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Review

The Role of Chronic Inflammation in Pediatric Cancer

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Simple Summary: Chronic inflammation is associated with the onset and progression of many non-human diseases including type-2 diabetes, coronary artery disease, and cancer. The effects of chronic inflammation in adult cancers are widely studied. However, pediatric cancers demonstrate significant genetic/epigenetic disparities from their adult counterparts, requiring separate classifications. Because of this, findings from adult malignancies cannot be applied to pediatrics cancers. In this review, we examine how chronic inflammation contributes to the unique genetic and epigenetic changes, tumor microenvironment, and immune response that underly pediatric cancers. Finally, we highlight current and developing therapies aimed at restoring inflammatory balance during and after treatment.

Abstract: Inflammation plays a crucial role in wound healing and the host immune response following pathogenic invasion. However, unresolved chronic inflammation can result in tissue fibrosis and genetic alterations that contribute to the pathogenesis of human diseases such as cancer. Recent scientific advancements exploring the underlying mechanisms of malignant cellular transformations and cancer progression have exposed significant disparities between pediatric and adult-onset cancers. For instance, pediatric cancers tend to have lower mutational burdens and arise in actively developing tissues, where cell-cycle dysregulation leads to gene, chromosomal, and fusion gene development not seen in adult-onset counterparts. As such, scientific findings in adult cancers cannot be directly applied to pediatric cancers, where unique mutations and inherent etiologies remain poorly understood. Here, we review the role of chronic inflammation in processes of genetic and chromosomal instability, the tumor microenvironment, and immune response that result in pediatric tumorigenesis transformation and explore current and developing therapeutic interventions to maintain and/or restore inflammatory homeostasis.

Keywords: cancer; inflammation; epigenetics; therapeutics; immunology

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1. Introduction

Inflammation is a central biological element of host defense and immunosurveillance [1,2]. Acute inflammation is beneficial to the local innate immune response following cell and tissue injury or pathogenic invasion. The inflammatory cascade is activated by tissue-resident macrophages and mast cells leading to localized vasodilation and the secretion of proinflammatory mediators. These mediators recruit neutrophils and monocytes

that clear cellular debris and assess the need for a larger adaptive immune response [3–5]. Resolution of this localized pro-inflammatory state is a complex, step-wise, and tightly managed process. Activated immune cells either undergo apoptosis or transform to an inactive "sentinel" state, infiltrating neutrophils undergo efferocytosis, and there is an increase in secretion of pro-resolving and anti-inflammatory mediators [6–9]. Dysregulation in any or all of these resolving processes can result in a chronic state of inflammation that damages affected cells and tissues.

Chronic inflammation is associated with the pathophysiology of many non-communicable diseases, such as metabolic syndrome, type-2 diabetes mellitus, coronary artery disease, neurodegenerative diseases, and many types of cancer [10–15]. Extended exposure to pro-inflammatory mediators, such as chemokines, cytokines, and eicosanoids, can help promote the immune response to curb further tumor advance. However, chronic exposure also negatively impacts the healthy immune response and microenvironment through the disruption of cell-cycle checkpoints and interference with DNA repair promoting tumor growth and progression [16–19]. Chronic inflammation also contributes to pathological epigenetic changes, resulting in chromosomal abnormalities and aberrant histone modifications [16–19]. Together, these inflammation-associated biologic and epigenetic alterations have been shown to contribute to the onset and progression of disease.

Cancer is a multifaceted disease that is a major worldwide socioeconomic health problem and the second leading cause of death in the United States [20–23]. In adults, common risk factors include carcinogenic exposure, age, lifestyle, obesity, genetic predisposition, viral and/or bacterial infection, and chronic inflammation, a known comorbidity in colorectal, pancreatic, lung, lymphoma, breast, and cervical cancers [18,24–29]. Over time, repeated damage from these factors can result in genetic instability, epigenetic, and microenvironmental alterations that contribute to tumor cell carcinogenesis, proliferation, and metastasis [30–32].

Recently, scientific advancements have helped characterize the underlying mechanisms of many of these alterations and have exposed significant disparities between pediatric and adult-onset cancers [17,33,34]. In children and adolescents, cancer stands as the second leading cause of mortality [17,23,35,36]. Unlike their adult counterparts, pediatric cancers tend to harbor a lower overall mutational burden and arise in actively developing tissues targeting primarily undifferentiated stem or progenitor cell populations [37,38]. Mutations or dysregulations in the cell-cycle of these cell populations lead to the development of fusion genes (rarely detected in adult-onset cancers), epigenetic dysregulation, and pro-oncogenic changes to the tissue microenvironment [39–41]. The result of these genetic alterations is a sub-population of malignantly transformed cells with a stem-like phenotype that contribute to tumor growth, disease progression, and therapeutic resistance [42–44].

Many pediatric mutations are unique and their underlying etiology and molecular mechanisms remain poorly understood. Similarly, the role of chronic inflammation in pediatric tumorigenesis and therapeutic resistance has yet to be fully elucidated. This review will examine the role of inflammation in the processes of genetic and epigenetic instability, the tumor microenvironment, and immune response that result in pediatric malignant-transformation (Figure 1). Finally, we explore current and developing therapeutic interventions to maintain and restore inflammatory homeostasis during and after clinical treatment.

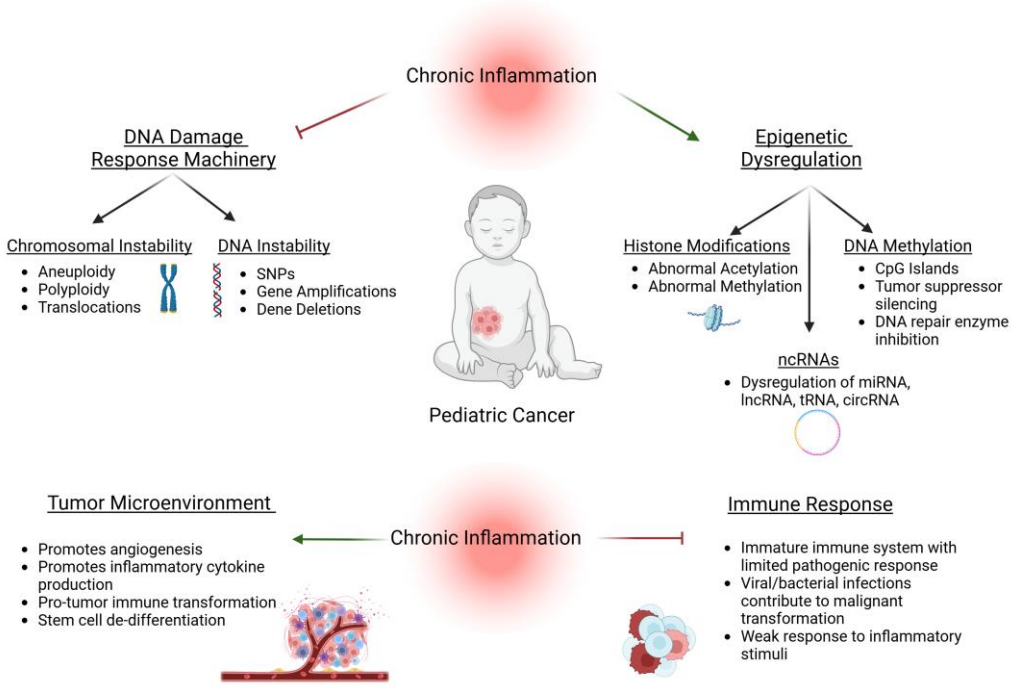

Figure 1. Chronic inflammation in pediatric cancer. Chronic inflammation plays a unique role in pediatric cancer, targeting differentiating cells and tissues. Alterations in the normal regulation of DNA repair, and abnormal epigenetic and chromosomal regulation alter the tumor microenvironment, promoting malignant transformation and tumor progression. The undeveloped and weakened pediatric immune system is limited in its ability to recognize and counter malignant cells contributing to cancer onset.

2. Materials and Methods

A PUBMED literature review was conducted to search for original papers on pediatric cancers and the role of chronic inflammation in cancer onset, progression, metastasis, drug resistance, and clinical outcomes. Key words included in the searches were "chronic inflammation and pediatric cancer", "pediatric cancer and inflammation", "chronic inflammation and genetic instability in pediatric cancer", "genetic and epigenetic dysregulation in pediatric cancer", "inflammation and epigenetic dysregulation in cancer", "chronic inflammation and immune cells", "chronic inflammation and the pediatric tumor microenvironment", and "chronic inflammation and immune cells in pediatric cancer." All figures were created with Biorender.com accessed on 4 December 2024.

3. Chronic Inflammation and Genetic Instability

Genetic instability is a well-known hallmark of cancer [40,45]. Normally, instabilities are identified and managed by the DNA damage response machinery (DDRM), a network of cell-intrinsic and cell-extrinsic components that maintain genomic stability via efficient DNA repair, activation of cell-cycle checkpoints, or through induction of apoptosis and immune clearance of cells possessing unrepairable DNA damage [46–48]. In conditions of acute inflammation, these activities help to clear cells damaged by pathological infection and maintain cell and tissue homeostasis [48,49]. Chronic inflammation, however, inhibits the DNA response machinery, contributing to reduced onco-suppressive surveillance and increased risk of malignant abnormalities in both pediatric and adult cancers [50–53]. Inflammation-induced inhibition of the DNA damage response machinery results in transcriptional changes that negatively impact both chromosomal and genetic stability (Figure 2) [51,54,55].

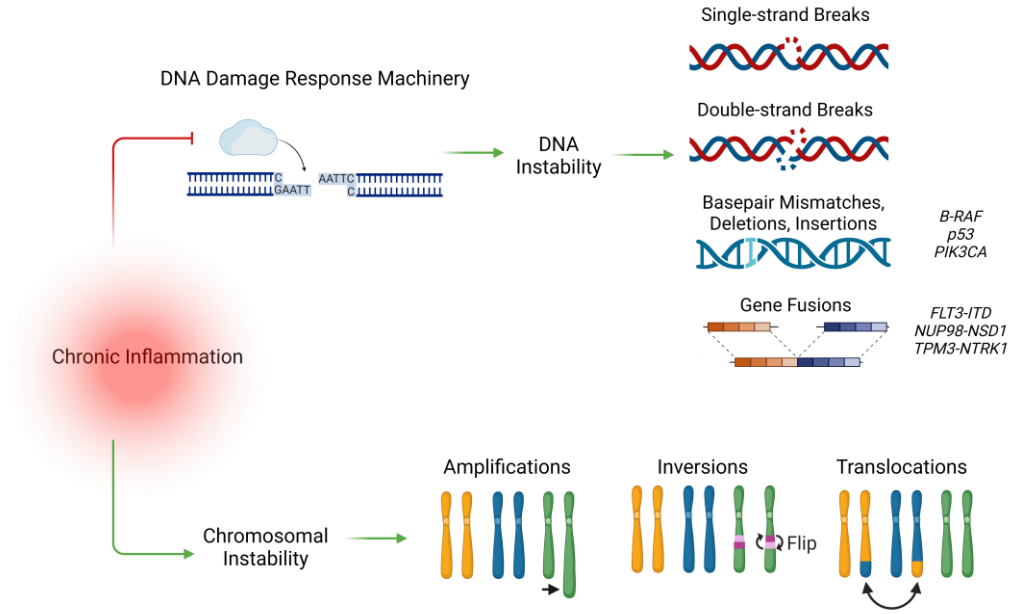

Figure 2. Chronic inflammation contributes to DNA and chromosomal instability. Chronic inflammation impairs the DNA damage response machinery resulting in the maintenance of oncogenic DNA breaks, splicing errors, and gene fusions. Exposure to chronic inflammation also contributes to the chromosomal abnormalities associated with pediatric cancer.

Chromosomal instability, while rarer in pediatric cancers, is still an established contributing factor, particularly when defects alter the activity and/or function of oncogenes or tumor suppressors [56–58]. For instance, the gain or loss of a whole chromosome (aneuploidy) has been associated with the development of a variety of pediatric cancers including astrocytoma, B-cell acute lymphoblastic leukemia (ALL), optic tumors, neuroblastoma (NB), rhabdomyosarcoma, and osteosarcoma (OS) [59–62]. Similarly, the gain of whole chromosome sets (polyploidy) has been identified in pediatric oligodendroglioma, rhabdomyosarcoma, ALL, Ewing sarcoma, and testicular germ cell tumors [63–66]. Changes in chromosome structure are also prevalent in pediatric cancers leading to abnormal fusion, amplification, or chromosomal translocation [32,67]. Indeed, structural changes have been identified and linked to predicted clinical outcomes in astrocytoma, ALL, renal cell carcinoma, and several pediatric sarcomas such as Ewing sarcoma, OS, rhabdomyosarcoma, and synovial sarcoma [67–71]. Finally, inactivation or deletion of chromatin remodeling genes have also been shown to contribute to chromosomal instability. For instance, inactivating mutations in the SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily b member 1 (SMARCB1) have been identified in pediatric malignancies such as medulloblastoma (MB), atypical teratoid rhabdoid tumors (ATRT), and ovarian carcinomas, which impair cell differentiation and maintains the cancer stem cell-like phenotype [72–75].

The loss of normal DNA repair mechanisms following exposure to chronic inflammation also negatively impacts DNA stability and permits abnormal promoter defects, gene duplication, gene fusion, single nucleotide variants (SNVs), and gene copy number changes [48,76–80]. These germline variants, found in around 10% of pediatric cancer patients, can either be inherited or occur de novo [81,82]. Increases in genetic testing have identified a number of point mutations such as B-RAF (*BRAF*^{V600E}), tumor protein P53 (*p53*), phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*), Kirsten rat sarcoma virus (*KRAS*), and catenin beta 1 (*CTNNB1*) [83–91]. Gene fusions have also been identified in pediatric cancers. Some of these, such as *FLT3–ITD*, *NUP98–NSD1*, and *TPM3–NTRK1* fusions in hematologic neoplasms, the *EWS–FLI1* fusion in Ewing sarcoma,

and *PAX–FOXO1*, associated with rhabdomyosarcoma, have been clinically linked and functionally examined, but many still remain identified but unexplored [92–98]. Gene amplifications and deletions such as MYCN proto-Oncogene (*MYCN*), cyclin-dependent kinase inhibitor 2A (*CDKN2A*), mitogen-activated protein kinase (*MAPK*), epidermal growth factor receptor (*EGFR*), fibroblast growth factor receptor (*FGFR*), wingless (*WNT*), and sonic hedgehog (*SHH*) have been identified and are associated with risk stratification and prediction of clinical outcomes [99–103]. Finally, cancer cells themselves are known to directly contribute to the proinflammatory milieu and further DNA damage. Due to an elevated cellular metabolism and mitochondrial dysregulation, cancer cells generate free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). Neoplastic cells also secrete proinflammatory cytokines, such as nuclear factor kappa-light-chain-enhancer of activated B (NF-κB), transforming growth factor beta 1 (TGFβ-1), and tumor necrosis factor alpha (TNF-α) [104–109]. Together, these compounds damage both DNA and RNA, contribute to lipid peroxidation, and activate signaling pathways governing angiogenesis, invasion, and metastasis [110–113].

4. Chronic Inflammation and Epigenetic Dysregulation:

Chronic inflammation plays a role in epigenetic dysregulation, which contributes to the pathogenesis of numerous diseases including osteoarthritis, pulmonary disease, metabolic diseases, and cancer [114–117]. In pediatric cancers, studies have not only identified many epigenetic modifications but have also demonstrated strong correlations between these modifications and drug response, progression, and overall predicted outcome [118–121]. These changes may be of either mitotic or meiotic in origin and alter epigenetic regulation of DNA access, histone access, or the activity of non-coding RNAs (Figure 3). These changes alter the degree and/or timing of pathways associated with differentiation, growth and specialization [122–124]. Of particular interest in developmentally based pediatric cancers, oncogenic epigenetic changes are known to affect genes, such as SRY (sex-determining region Y)-box 2 (*SOX2*), CD44 molecule (*CD44*), and prominin-1 (*CD133*), contributing to enhanced capacity for self-renewal and stem-cell-like phenotypes [40,125–127].

Chronic inflammation is known to contribute to changes in DNA methylation patterns in cancer, multiple sclerosis, and autoimmune diseases [128–131]. For example, adult dialysis patients demonstrate elevated inflammation markers and significantly higher global DNA methylation patterns compared to age-matched healthy controls [132]. Epigenetic profiling in the pediatric population has also uncovered elevated DNA methylation patterns associated with the development and progression of atopic asthma, Crohn's disease, and ulcerative colitis [133–136]. The process of DNA methylation is a tightly regulated process in which enzymes known as DNA methyltransferases (DNMTs) add methyl groups to specific DNA locations [137]. DNA methylation alters the three-dimensional confirmation and modifies DNA access and the binding potential of various transcription factors and associated proteins [138].

DNA methylation is particularly important during development, where it assists in the tight regulation of gene expression, cell and tissue differentiation, and genomic stability [139]. One common dysregulation associated with pediatric cancers involves abnormal methylation of CpG islands. CpG islands are short regions of DNA, approximately 500–1000 base pairs in length, with an elevated percentage of cytosine–guanine dinucleotides [140,141]. CpG islands are common at or near promoter regions and under normal conditions are not usually methylated [50,142]. In pediatric cancer, however, genetic studies have uncovered abnormal CpG island methylation in patients with ALL, OS, gastric carcinoma, and brain tumors [51,143–145]. Abnormal methylation of CpG islands results in transcriptional silencing of key tumor suppressor gene promoters (such

as alpha-thalassemia mental retardation X-linked (ATRX) and cyclin-dependent kinase inhibitor 2A (CDKN2A)) in addition to DNA repair enzymes (such as O6-methylguanine methyltransferase (MGMT)), resulting in abnormalities in the cell cycle, DNA repair, and apoptotic pathways [51,146,147]. Methylation status has also been linked to prognosis, drug resistance, and metastasis [148–152]. As such, therapeutic treatments targeting DMNTs are being used to reactivate these pathways and decrease overexpression of oncogenic targets in cancer cells [153–155].

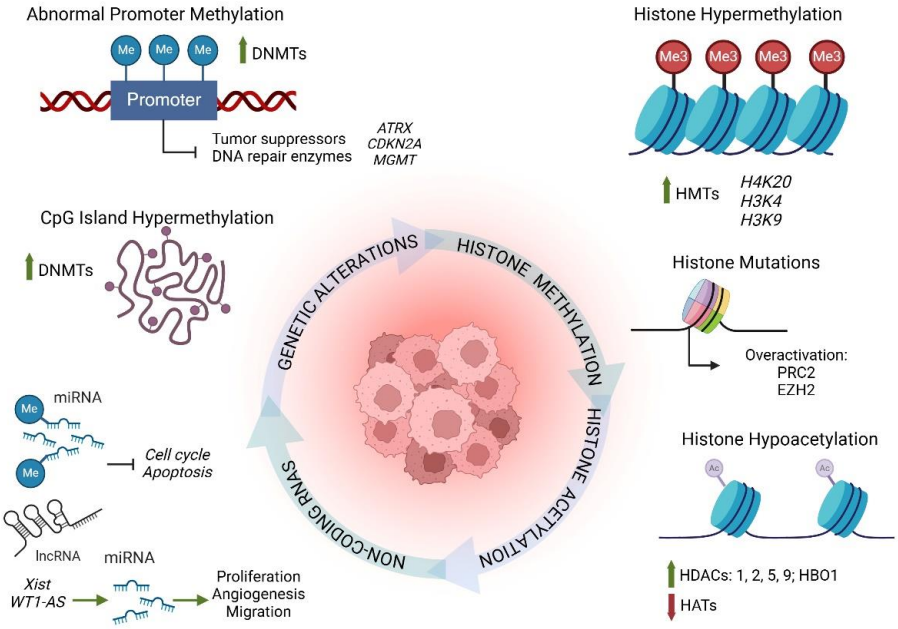

Figure 3. Chronic inflammation contributes to oncogenic genetic and epigenetic alterations. Exposure to chronic inflammation results in abnormal DNA and promoter methylation patterns that promote tumor growth and progression. Abnormal histone methylation and acetylation in malignant cells contribute to altered gene expression patterns affecting prognosis and drug response. Non-coding RNA alterations inhibit normal cell-cycle regulation and promote cancer cell migration.

Along with DNA methylation, transcriptional activity and timing are regulated via histone function. Histones are proteins enriched in the amino acids arginine and lysine, which organize DNA into nucleosomes to regulate gene function and protect against DNA damage [156,157]. There are five main core histone proteins (H1/H5, H2A, H2B, H3, and H4) responsible for establishing the tightly compacted nucleosome structure [158,159]. Post-translational modifications, such as methylation, acetylation, ubiquitination, and phosphorylation, further contribute to transcriptional control by inducing conformational change [160,161]. In cancer, epigenetic regulation of histone post-translational modifications is dysregulated, disrupting normal cell proliferation and differentiation [159,162,163]. Of the post-translational histone modifications associated with pediatric cancer, abnormalities in histone methylation and acetylation are the most widely studied.

Proper activity of histone-methylating enzymes is necessary for cell differentiation and tissue development. Histone methyltransferases (HMTs) are responsible for the addition of methyl groups, which can later be removed via the activity of histone demethylases (HDMTs) [112,164]. The effects of histone methylation are site-specific and relative to the degree of methylation, i.e., the addition of single or multiple methyl groups [161,165]. The degree of histone methylation can also be modified by inducible Jumonji enzymes. Jumonji domain-containing protein-3 (Jmjd3, also known as KDM6B) plays a critical role in epigenetic regulation of stem cell differentiation and cellular reprograming [166–168]. Exposure to bacterial proteins and inflammatory cytokines results in increased Jmjd3 expression,

demonstrating a link between the inflammation and epigenetic alteration [169,170]. In the pathogenesis of pediatric cancers, multiple disruptions in histone methylation have been identified. For instance, a hypermethylation of histone 4 lysine 20 (H4K20) compared to levels detected in healthy tissue has been identified in some pediatric astrocytomas, ependymomas, and diffuse pontine gliomas [171–174]. H4K20 is of particular importance since it is known to regulate genes maintaining telomere length and governing epithelial–mesenchymal cell differentiation [175,176]. Furthermore, hypermethylation of H4K20 contributes to gene silencing in pediatric leukemia and NB that inhibit the DNA repair machinery and enhance cancer cell invasion into surrounding tissues [177–179]. Trimethylation of histone 3 lysine 4 (H3K4me3) has been identified in ependymomas and MB and been shown to correlate with both tumor grade and increased chemotherapeutic resistance [180–182]. Missense mutations in glycine 34 of histone 3 (H3G34) have been shown to directly contribute to the genetic instability and oncogenic expression profiles of pediatric gliomas, sarcomas, and bone cancers [181,183–186]. These mutations are frequently observed in pediatric cancers and function to impede SETD2 trimethylation of H3K36 to promote increased activity of polycomb group protein 2 (PRC2), which silences key cell-cycle regulators, impairs normal DNA damage responses, and increases proinflammatory cytokine production [187–189]. Increased methylation of histone 3 lysine 9 (H3K9) is associated with increased chromosomal instability, higher astrocytoma tumor grade and poor prognosis [174,190]. Mutations also occur in histone methyltransferases. One of the best studied examples is an overexpressing mutation in histone methyltransferase enhancer of zeste hologog 2 (EZH2), which has been identified in MB, gliomas, soft tissue carcinomas, sarcomas, rhabdoid tumors, and both B-cell and T-cell lymphoproliferative disorders [191–194]. Overexpression of EZH2 promotes overexpression of H3K27-specific demethylases, resulting in altered chromatin structure and reduced DNA damage response, and confers radiation resistance [40,195].

Histone acetylation, the addition of an acetyl group, also causes confirmation changes that can alter gene access and transcription. The addition of an acetyl group, catalyzed by histone acetyltransferases (HATs), loosen DNA–histone binding to permit gene access for transcription [196]. This process, like histone methylation, is tightly regulated and reversible. Acetyl groups can be removed from histones (or histone side chains) to inhibit transcription by histone deacetylases (HDACs), which are grouped into four classes based on structure, function, and location [197–199]. Abnormal histone acetylation or HAT/HDAC interactions with histone-associated co-factors are known to play a role in pediatric cancer and have been correlated with cancer onset, therapeutic response, and overall prognosis [124,200]. The elevated activity of HATs not only alters histone modification but is known to contribute to chronic inflammation via increased expression of pro-inflammatory cytokines such as interleukins 2, 8, and 12 (IL-2, IL-8, IL-12). NF-κB signaling, significantly upregulated in many pediatric cancers, also plays a role in the maintenance of abnormal histone acetylation, particularly histone 3, where acetylation promotes inflammatory chemokine and cytokine production [169,201–204]. Changes in the expression and activity of HATs and HDACs have been described in solid tumors, B-cell progenitor acute lymphoblastic leukemia, ALL, acute myeloid leukemia (AML), and OS [205–208]. An increase in histone 3 lysine 16 (H3K16) acetylation has been associated with diffuse intrinsic pontine gliomas, and high expression profiles of HDAC5 and HDAC9 have been associated with MB subgroups that typically present with high risk and poor overall survival [124,171,209]. Similarly, high expression profiles of HDAC1 and HDAC2 have been identified in cancer-associated fibroblasts of pediatric hepatoblastoma and hepatocellular carcinoma patients, which contributes to lung metastases and promotes elevated expression of p21, a known inhibitor of cell-cycle regulation that af-

fects proliferation [210,211]. Cancer-associated gene mutations and amplifications also play a role in epigenetic dysregulation of histone acetylation. In childhood midline tract carcinomas, gene fusions in NUT midline carcinoma family member 1 (*NUTM1*) affect the activity and function of bromodomain-containing 4 (*BRD4)*, a chromatin scaffold protein with intrinsic histone acetyltransferase activity [212,213]. Overexpression of histone lysine acetyltransferase HBO1 (KAT7), which acetylates histones 3 and 4, is associated with OS cancer proliferation and enhanced cell migration [207,214]. In MB, amplifications of *MYCN* and MYCL proto-oncogene (*MYCL1*) have been identified and correlated with cancer aggressiveness and increased risk of metastasis [215,216]. This amplification can also dysregulate epigenetic regulation of histone acetylation via the recruitment of HATs, resulting in enhanced metabolism, proliferation, and viability of cancer cells [217,218]. CREB-binding protein, CREBBP, is a protein with intrinsic acetylase function known to add acetyl groups to not only histone residues but also various transcription factors [219]. In pediatric hematological malignancies, CREBBP is overexpressed compared to healthy controls and this overexpression is typically correlated with a higher risk stratification and poorer prognostic outcome [208,220]. Furthermore, studies have demonstrated that mutations in HAT expression and activity are associated with an increased chemotherapeutic resistance in both B-cell progenitor- and acute lymphoblastic-leukemias [205,208]. Finally, dysregulation of histone acetylation has been shown to directly influence the pro-inflammatory cancer microenvironment through hyperacetylation of pro-inflammatory transcription factors such as signal transducer and activator of transcription 1 and 3 (STAT1/3) and NF-κB [221,222].

Non-coding RNAs are another well-established means of epigenetic regulation in cancer. Regulatory function typically occurs via one of two methods: complementary base pairing to 3′ untranslated regions to inhibit translation or targeting mRNAs for degradation by direct complementary binding [223,224]. Non-coding RNAs are also a well-established player in the regulation of chronic inflammation, where they are known to regulate immune cell differentiation and development, the expression of pro- and anti-inflammatory cytokines, and the resolution of the acute inflammatory response [123,225,226]. Additionally, non-coding RNAs are capable of directly impacting the epigenetic landscape by targeting the activity of other epigenetic regulators, such as DNA and histone methyltransferases and deacetylases [227–229]. Non-coding RNAs comprise several classes based on size, function, and structure [123,225]. These include microRNAs (miRNAs), transfer RNAs (tRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), among others. Studies of these classes have identified dysregulations associated with cancer and other human pathologies [230,231]. In developmental diseases such as pediatric cancer, lncRNAs and miRNAs play a large role in cell differentiation and tissue development [232,233]. For instance, lncRNA XIST, an X-chromosome inactivator that interacts with polycomb repressive complexes (PRC1/2) mediates the ubiquitination and methylation of histones to modulate gene expression during female development [234–236]. XIST is abnormally upregulated in pediatric brain cancers like gliomas, pituitary endocrine tumors, and neuroblastoma, where it interacts with various miRNAs to increase cell proliferation, migration, and angiogenesis, and inhibit apoptosis [237–239]. Similarly, abnormal miRNA interactions with lncRNA WT1-AS, a non-coding RNA that modulates developmental nephrogenesis and EZH2 suppression, have been shown to play a role in the pathogenesis and increased malignancy of Wilms' tumors [123,240]. Other lncRNAs have also been found to be abnormally expressed and play an oncogenic role in cell proliferation, migration, progression, and drug resistance in lymphoblastic leukemia, OS, retinoblastoma, NB, and MB [241–244]. In Hodgkin's lymphoma, a pediatric cancer with a well-studied pro-inflammatory milieu, recent studies have identified numerous dysregulated miRNAs [245–247]. Methylation

studies have also uncovered abnormal methylation patterns that disrupt normal miRNA function in pediatric cancers. In NB and MB, activating methylation of miRNAs disrupts cell-cycle progression and apoptosis and enhances MYCN proto-oncogene function and increases cancer cell migration [248–253]. The function of tumor suppressor miRNAs is inhibited through enhanced methyltransferase activity in Hodgkin lymphoma, ALL, AML, and hepatocellular carcinoma [254–256]. Recent studies have also implicated miRNAs in the acquisition of chemotherapy resistance in OS, primary malignant brain tumors, and leukemias [257–259].

5. Chronic Inflammation and the Tumor Microenvironment

The tumor microenvironment (TME) of adult and pediatric cancers is complex, heterogenous, and dynamic. The TME includes a wide array of cell types including malignantly transformed cancer or cancer stem cells, non-cancerous stromal cell populations (such as endothelial cells, fibroblasts, pericytes, neuronal cells, and adipocytes), various types of infiltrating immune cells (such as T-cells, B-cells, macrophages, and dendritic cells), components of underlying and supportive extracellular matrix and vascular system, and various signaling molecules responsible for tissue homeostasis and inter-/intra-cellular communication [260,261].

Comprehensive molecular analyses of adult cancers have greatly improved our knowledge regarding the adult TME, particularly the various types of infiltrating immune cells and their biological roles in adult malignancies [262–264]. However, these findings cannot be applied directly to pediatric tumors due to numerous disparities in affected cell types, underlying genetic/epigenetic abnormalities, and developmental status between adult and childhood cancers [34,265,266]. As such, further research is needed to better elucidate the complex web of chemical and cellular signaling that drives pediatric cancer onset, progression, and therapeutic resistance.

Further complicating the direct use of adult studies in pediatric cases, there are developmental differences in pediatric immune systems, critical in the early detection and removal of malignant cells [267]. The adult immune system consists of B- and T-cells with extensive memories for antigen recognition following infection or pathogenic invasion [268–271]. Over time, fetal-derived immune cells and repeated exposure to pathogens, allergens, and vaccines builds a complex and varied immune system capable of responding to a wide variety of threats, including early detection of malignant cell types [272–274]. This is of importance since microorganisms are known to cause a significant number of adult cancers [275–277]. In childhood, however, this immune barrier has yet to be established and the immune system is comparatively weak. In newborns, macrophage and monocyte populations are immature and neutrophil responses to pathogens is weak [278–281]. This leaves newborns and infants more susceptible to bacterial and viral infections and reduces tissue repair mechanisms [282,283]. The weakened immune response to inflammatory stimuli also contributes to the pathogenesis of several childhood cancers. For instance, the Epstein–Barr herpesvirus (EB) has been linked to Burkitt lymphoma, Hodgkins' disease, and cases of nasopharyngeal carcinoma [284–286]. This is thought to occur through the onset of genomic instability brought about by B-lymphocyte interactions with EB structural proteins [287,288]. Viral infection with human neurotrophic polyomavirus (JCV) has also been linked to the development of CNS tumors. Here, JCV T-antigens inhibit critical cell-cycle regulators such as p53 and retinoblastoma protein (pRb) contributing to CNS tumor onset and progression in humans and animal models [276,289–291].

Inflammation plays a pivotal role in immune cell recruitment to both healthy tissues and the TME. Following the onset of acute inflammation due to infection or tissue damage, various cytokines and acute proteins activate the innate immune response

through the recruitment of neutrophils and macrophages [292,293]. If the infection or injury persists, antigen-presenting cells activate and recruit T-cells as part of the adaptive immune response [294,295]. Once the injury or infection is resolved, acute inflammation subsides. Chronic inflammation, however, is a prolonged response resulting in a damaging pro-inflammatory microenvironment and abnormal levels of immune cell infiltration. In the TME, cancer or cancer stem cells secrete pro-inflammatory agents, such as cytokines, chemokines, and prostaglandins, to maintain inflammation, promote angiogenesis and fibrosis, and foster an immunosuppression via deregulated immune cell function (Figure 4) [296–299]. Recently, studies have examined differences in the pediatric TME towards the goal of immunotherapy development. These studies have revealed pediatric cancer TMEs demonstrate distinct immuno-profiles that vary between tumor type, subtype, and stage, and correlate with identified underlying genetic and epigenetic abnormalities [300–303]. Specifically, many of these studies have examined alterations in infiltrating myeloid precursors, macrophages, and dendritic cells of the pediatric TME in relation to their biological function and clinical outcomes.

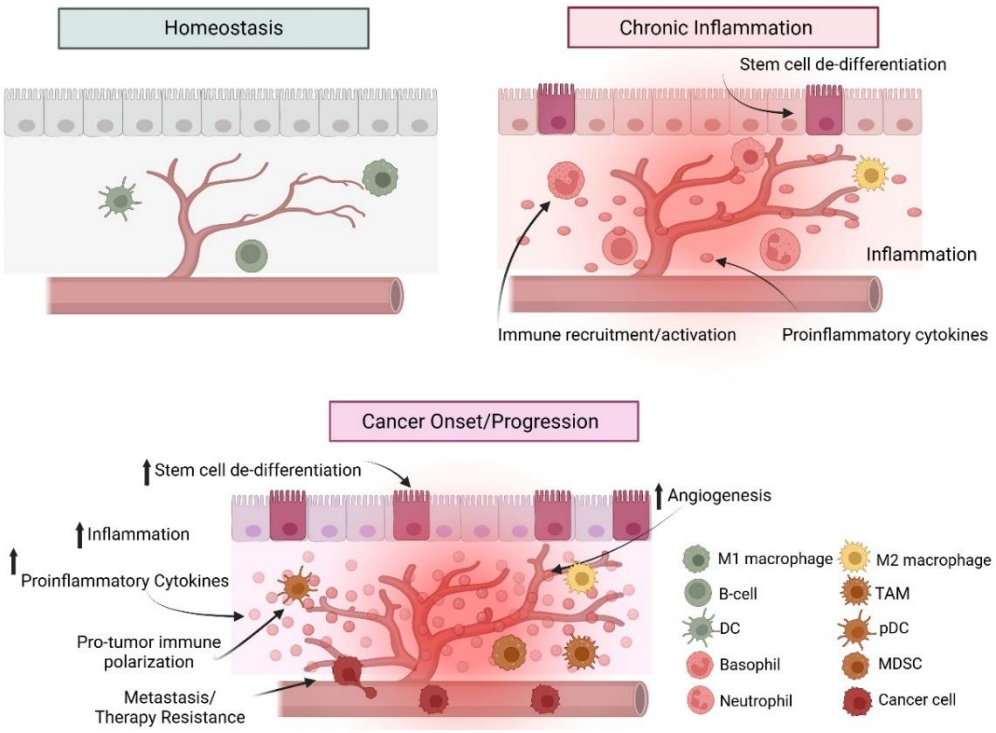

Figure 4. Chronic inflammation alters the tissue microenvironment and immune recruitment to promote tumor onset, progression, and metastasis. Chronic inflammation promotes de-differentiation and/or malignant transformation of cells within the microenvironment, increased angiogenesis, and proinflammatory cytokine release. Conditions within the tumor microenvironment (TME) promote metastasis and inhibit immune cell recognition and targeting of malignantly transformed cancer cells. Arrows indicate an increase.

Myeloid precursors play a vital role in host defense against pathogens and in tissue repair following injury. These immature cells are capable of differentiating into a variety of cell types including macrophages, dendritic cells (DCs), and granulocytes [304,305]. However, in the TME upregulation of pro-inflammatory cytokines, such as IL-1β and IL-6, and prostaglandin E2 (PGE2) disrupts normal myeloid cell differentiation that results in an accumulation of immunosuppressive myeloid-derived suppressor cells (MDSCs) [304,306]. TME MDSCs promote angiogenesis via secretion of matrix metalloproteinase 9 (MMP9), maintain the inflammatory microenvironment through the generation of ROS and RNS,

and inhibit T-cell function via secretion of arginase 1 (ARG1) [307–309]. Clinically, elevated MDSC levels are associated with pediatric gliomas, NBs, sarcomas, and leukemias where levels correlate with cancer stage, metastatic capacity, and overall survival [307,310–312].

Macrophages are an abundant heterogenous population of white blood cells that play crucial roles in development, host immune surveillance, intracellular communication, and the inflammatory response [313,314]. Macrophage origins vary depending on age and tissue of origin, deriving from hematopoietic stem cells (HSCs), monocytes, or tissue-resident macrophages of the fetal liver [315]. Macrophages are first recruited via secretion of macrophage colony-stimulating factor (M-CSF) and recruitment is enhanced through secretion of vascular endothelial growth factor (VEGF), TNF-α, and monocyte chemoattractant protein 1 (MCP-1; also known as CCL2 (C-C motif chemokine ligand 2) signaling [316,317]. Following recruitment, these cells are polarized to either an M1 or M2 state based on the regulatory molecules found in the tissue microenvironment. M1 macrophages are polarized by environmental cues such as interferon-gamma (IFN-γ) secreted by $CD4^+$ T-helper or natural killer cells or TNF-α from macrophages and antigen-presenting dendritic cells [318,319]. M1-polarized macrophages secrete cytokines such as TNF-α and IL1-β and are known to upregulate major histocompatibility complex call 2 (MHC-II) to initiate CD4+ T-cell activation and coordinate immune cell activity [320,321]. Alternately, macrophages can also be polarized to the anti-inflammatory M2 phenotype. In the TME, M2 macrophages serve an immunosuppressive function via secretion of immune inhibitory cytokines such as TGF-β and interleukin-10 (IL-10) [305]. Also, M2 macrophages promote tumor growth and progression through secretion of angiogenic VEGF and growth factors such as platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF)) [322,323]. M2 macrophages have also been shown to inhibit cytotoxic CD8+ T-cell identification and clearance of tumor cells in adult cancer through surface expression of programmed cell death ligand 1 (PD-L1) [324,325]. Interestingly, in pediatric cancers, M2 expression of PD-L1 has been shown to be extremely low to non-existent, which may explain why current PD-1/PD-L1 immunotherapies demonstrate mixed results [312,326–328]. In pediatric cancers, the polarization state of infiltrating macrophages in the TME have been linked to prognosis, invasiveness, and risk of metastasis. For instance, a TME enriched with a higher proportion of M2 immunosuppressive macrophages has been shown to correlate with more aggressive and metastatic OS tumors and a poorer prognosis [329–331]. Conversely, TMEs with a higher percentage of M1 macrophages predict better therapeutic responses and overall survival in MB, NB, and pediatric gliomas [260,323,332].

Dendritic cells (DCs) are immune cells with a critical role in communication between the innate and adaptive immune systems [333,334]. Following injury or pathogen recognition, mature DCs are responsible for antigen presentation and subsequent activation of naïve T-cells to support anti-tumor T-cell maturation and function [305,335]. DCs are separated into two categories depending on location, expression profile, and phenotype: classic DCs (cDCs) and plasmacytoid DCs (pDCs) [336,337]. While the exact function of each type of DC is still being determined, studies have indicated that cDCs prime CD8+ T-cells for anti-tumor recognition while pDCs produce high levels of interferon gamma (INF-γ), which promotes an immunosuppressive TME [338–340]. Recent studies have examined DC prevalence within the TME of adult and pediatric malignancies and shown that DC infiltration is significantly lower in pediatric tumors [341]. Furthermore, studies have shown that DC maturation is inhibited in the TME of pediatric Ewings, ATRTs, gliomas, and hematologic malignancies to favor tumor growth and progression [342–345]. Given these findings and the crucial role of DCs in tumor recognition and anti-tumor host response, cancer vaccine and immunotherapy developments are underway utilizing DC as a potential vehicle [346,347].

The TME can also be altered during necrosis, unregulated cell death. Cells undergoing necrosis swell and release cellular contents into the surrounds tissue. Within a tumor, the core is typically populated with cells that have undergone necrosis and the presence of these areas are often associated with metastatic capacity and poor prognosis [348,349]. Necrotic cells release a potent mixture of damage-associated molecular patterns (DAMPs) that contribute to the chronic inflammatory milieu and promote tumor growth [350,351]. Furthermore, necrotic cells release high amounts of potassium during cell rupture, which inhibits the function of activated T-cells [352,353]. Also, necrosis can form as a result of chemotherapy in a variety of cancer types such as OS, NB, and ALL [354–356].

6. Conclusions

Pediatric cancer, while relatively rare, remains a serious public health concern. The most common childhood cancers between birth and early teens remain leukemia, central nervous system (CNS) cancers, and lymphoma [23,123]. The past few decades have seen a decline in overall mortality rates due to breakthroughs in diagnostic imaging and clinical treatments, improvements in genetic testing rates, and novel immunotherapies [76,77,357,358]. However, for pediatric bone and CNS cancers, incidence and overall survival has not changed significantly due to factors such as tumor accessibility, stage at diagnosis, underlying genetic alterations, and a unique stem-cell-like population of transformed cells that possess the means to modulate the TME to avoid immune detection [23,50]. Cancer-cell-mediated alterations to the TME often involve hijacking the host inflammatory response to promote tumor growth and progression.

The pathological switch from an acute inflammatory response to one of chronic inflammation contributes to the pathophysiology of numerous adult and pediatric diseases. The chronic, pro-inflammatory milieu of pediatric cancers promotes tumor growth and progression via secretion of angiogenic chemokines, growth factors, and suppression of the immune response [7,359]. Several key pro-inflammatory cytokines play roles in the pathogenesis of both adult and pediatric cancers. For instance, in adults, TNF-α, produced by immune cells such as lymphoid and macrophage populations, can inhibit T-cell response and activation of cancer cytotoxic T-call activation through interactions with its receptor TNFRSF1B (TNFR2) [360,361]. In pediatric cancer, TNF-α has been shown to promote de-differentiation of OS [362], Furthermore, the immature state of pediatric T-cells has been shown to contribute to reduced expression of CD40, a tumor necrosis factor receptor family member [363]. Known to promote M2 to M1 polarization in monocytes and macrophage populations, reduced CD40 expression in pediatric immune cells results in reduced anti-tumor response [364]. Interleukin 1 (IL-1) is another pro-inflammatory cytokine with known connections to the tumor microenvironment. IL-1 can activate NF-κB and MAP kinase pathways via the IL-1R1 receptor [365]. Expressed by cells of the innate and adaptive immune systems, the expression of this receptor in immune cells has been linked to cancer stages and correlates with the degree of IL-1 pro-inflammatory stimulation in the TME [366,367]. The underdeveloped pediatric immune system is unable to properly resolve inflammation, and levels of IL-1 are significantly upregulated in pediatric cancer patients contributing to further DNA and tissue damage and metastasis in ES and OS [368,369]. A third critical potent pro-inflammatory cytokine in the TME is IL-6. IL-6 is known to play a role in various physiological processes such as immune function, inflammation, development, and bone metabolism, all of which are affected in pediatric cancer development and metastasis [370]. In adult cancers, acquired oncogenic alterations and age-related immune decline contribute to altered expression of NF-κB, IL-6 (a downstream target of NF-κB), and STAT3 signaling, altering immune recognition and cellular senescence [370,371]. In pediatric cancers, higher levels of IL-6 were detected in patients with poorer prognosis, since

IL-6 is known to contribute to accelerated tumor growth [372,373]. Also, TAM production of IL-6 has been shown to support bone metastasis in NB and OS, since IL-6 can stimulate the activity of bone marrow mesenchymal stem cell and bone-resorbing osteoclasts [374,375]. These potent cytokines and others involved with chronic inflammation inhibit the DNA damage response machinery, anti-tumor immunosurveillance, and contribute to malignant genetic and epigenetic changes [48,192].

Given the importance of chronic inflammation in the onset, progression, and treatment response, therapies are being developed to target the effects of inflammation both during and after clinical treatment. For instance, high-risk ALL patients who undergo allogenic hematopoietic stem cell transplant that develop graft-versus-host disease often present with a pro-inflammatory gut microbiome, placing them at risk for chronic adult diseases [376]. Clinical strategies such as nutritional intervention, application of enteral nutrition, targeted antibiotic therapies, and prebiotics are currently under evaluation [377,378]. In OS, the extent of tumor and stromal inflammation correlates with tumor aggressiveness, and therapeutic approaches often include anti-inflammatory drugs [329,379]. Immune checkpoint inhibitors, which function to promote T-cell targeting of cancer cells, have shown considerable effectiveness in treating adult cancers and are currently under evaluation for pediatric malignancies [380,381]. PD-1/PD-L1 blocking drugs, which are effective in adult cancers, have demonstrated mixed effectiveness in pediatric populations due to variations in PD-L1 presentation [326]. However, application of immune checkpoint inhibitors (such as FDA-approved pembrolizumab) have shown promise in the treatment of Hodgkin lymphoma [382,383]. Inhibitors with alternative targets, such as T-cell Ig and mucin domain 3 (TIM-3), indoleamine 2,3-dioxygenase (IDO-1), and B- and T-lymphocyte attenuator (BTLA), are also being explored, though clinical data are scarce [384,385]. Ipilimumab, a therapy targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), was well tolerated but demonstrated little effectiveness, though it is FDA approved for the treatment of unresectable childhood melanoma [384,386]. Nivolumab is another checkpoint inhibitor FDA approved for use in pediatric patients, where it shows good responses in hypermutated CNS cancers [297,387,388]. Finally, histone deacetylase inhibitors (HDACis), which activate pro-inflammatory transcription factors such as STAT 1/3 and NF-κB, are being investigated for future therapeutic potential to arrest tumor growth and promote cancer cell apoptosis in both in vivo and in vitro models [389,390]. For instance, preclinical studies employing the drug CUDC-907, a dual P13K and HDAC inhibitor, demonstrate a reduced growth rate in NB patients [391]. Also, combination therapy using imipridones drugs alongside other HDACi (such as FDA-approved vorinostat or panobinostat) induced cell death in pre-clinical studies of ES and NB cell lines [392].

The effects of chronic inflammation in the pathogenesis of adult cancers are widely studied. However, recent studies have uncovered significant genetic and epigenetic disparities, resulting in distinct pediatric classifications [34]. Because of this, findings from adult malignancies cannot be directly translated into effective therapeutic strategies in pediatrics. While studies are beginning to explore alterations specific to pediatric TMEs, there is still a scarcity of data regarding the biological significance of the complex interplay between cell populations, the extracellular matrix, and signaling molecules, prompting the need for further studies. In the meantime, insights gleamed into the effects of chronic inflammation in pediatric cancers are being utilized to evaluate novel paradigms for therapies and supportive care.

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