ensure survival and growth, but it depends on the TME these clones are placed into and represents the adaptive nature of the oncogenic process [16]. Moreover, it has been found that inflamed and stressed tissue can be conductive to initiating the growth of tumors, while normal and unaffected tissues would block it. At the same time, inflammation can trigger dormant clone growth. Some mechanisms responsible for this phenomenon may intersect with the cytokine's ability to enhance survival and proliferation [5]. Inflammation can change the HSPC selection toward oncogenic CEBPA gene mutations often found in leukemia. Although inflammation may be the process of fighting infection, it may also have adverse reactions that pose significant risks to people's health, especially when it becomes chronic. Kumar (2021) suggests that chronic infections and arthritis may cause long-term inflammation. However, there are cases when the main inflammation cause is old age. When people get older, many become chronically inflamed [9]. People experience different inflammation levels, and higher levels usually coincide with worse health outcomes. The researcher finds that chronic inflammation may cause increased leukemia rates [9].

CONCLUSION

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The analysis of literature sources has shown that there is a link between inflammation and tumor development and depends on two different phenomena. Genes that participate in cancer development can enhance inflammatory processes. At the same time, inflammation increases the cancer risk by suppressing antitumor responses of the immune system and creating conditions that are favorable for mutation accumulation, the creation of blood vessels that nourish tumors, the growth and survival of tumor cells, as well as the tumor mass ability to invade surrounding tissues and to stimulate metastases [11]. Inflammation induction in the TME has distinct timing and may occur before or after tumorigenesis initiation or can become evident only at the later tumorigenesis stages. Timing, a characteristic feature of some tumor types and the contribution of tumor-promoting, may emerge very early or remain silent until late metastasis stages. Tumor-infiltrating leucocytes and cytokine-related signaling pathways are the components that play a vital role in the development of the inflammatory tumor microenvironment. Certain principles and mechanisms help inflammation promote cancer. The research has enabled to identify of a strong link between chronic inflation and some cancer types, including blood cancer. The review provides evidence of the relationships between chronic inflammation and many cancer types, particularly blood cancer.

Research indicates that several distinct stimuli cause inflammation in tumors. Some of them, for instance, low-grade inflammation (obesity) [19], environmental pollutants (smoke), carcinogenic microbes, and others, may serve as essential targets responsible for cancer prevention through the reduction of tumor-initiating inflammation [12]. Dietary interventions, vaccinations, improved environmental protection, and antibiotics use can help achieve it. Other stimuli, such as cell death, hypoxia, and genetic or epigenetic modulation of tumor suppressors, are extremely valuable to understanding cancer biology [16]. However, they can be targeted only in terms of cancer therapy and through the modulation of the signaling events and signal transduction hubs. In addition, the inflammatory tumor microenvironment is characterized by the host leukocyte presence in the supporting stroma and tumor areas. Tumor-infiltrating lymphocytes enhance cancer growth and spread, increasing the immunosuppression associated with cancer.

The analysis of literature sources implies the need for getting an insight into the roles of each cell type and signaling pathway in cancer initiation and progression to discover biomarkers that target cancer inflammation. As inflammation can play a critical role during all tumor development stages, further research may address the question of molecular and cellular mechanisms and operation modes for immune cells and

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inflammation, especially in early tumor initiation, as well as metastatic spread and outgrowth. Moreover, information about transcriptional elucidation and other signaling programs that define cellular plasticity within the TME may help examine cellular interaction and functional diversification [5]. Thus, irrespective of the ongoing research in the sphere of different cancer types and inflammation, many questions remain unaddressed.

References

[1] Aran D, Lasry A, Zinger A, Biton M, Pikarsky E, Hellman A, Butte AJ, Ben-Neriah Y. Widespread parainflammation in human cancer. Genome Biol 2016;17:145.

[2] Bello A, Wiebe N, Garg A, Tonelli M. Evidence-based decision-making 2: systematic reviews and meta-analysis. Methods Mol Biol (Clifton, NJ) 2015;1281:397-416.

[3] DeGregori J. Connecting cancer to its causes requires incorporating effects on tissue microenvironments Cancer Res 2017, 77:6065-6068.

[4] Giang HTN, Banno K, Minh LHN, Trinh LT, Loc LT, Eltobgy A, et al. Dengue hemophagocytic syndrome: a systematic review and meta-analysis on epidemiology, clinical signs, outcomes, and risk factors. Rev Med Virol 2018;28(6):e2005.

[5] Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immun 2016;51(1):27-41.

[6] Grivennikov SI. Inflammation and colorectal cancer: colitis-associated neoplasia Semin. Immunopathol 2014;35:229-244.

[7] Guthrie GJ, Charles KA, Roxburgh CS, Horgan RG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit. Rev. Oncol. Hematol 2013;88:218–230.

[8] Hassuneh MR, Nagarkatti M, Nagarkatti PS. Role of interleukin-10 in the regulation of tumorigenicity of a T cell lymphoma. *Leuk Lymphom.* 2013;54:827–34.

[9] Kumar D. The bone microenvironment role in breast cancer. Onc. Times 2021;43:12/

[10] Lam NL, Ho SS, ShenYJ, Tang GM, Xiong JL, Croxford CX, Akira S et al. RAE1 ligands for the NKG2D receptor are regulated by STING-dependent DNA sensor pathways in lymphoma Cancer Res 2014;74:2193-2203.

[11] Mantovani A, Ponzetta A, Inforzato A, Jaillon, S. **Innate immunity, inflammation and tumour progression: double-edged swords** J. Intern. Med 2019;285:524-532.

[12] Mikolajewicz N, Komarova SV. Meta-analytic methodology for basic research: a practical guide. Front. Physiol 2019;10:203.

[13] National Cancer Institute 2015. Chronic inflammation. https://www.cancer.gov/about-cancer/causes-prevention/risk/chronic-inflammation

[14] Öhlund D, Handly-Santana A, Biffi G, Elyada E, Almeida AS, Ponz-Sarvise, M et al. Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer J. Exp. Med 2017;214:579-596.

[15] Schaue D, Micewicz ED, Tarikan JA, Xie MW, Cheng G, McBride WH. Radiation and inflammation. Semin Radiat. Oncol 2015;25:4–10.

[16] Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. Ann Afr Med. 2019 Jul-Sep;18(3):121-126.

[17] Tang W, Chen Z, Zhang W, Cheng Y, Chang B, Wu F, Wang Q, Qnag S, Rong D, Reiter FP, De Toni EN, Wang, X. The mechanisms of sorafenib resistance in hepatocellular carcinoma: theoretical basis and therapeutic aspects. Signal Transduct. Target Ther 2020;5:87.

[18] Tawfik GM, Dila KAS, Mohamed MYF. A step by step guide for conducting a systematic review and meta-analysis with simulation data. Trop Med Health 2019;47: 46.

[19] Tzenios, N., Tazanios, M., & Chahine, M. (2022). The impact of BMI on Ovarian Cancer-An Updated Systematic Review and Metanalysis.

[20] Tzenios, N., Tazanios, M. E., & Chahine, M. (2022). The impact of body mass index on prostate cancer: An updated systematic review and meta-analysis. *Medicine*, *101*(45).

[21] Tzenios, N., Lewis, E. D., Crowley, D. C., Chahine, M., & Evans, M. (2022). Examining the Efficacy of a Very-Low-Carbohydrate Ketogenic Diet on Cardiovascular Health in Adults with Mildly Elevated Low-Density Lipoprotein Cholesterol in an Open-Label Pilot Study. *Metabolic syndrome and related disorders*, *20*(2), 94-103.

[22] Vasan N, Baselga J, Hyman DM. A view on drug resistance in cancer. Nature 2019;575: 299–309.

[23] Zhao H, Wu L, Yan G et al. Inflammation and tumor progression: signaling pathways and targeted intervention. Sig Transduct Target Ther 2021;6:263.