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Review Article

Genetic and chromosomal dysregulations of progenitor cells in the etiology and pathogenesis of pediatric cancers

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Abstract: Pediatric cancers (PCs) differ significantly from adult cancers in terms of etiology and response to treatment. Although environmental factors have been implicated in the development of some PCs, accumulating evidence indicates that these cancers may arise from genetic dysregulation, which introduces errors within the precursor cells and the progenitor cell machinery during the early developmental stages. Such dysregulations are often explained by a "multi-hit model", in which progenitor cells acquire an initial prenatal mutation that predisposes them to subsequent postnatal hits, eventually driving malignant transformation. This review aims to consolidate emerging evidence on the role of these dysregulated progenitor cells (dPCs) as tumor cells of origin in PCs and to examine how their identity and developmental timing shape tumor phenotype, latency, and clinical behavior. Evidence drawn from monozygotic twin studies, germline predisposition syndromes, and genetically engineered mouse models were discussed for selected PC categories. This review also analyzes the current targeted therapeutic approaches. Such evidences indicate a firm and recurring role for dPCs across diverse PC subtypes, though a complete functional understanding of their dysregulation and the identification of reliable therapeutic targets remain in their early stages. Unlike adult cancers, therapeutic strategies for PCs should account for developmentally timed vulnerabilities intrinsic to their cells of origin, positioning dPCs as a potential therapeutic target.

Keywords: Multi-hit model, germline predisposition, targeted therapy, tumor cell of origin, tumor microenvironment, leukemia, neuroblastoma, Ewing sarcoma, epigenetic dysregulation and dysregulated progenitor cells

Introduction

In children, cancer is the second leading cause of death after accidents [1]. Though prenatal and early life exposures to environmental risk factors such as maternal and paternal smoking, alcohol consumption, and radiation exposure during pregnancy may impact the development of the fetus, they do not form a sole significant attribute for the incidence of various Pediatric cancers (PCs) [2, 3]. Also, PCs are much less complex than adult cancers in terms of mutation burden [3]. They often exhibit specific genetic alterations that are highly oncogenic, such as chromosomal rearrangements or gene fusions, endogenous developmental mutations, and predisposing germline mutations, as in Li-Fraumeni syndrome and Down syndrome, which increase the risk of PCs [4]. These alterations can activate oncogenes or inactivate tumor suppressor genes, profoundly affecting cell behavior even with fewer overall mutations [5]. The significant impact of relatively few mutations reflects the fact that stem and progenitor cells rely on tightly coordinated gene expression programs and stable chromosomal architecture to self-renew and differentiate appropriately. When these regulatory circuits are disrupted, whether through structural chromosomal abnormalities such as translocations, aneuploidy, and chromothripsis, or through dysregulated expression of key transcription factors and epigenetic regulators, stem and progenitor cells can become locked in an aberrant, proliferative state rather than progressing through normal differentiation [6, 7]. This convergence of chromosomal instability and abnormal gene regulation within the stem cell compartment is increasingly recognized as a defining feature underlying childhood cancers, distinguishing their pathogenesis from the more gradually acquired mutation-

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al landscape typical of adult malignancies [8]. Historically, progress in treating PCs has largely relied on the empirical application of multimodal therapy; however, a deeper understanding of the biology and origin of PCs is increasingly recognized as essential to further improving outcomes. Hence, it is necessary to examine not only the range of molecular abnormalities associated with distinct cancer subtypes but also the role of dysregulated progenitor cells (dPCs) during early developmental stages and their transition into tumor cells of origin with unique biological properties, thereby elucidating the process of oncogenesis. This review presents current information, summarizing emerging evidence suggesting that genetically dysregulated progenitor cells (dPCs) serve as tumor cells of origin in PCs.

Significance of dPCs

During embryonic development, cells undergo a highly orchestrated process of rapid division and differentiation, resulting in the formation of specialized tissues and organs. This process is governed by the activation and regulation of various genetic pathways, which can be disrupted by genetic mutations in progenitor cells, thereby generating dPCs [9]. These dysregulated cells are highly susceptible to further genetic mutations due to their active proliferation and genetic changes [10]. For example, in most pediatric malignancies, the origin of tumor cells can be traced to specific progenitor populations; in some cases, however, as in Ewing's sarcoma, the tumor cell of origin remains the subject of ongoing research and is associated with ambiguous stem or progenitor cells [11]. Genetic dysregulation in progenitor or precursor cells that leads to various PCs is summarized in (**Table 1**). It can be presumed that mutations such as chromosome rearrangements, chromothripsis, and other endogenous genomic alterations can occur in these susceptible dPCs with impaired DNA repair mechanisms during development [12]. The mechanistic basis of such alterations is increasingly attributed to errors occurring during mitosis in rapidly dividing progenitor cells. Mis-segregated chromosomes can become sequestered into micronuclei, where they undergo asynchronous replication and premature chromosome condensation, ultimately leading to fragmentation, or pulverization, of the enclosed chromosome. These fragments are subsequently reincorporated into the daughter nucleus and rejoined, often through error-prone non-homologous end joining, generating the clustered rearrangements characteristic of chromothripsis [13, 14]. Similar catastrophic rearrangements can also arise from dicentric chromosome bridges formed during anaphase, as well as from telomere erosion and replication stress at fragile genomic sites [13]. Progenitor cells are particularly susceptible to these events when canonical DNA damage response and repair pathways are compromised: loss of TP53 function, in particular, permits cells harboring pulverized chromosomes to bypass apoptosis and cell-cycle checkpoints, allowing chromothriptic rearrangements to persist and propagate [14, 15]. Constitutional DNA repair disorders such as ataxia telangiectasia, Nijmegen breakage syndrome, and Bloom syndrome, which impair double-strand break sensing and homologous recombination, similarly predispose progenitor cells to chromosome instability and complex rearrangements [14]. In pediatric malignancies such as medulloblastoma and osteosarcoma, these processes are especially prominent, with chromothripsis detected in a substantial proportion of tumor genomes and frequently co-occurring with germline or somatic TP53 alterations [15, 16]. Collectively, these findings suggest that the combination of high proliferative activity, developmentally permissive chromatin states, and compromised genome surveillance renders progenitor cells uniquely vulnerable to the endogenous genomic catastrophes that form the basis of pediatric oncogenesis.

Beyond chromosomal instability, genetic regulatory abnormalities in progenitor cells commonly arise from the hijacking of normal transcriptional and epigenetic control mechanisms. Chromosomal translocations that generate fusion oncoproteins, such as EWSR1-FLI1 in Ewing sarcoma or PAX3-FOXO1 in alveolar rhabdomyosarcoma, do not merely create novel proteins but actively rewire the progenitor cell's transcriptional network, binding to and activating lineage-inappropriate enhancers and repressing normal differentiation programs [17, 18]. In parallel, aberrant epigenetic reprogramming, including altered DNA methylation at tumor suppressor loci and dysregulated histone modifications, can lock progenitor cells

Table 1. List of Genetic dysregulations of progenitor cells in various pediatric cancers (PCs)

Cancer	Mutations or Dysregulation	Cell of Origin	Onset of Disease	References
AML	*KMT2A* (MLL), *CBFA2T3*, *MNX1*, t(8;21) translocations (*RUNX1-RUNXT1*), *CBFB*, and *RARA*	HSPCs	Infancy	[86]
ALL	*KMT2A* (MLL), *CBFA2T3*, *MNX1*, *ETV6-RUNX1* (TEL-AML1), and *TCF3-PBX1*	HSPCs	Post Infancy	
NHL	t(8;14)(q24; lq32), t(1:1 7)(p36:q2 1), t(1;14)(p36:q22) and disorder of immune dysfunction may also predispose the child to NHL	GC-B cells of lymph nodes) and DZ centroblast	Early childhood to adolescents	[87]
Neuroblastoma	*PHOX2B*, *ALK*, *KIF1Bb* and predisposing syndromes Costello syndrome, Noonan syndrome, and neurofibromatosis type 1	Neural crest progenitor cells/sympathoadrenal lineage of neural crest cells and Schwann cell precursors that were recently identified as the source of adrenal chromaffin cells.	Infant to toddler	[88]
Retinoblastoma	*RB1* gene mutation	retinal progenitor cells and retinal transition cells/maturing cone precursor	Young children	[63, 64]
Ewing Sarcoma	EWS-FLI1 (t(11;22)(q24;q12)); CNV (gain of chromosome 1q, 8, 12 and loss of 9p21 and 16q) and gene mutations such as in STAG2, TP53 and Rb1genes	MSCs/NCCs/OCPCs	Children and yound adults	[89, 90]
Osteosarcoma	recurrent deletions *TP53*, *RB1*, *CDKN2A/B* genes, or recurrent amplifications, *COPS3*, *CCNE1*, *MDM2/CDK4*, *MYC* genes, and 6p12.3 amplifications	MSCs/MSC-derived osteogenic cell types	Children and adolescents	[91]
Glioblastoma	H3 gene mutations, alterations in MAP kinase pathway, mutations in TP53 or PPM1D, homozygous deletion of CDKN2A or CDKN2B; NF1; TST1or CMMRD; Nevoid BCC Syndrome/(GS)	NSC/OCPs	Younger children (midline Glioma) and Adolescents and young adults (high grade gliomas)	[36, 92]
-Rhabdomyosarcoma	Fusion-Negative: TP53, RAS Pathway mutations, alterations in the PI3K-AKT-mTOR pathway, and alterations in the *MYCN* oncogene Fusion-Positive: Pax3:Foxo t(1;13) or t(2;13)	MSCs/EPCs	Children and young adults	[93]

Abbreviations: AML: Acute Myeloid Leukemia; HSPCs: Hematopoietic stem or progenitor cells; ALL: Acute Lymphoblastic Leukemia; NHL: Non-Hodgkins lymphomas; GC: Germinal Center; DZ: Dark Zone; CNV: Copy Number Variation; MSCs: Mesenchymal Stem Cells; NCCs: Neural Crest Cells; OCPCs: Osteochondrogenic Progenitor Cells; NF1: Neurofibromatosis Type 1; TST1: Turcot Syndrome Type 1; CMMRD: Constitutional Mismatch Repair Deficiency; BCC: Basal Cell Carcinoma; GS: Gorlin Syndrome; NSCs: Neural Stem Cell; OCPs: Oligodendrocyte precursor cells; EPCs: Endothelial progenitor cells.

into a self-renewing, undifferentiated state by silencing the genetic programs that would normally drive maturation [19]. Because progenitor cells rely on finely tuned, developmentally timed activation and repression of transcription factor networks to progress through differentiation, even a single regulatory lesion introduced at a permissive developmental window can propagate across subsequent cell divisions, compounding into the broader dysregulated phenotype that characterizes dPCs. These aberrations can persist throughout the developmental stage of the fetus and can either present with cancer at an early age or in adolescence [20]. Identification of such distinctive age-related patterns in the onset of cancer implies a specific developmental phase during which certain tissues or cells exhibit a heightened susceptibility to molecular and cellular changes leading to the disease [21]. Hence, the complex and heterogeneous nature of cancer biology contributes to ongoing challenges, including genetic variability within tumors, risk of secondary malignancies, aggressive recurrence, and resistance to therapy, which remain difficult to fully overcome [22, 23]. As one avenue for identifying novel cancer therapeutic targets, it makes a compelling case for understanding the origin of tumor-initiating dPCs and their roles in PC initiation, tumorigenesis, and metastasis.

Fundamental basis of precursor cell dysregulations

Studies conducted in mouse models report that PCs exhibit a "multi-hit model" of disease development, which suggests that cancer is caused by the accumulation of multiple genetic mutations or "hits" over time [24]. This model proposes that children born with a small number of mutations in progenitor cells during development are predisposed to additional mutations that accumulate and transform these cells into dPCs as they grow and mature, ultimately leading to cancer. These dPCs are susceptible to malignant transformation and sustain disease progression (**Figure 1**).

Leukemia

A study on the whole genomes of leukemic cells from two sets of monozygotic twins with acute lymphoblastic leukemia (ALL), which is the most prevalent subtype of leukemia, accounting for approximately 80% of cases, suggests that childhood ALL can develop in the absence of genetic instability and with only a small number of driver mutations [25]. It was revealed that shared, prenatal coding regions with single-nucleotide variants were limited to the putative initiating lesions. In contrast, all other nonsynonymous single-nucleotide variants were distinct between tumors and therefore secondary and postnatal [26]. Furthermore, noncoding mutational changes were almost entirely discordant in twin pairs, likely representing passenger mutations acquired during leukemic cell proliferation. Similarly, another study on monozygotic twins with concordant hyperdiploid B-ALL but different RAS mutations provides further evidence that hyperdiploidy occurs prenatally, with *RAS* mutations developing postnatally. This supports the multi-hit model, in which environmental exposures did not appear to be a clear contributing factor [27]. Certain germline mutations or syndromes were also known to predispose the child to ALL. These genetic conditions often involve the same genes that are targeted by somatic mutations in ALL blasts, such as *PAX5*, *IKZF1*, *ETV6*, and *PTPN11* [28]. Some of these conditions, including those caused by germline alterations in *PAX5*, *IKZF1*, and *ETV6*, primarily predispose individuals to develop ALL. Examination of the genetic status of leukemic blasts provides important clues to the underlying ALL predisposing condition, such as a low hypodiploid karyotype in blasts from individuals with LFS, or a hypermutator phenotype in blasts from individuals with Constitutional Mismatch Repair Deficiency (CMMRD) [29]. Full-blown leukemia in Down syndrome was dependent on additional genetic mutations, specifically deletion of cohesion genes, including *STAG2* (STAG2ko). Such mutations occurred in progenitor cells during the fetal and early postnatal stages; however, adult-derived bone marrow hematopoietic stem and progenitor cells were unable to undergo the same leukemic transformation [30]. This suggests that it is crucial to identify and understand the cell of origin (COO) of PCs and the mechanism of their dysregulation to develop an effective therapy. For instance, a study on AML that transplanted bone marrow cells transduced with a retrovirus expressing NUP98-HOXA9 revealed that the age of the COO determines not only the latency

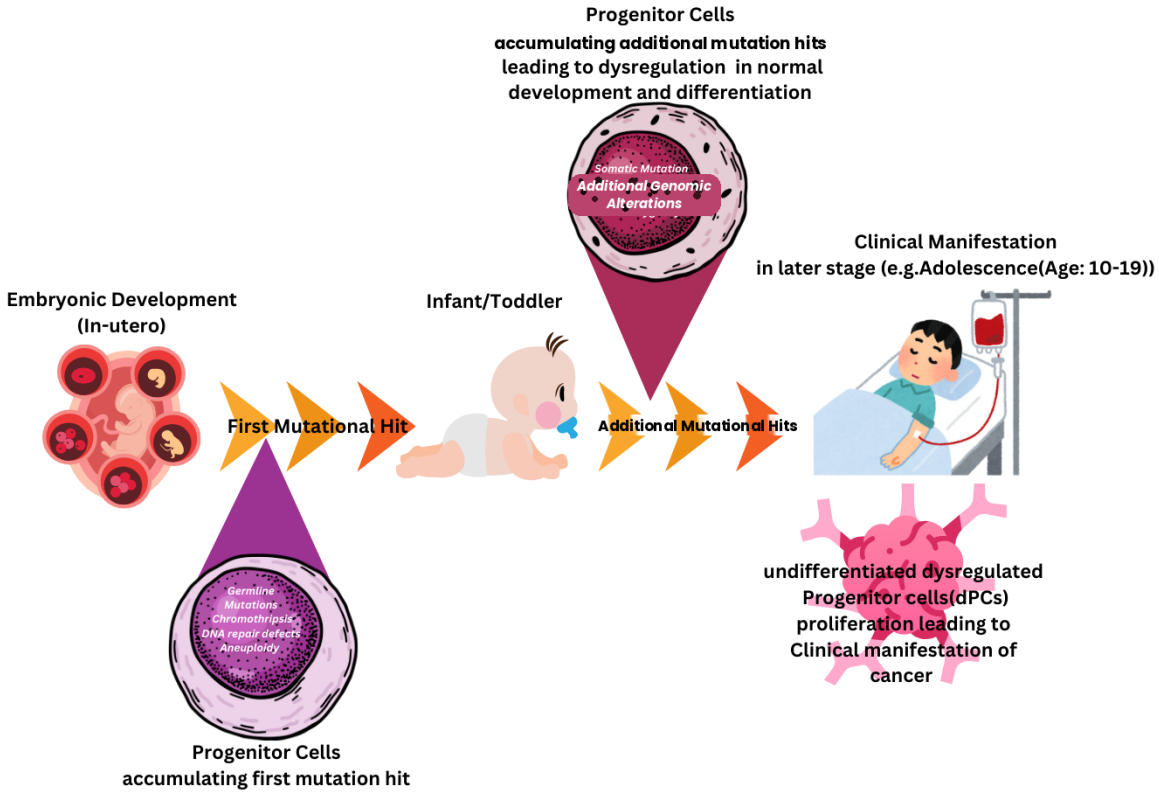

Figure 1. Schematic illustration of multi-hit model of progenitor cell dysregulation. Majority of pediatric cancers (PCs) exhibit the multi-hit model of cancer manifestation, suggesting that the multiple genetic mutation hits are accumulated over time across various developmental phases initiating from *in utero* till adolescence. Mutations acquired in early developmental phases such as during embryonic development (*in utero*) predispose them to additional mutations that transform the progenitor cells to a dysregulated state, ultimately leading to the development of various PCs.

period for disease development but also the lineage phenotype and changes in the bone marrow (BM) niche, highlighting the importance of COO [31]. But in the current scenario, there is still ambiguity in defining or pinpointing a COO for any PCs, as the embryonic developmental phases are layered. However, it is believed that the COO may be hematopoietic stem cells (HSCs) or progenitor cells that undergo prenatal genetic aberrations. Studies have suggested that HSC-independent progenitor cells can also be subject to genetic hits occurring prenatally due to their proliferation rate in a limited time frame [32], leading to a pre-leukemic state which then requires multiple genetic hits before an overt manifestation of the disease [33]. For instance, erythro-myeloid progenitors (EMPs), which sustain fetal myelopoiesis and persist in adults, can harbor mutations such as *PTPN11,* which lead to a distinctive case in children around 2 years of age known as juvenile myelomonocytic leukemia (JMML), a type of leukemia with high relapse rates after HSC transplantation and plausible in *utero* initiation [34]. Next, lymphoid-primed multipotent progenitors are another type of HSC-independent progenitor that has emerged as a potential cell of origin in B-cell acute lymphoblastic leukemia (B-ALL) with *MLL-AF4* translocation [35].

Pediatric brain tumors

Pediatric brain tumors encompass a heterogeneous group of cancers with diverse developmental origins and genetic mutations. Midline gliomas primarily affect younger children and are associated with specific mutations in the H3 genes. In contrast, high-grade gliomas within the cerebral lobes occur in adolescents and young adults and exhibit different mutations [36]. Medulloblastomas, a type of embryonal tumor, are believed to arise from immature neuronal precursors in the external granular cell layer of the cerebellum, contributing to their

localization primarily in the pediatric cerebellum [37]. Certain rare pediatric CNS tumor types are associated with germline mutations in predisposition genes; *DICER1* [38] and *RB1* [39] mutations can predispose patients to pineoblastoma. Dysplastic cerebellar gangliocytoma is pathognomonic for Cowden syndrome, caused by germline mutations in the *PTEN* gene [37]. Pediatric high-grade gliomas (pHGGs) exhibit distinct molecular alterations, including mutations in the genes H3F3A and HIST1H3B, leading to specific amino acid substitutions in histone proteins. These mutations exhibit a characteristic distribution pattern, suggesting distinct cell-of-origin for pHGG subgroups [40]. High-grade gliomas (HGGs) in children and adolescents exhibit distinct patterns of occurrence by location and genetic mutations [41]. Recent evidence from genetic mouse models indicates that introducing classic genomic alterations associated with midline gliomas during prenatal brain development does not result in immediate tumor formation but instead gives rise to neoplasms only in the postnatal period. This highlights that glioma initiation is constrained to a specific developmental window, emphasizing the importance of neurodevelopmental timing in tumor latency and onset [42]. Additionally, while these mutations in *vitro* can transform neural stem cells, the resulting tumors do not resemble the typical histological appearance of diffuse midline gliomas when transplanted into the mouse brain. Similar mechanisms have been observed in adult glioblastoma (GBM), where mutations in neural stem cells give rise to tumors only when those stem cells differentiate into oligodendrocyte precursor cells (OPCs) [43], which are neural precursor cells involved in myelination. It is believed that GBMs can originate from both neural stem cells and OPCs, but the specific molecular subtype is determined by the COO [44]. A study explored the cellular origins of CNS tumors by analyzing INSM1 expression at the transcriptional and translational levels using publicly available microarray data. The findings showed higher *INSM1* transcript levels in medulloblastoma than in extracerebellar embryonal tumors. Notably, most medulloblastomas arise from immature neuronal precursors within the external granular layer of the developing cerebellum, which explains their predominant localization in the pediatric cerebellum [37].

Pediatric embryonal tumors

Neuroblastoma, a pediatric embryonal tumor, is an aggressive childhood cancer arising from the developing peripheral nervous system, specifically the neural crest [45]. While the exact cause is unknown, genetic predisposition and dysregulation of neural crest development are believed to play a role. Neuroblastoma was presumed to originate from sympathoadrenal precursor cells, a specific lineage of neural crest precursor cells that fail to mature into functional nerve cells, and mutations in *MYCN*, *PHOX2B*, *ALK*, and *RAS* pathway genes in these cells have been demonstrated to increase the risk [45]. Thus, understanding the precise origin and the factors that influence the development of neuroblastoma is crucial for developing targeted therapies and improving prognosis to overcome treatment resistance.

Another type of embryonic tumor prevalent in children is retinoblastoma, which arises from the abnormal development of retinal cells, most often in young children. Earlier studies suggested that retinoblastoma develops due to mutations in the Rb1 gene. However, studies using an inherited mouse model with Rb loss challenge this view by findings suggesting that the COO for retinoblastoma may be a specific retinal cell type that is naturally resistant to cell death triggered by Rb loss, likely a susceptible progenitor cell [46]. Tumor formation appears to involve these cells escaping a normal growth arrest process that occurs during retinal development, rather than acquiring resistance to cell death [47].

Lymphoma

Pediatric lymphomas are influenced by the age-specific pathway of cell transformation and the cells in which the mutational hits are acquired. Burkitt lymphoma (BL), for example, may develop from a centroblast [48], which, in turn, is a proliferative, immature cell at risk of transformation by a GECC (great effect chromosomal change) carrying Ig/*MYC* translocations. However, the rarity of centroblast transformation by a GECC is attributed to the death of many cells with severe DNA injuries caused by EBV infections. Anaplastic large cell lymphoma (*ALK*+ ALCL) is another pediatric lymphoma that primarily affects children and adolescents. It is thought to result from rapid cell transfor-

mation of a differentiating T-cell, possibly a "T-immunoblast" precursor [49]. These T-immunoblasts, which exhibit an anaplastic morphology, have a risk of transformation by GECCs such as t(2;5). T-cell lymphoblastic lymphoma (T-LBL), a rare lymphoma occurring primarily in older children and young adults, was believed to arise from the rapid transformation of a T-lymphoblast, possibly originating in the thymus, as this stage is naturally high-risk because DNA is actively being modified. Thymic involution during puberty may contribute to the risk of T-lymphoblast injury, leading to T-LBL. GECCs, such as certain TCR (T-Cell Receptor) gene-related translocations, were speculated to trigger oncogenic transformation in T-LBL [50].

Cancer of connective tissues

Rhabdomyosarcoma (RMS): The precise COO for RMS remains under investigation, with various candidates being explored. Mesenchymal Stem Cells (MSCs) are considered potential candidates, particularly due to their ability to differentiate into various cell types, including muscle cells [51]. While a few reports suggest a link, conclusive evidence that MSCs are the sole source remains lacking [52]. A study suggested that genetic modifications in muscle progenitor cells, particularly those expressing Myf6 or MyoD, can lead to RMS development, especially embryonal RMS (eRMS) [53]. Fibroadipogenic Progenitor (FAPs) cells were found to contribute to muscle repair and can switch between muscle and fat lineages. FAPs can be considered potential candidates for studying the origin of RMS, especially given their role in dystrophic muscle degeneration [54]. Pericytes and PW1+Pax7-Interstitial Cells are other cell types residing within muscle tissue with progenitor potential. Their role in RMS development is underexplored but cannot be ruled out [55]. RMS development likely involves a combination of genetic and environmental factors: Specific mutations, like *PAX3-FOXO1* gene fusions, are almost always observed in alveolar RMS (aRMS) and are considered a hallmark of this subtype [52]. Mutations in genes like p53, dystrophin, and telomerase may also play a role [56]. The Sonic hedgehog (Shh)-Smoothened (Smo)-Patched (Ptch) signaling pathway appears to be involved in eRMS development, potentially by activating early myogenic genes in adipogenic cells [57]. RMS development may be specific to certain cell populations or tissues due to the permissive environment of these tissues. For example, Shh signaling induced tumors only in brown adipose tissue, not in white adipose tissue, highlighting the importance of cellular context [57]. A study on FN-RMS (Fusion Negative-Rhabdomyosarcoma) traced the development of cancer and found that it originates from endothelial progenitor cells, but not from the skeletal muscle cells, within the head and neck region. Most importantly, it was found that the hedgehog signaling pathway, aberrantly activated in FN-RMS, causes these progenitor cells to adopt a skeletal muscle-like fate. This finding suggests that FN-RMS may have multiple cellular origins and that understanding these origins is crucial for developing targeted therapies [58].

Ewing sarcoma (ES): ES presents a significant challenge in understanding its cellular origins [59]. Despite the absence of distinct genetic subtypes, suggesting a single source cell, the precise lineage from which this malignancy arises remains elusive [60]. This obscurity is complicated by the tumor's undifferentiated phenotype and its unique gene expression profile [60, 61]. One hypothesis posits that neural crest stem cells, when exposed to EWSR1-FLI1, exhibit a gene expression pattern strikingly similar to that of ES [62, 63]. MSCs also emerge as a candidate source [64]. These cells are susceptible to EWSR1-FLI1, and conversely, knockdown of this protein shifts the gene expression profile of ES cells closer to that of MSCs. Osteochondrogenic progenitors that give rise to bone and cartilage are also under investigation for their roles in YAP/TAZ signaling in bone development and sarcoma pathogenesis [65].

Emerging therapeutic targets of dPCs

Understanding dysregulation in progenitor cells and its contribution to cancer pathogenesis paves the way for predicting prognosis and identifying new therapeutic targets that can overcome the limitations of treating pediatric patients (**Figure 2**). Several important gene dysregulations that highlight their normal and tumorigenic roles in PCs are listed in (**Table 2**). The unique dysregulated expression of these genes during tumorigenesis underscores their

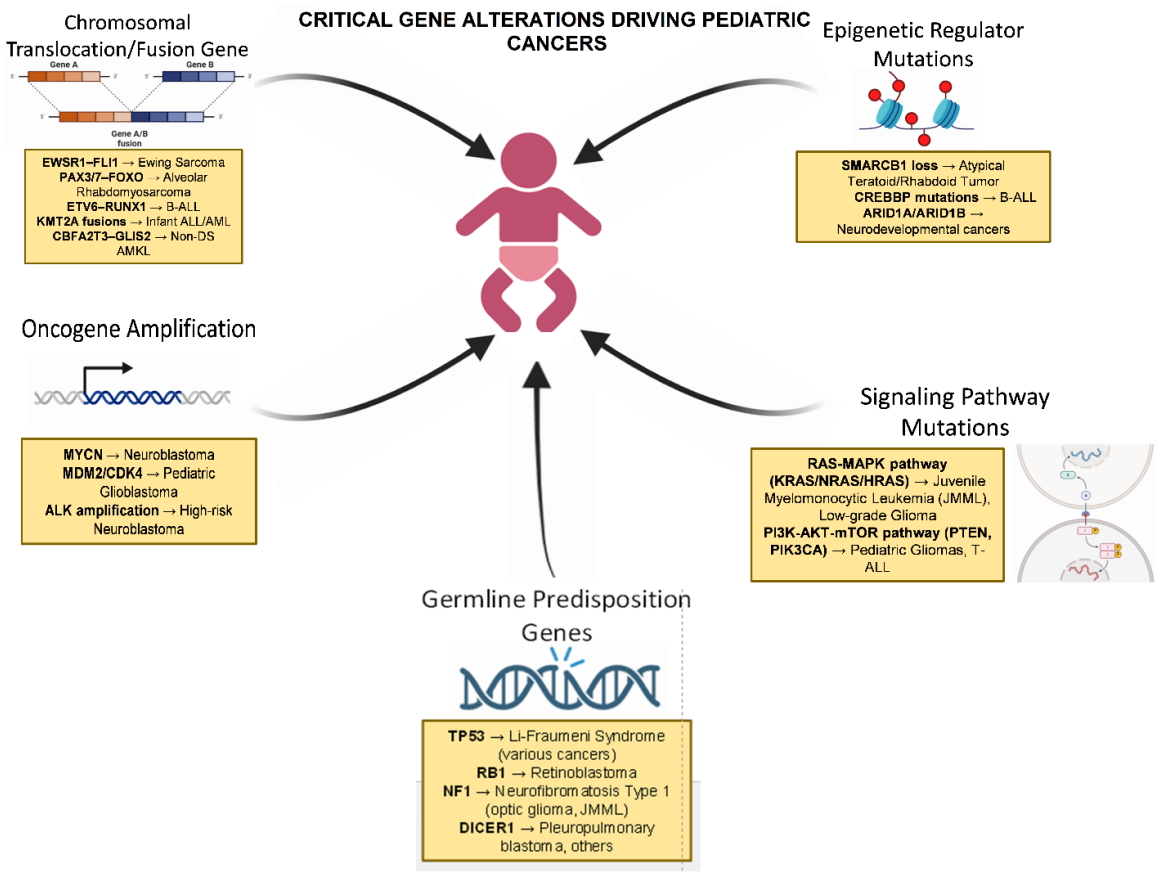

Figure 2. Schematic overview of key genomic perturbations driving pediatric cancers (PCs). Five main genomic alterations linked to pediatric tumors: Chromosomal translocations/fusions, Oncogene amplifications, Germline predisposition genes, Signaling pathway mutations, and Epigenetic regulator mutations.

importance as therapeutic targets. Fusion proteins resulting from chromosomal translocations and other genomic rearrangements are non-physiological and drive PC progression through continuous activation of growth and survival pathways, altered transcriptional regulation, and evasion of apoptosis. Current therapeutic strategies targeting these fusion genes include small-molecule inhibitors like imatinib for Philadelphia chromosome-positive ALL [66] and BCR-ABL-positive chronic myeloid leukemia in pediatric patients [67], and monoclonal antibodies such as blinatumomab for *ETV6-RUNX1* in ALL [68]. Current research on fusion oncoproteins in childhood sarcomas such as ES identifies several promising therapeutic strategies, including RNA interference [69] and immunotherapies targeting breakpoint regions [70]. Next, aberrant DNA methylation contributes significantly to tumorigenesis, as seen in ALL, where silencing of genes such as p15INK4B and p16INK4A has been observed [71], and in medulloblastoma, where methylation affects key *WNT* pathway genes [72]. Histone modifications, such as H3K27M mutations in DIPG [73] and HDAC overexpression in neuroblastoma [74], further contribute to oncogenesis. Non-coding RNAs, like miR-206 in RMS and *EWSAT1* in ES, also influence tumor behavior [75, 76]. The intricate interplay between the tumor and its tumor microenvironment (TME), comprising extracellular matrix, signaling molecules, and immune cells, determines the fate of tumor progression. For instance, studies on the tumor-progression mouse glioma model showed that macrophages transition from an immune-active to an immune-suppressive state, contributing to therapy resistance. That myeloid-derived suppressor cells (MDSCs) further strengthen this suppression [77]. Elevated levels of immune checkpoint molecules such as CD200, PD-L1, CTLA-4, and B7-H3 on tumor cells suppress anti-tumor immunity by inhibiting T-cell activa-

Table 2. Summary of genes indicating both their developmental role and their tumorigenic functions during their state of dysregulation/translocation or chimeric fusion in various pediatric cancers (PCs)

Cancer/Syndromes	Dysregulated genes	Normal Developmental Role	Tumorigenic Mechanism	References
Ewing Sarcoma	EWSR1-FLI1	*EWSR1:* Involved in RNA processing and transcription regulation. *FLI1:* Transcription factor regulating hematopoiesis and endothelial cell development.	EWS-FLI1 fusion acts as an aberrant transcription factor, binds to GGAA microsatellites and dysregulate gene expression. It blocks differentiation and promotes proliferation in mesenchymal progenitor cells.	[94]
Alveolar Rhabdomyosarcoma	PAX3/7-FOXO1	*PAX3*: Key in early muscle and neural crest development, promotes progenitor migration and commitment. PAX7: Maintains satellite (muscle stem) cells and supports muscle regeneration. FOXO1: Apoptosis regulator, cell proliferation, and stress response	Blocks myogenic differentiation, induces uncontrolled proliferation and survival signals, highly aggressive subtype.	[95, 96]
Neuroblastoma, Medulloblastoma	*MYCN*	Transcription factor regulating embryonic development, especially neural crest cell proliferation and differentiation.	Uncontrolled cell proliferation, impaired differentiation, It suppresses ERα and (NGF) signaling, maintaining an undifferentiated state and poor prognosis.	[97]
Neuroblastoma	*ALK*	Receptor tyrosine kinase involved in neuronal development and synaptic signaling.	*ALK* amplification or mutation leads to constitutive activation of MAPK/PI3K pathways, leading to proliferation.	[98]
Infant gliomas	*CDK4/6*	Kinases that promote G1-S phase progression in the cell cycle by phosphorylating RB protein.	Amplification overrides cell cycle checkpoints, leading to hyperproliferation.	[99]
Atypical teratoid/rhabdoid tumors	*SMARCB1 (INI1)*	Core component of the SWI/SNF chromatin remodeling complex; regulates gene accessibility and transcription.	Loss of function leads to widespread dysregulation of transcriptional programs and uncontrolled proliferation.	[100]
Rhabdoid tumors, Medulloblastoma	*EZH2*	Catalytic subunit of PRC2 complex; adds repressive H3K27me3 marks to silence gene expression.	Gain-of-function mutations lead to excessive gene silencing, particularly of tumor suppressor genes.	[101]
Leukemias	*CREBBP*	Histone acetyltransferase; promotes open chromatin and transcriptional activation.	Loss of function results in reduced acetylation, leading to impaired tumor suppressor gene expression.	[102]
Neuroblastoma	*ALK*	Receptor tyrosine kinase involved in neural crest development and survival.	Activating mutations cause constitutive signaling via *MAPK* and *PI3K* pathways, promoting growth.	[103]
Low-grade glioma, Juvenile JMML, Embryonal rhabdomyosarcoma	*RAS (HRAS, KRAS, NRAS)*	Regulates cell proliferation and differentiation via MAPK pathway.	Activating mutations lock *RAS* in GTP-bound active state, driving uncontrolled cell division.	[104, 105]
Pediatric ALL	*JAK2*	Key mediator in cytokine receptor signaling for blood cell development.	Mutations result in cytokine-independent activation of JAK/STAT pathway, driving leukemogenesis.	[106]
Li-Fraumeni Syndrome (various sarcomas, brain tumors, leukemias, adrenocortical carcinoma)	*TP53*	Tumor suppressor; guardian of the genome. Regulates cell cycle arrest, DNA repair, apoptosis.	Germline mutation leads to failure in responding to DNA damage, allowing accumulation of mutations.	[107]
Hereditary Retinoblastoma	*RB1*	Regulates cell cycle by inhibiting E2F transcription factors.	Loss of both alleles removes cell cycle checkpoint, leading to uncontrolled retinal cell proliferation.	[108]
DICER1 syndrome (pleuropulmonary blastoma, ovarian Sertoli-Leydig tumors, others)	*DICER1*	MicroRNA processing; regulates gene expression post-transcriptionally.	Mutation leads to dysregulation of miRNA networks, disrupting normal development and allowing oncogenesis.	[109]
Fanconi Anemia subtype D1, also linked to pediatric leukemia	*BRCA2*	Homologous recombination repair of DNA double-strand breaks.	Germline defects cause genomic instability, increasing susceptibility to leukemias and solid tumors.	[110]

Abbreviations: ERα: Estrogen Receptor Alpha; NGF: Nerve Growth Factor; JMML: Juvenile myelomonocytic leukemia; ALL: Acute Lymphoblastic Leukemia.

tion, leading to immune evasion and treatment resistance [78-80]. A dysregulated immune response reflects the state of the TME and can serve as a prognostic biomarker [81]. In recent times, immunotherapy approaches, along with traditional approaches such as surgery, radiation, and chemotherapy, have shown significant success, including CAR T-cell therapy, monoclonal antibody (mAb) therapy, and cytokine-based treatments, which are under active investigation [82]. Approximately 10% of PCs are linked to germline mutation variants, a significantly higher prevalence than in adult cancers [83, 84]. In PCs, as the somatic mutation burden is low compared to adult cancers, germline variants confer inherited risks of aiding tumor progression and present with cancers that are more aggressive and resistant to conventional therapies [39]. These germline mutations often affect key tumor suppressor genes and oncogenes, contributing to early-onset malignancies. Hence, identifying these germline variants is crucial for risk stratification, early diagnosis, and personalized therapeutic approaches. Genetic testing and counseling are recommended for pediatric patients' families to identify inherited predispositions, enabling targeted surveillance and early intervention [85]. Overall, integrating insights into germline variants enhances personalized pediatric oncology. Collectively, these findings underscore that, unlike adult cancers where targeted therapy chiefly addresses mutations accumulated over a lifetime, therapeutic strategies for PCs must additionally account for developmentally timed vulnerabilities intrinsic to dPCs.

Discussion

PCs, despite exhibiting fewer genetic mutations than adult cancers [3], exhibit intricate evolutionary trajectories that contribute significantly to their clinical complexity. During fetal development, a series of progressive changes occur in progenitor cells at the genetic, epigenetic, and microenvironmental levels, pushing them toward a dysregulated state and driving the disease from its origin to its full clinical presentation. Further, heterogeneities arise from a multitude of factors, including distinct mutational landscapes across different tumor types, cellular origins from embryonic and developmental precursors, and variations in TME, which collectively complicate diagnosis and treatment. While heterogeneity poses challenges, it simultaneously presents unique opportunities for therapeutic and preventive interventions. Targeted therapies tailored to specific genetic mutations or molecular pathways can exploit this heterogeneity to achieve more precise and effective treatment outcomes. It is imperative to understand the role of dPCs and the mode of dysregulation at the functional level to specifically identify appropriate therapeutic targets to combat PCs. However, full understanding of the heterogeneity and complexity of PCs, identification of foolproof drug targets, and effective therapeutics are still evolving and remain at a nascent stage; more research is warranted in this area. In our view, a major limitation constraining this field is the continued reliance on retrospective genomic and transcriptomic correlations to infer the cell of origin, rather than direct, real-time lineage tracing of the dysregulation event as it occurs. Much of the current evidence, while compelling, is circumstantial: it associates a mutational signature or gene expression profile with a candidate progenitor population without directly capturing the transformation event within that cell as it happens in *vivo*. We believe that dual-reporter and inducible lineage-tracing models, capable of marking a specific progenitor population at a defined developmental window and tracking its fate through to overt malignancy, represent a more direct approach to resolving COO ambiguity than correlative profiling alone, particularly for tumors such as Ewing sarcoma and rhabdomyosarcoma, where multiple candidate cells of origin remain under debate. We further contend that the field would benefit from greater emphasis on the developmental timing of the initiating lesion, not merely its identity, since the same mutation can yield markedly different phenotypic and clinical outcomes depending on when in the progenitor cell's differentiation trajectory it occurs. Addressing this temporal dimension, in our opinion, is likely to be as important for identifying viable therapeutic windows as identifying the responsible gene or fusion event itself.

Conclusion

In this review, we have highlighted how dysregulations in progenitor cell populations contribute to the initiation of PCs. To our knowledge, we have comprehensively summarized the existing literature, which strongly indicates that dPCs play a firm role in PCs, and that so-

lutions to target or circumvent them are only emerging. At the same time, their complete functional understanding appears quite challenging. Genetic and chromosomal dysregulations, arising from both structural genomic instability and aberrant transcriptional or epigenetic regulation, converge to lock progenitor cells into an oncogenic trajectory during a developmentally restricted window, distinguishing the pathogenesis of PCs from the more gradually acquired mutational landscape of adult malignancies. Continued application of lineage-tracing and reporter-based models will be essential to translate this understanding into viable, developmentally informed therapeutic strategies. These dPCs could serve as a potential "Achilles heel", offering promising avenues for targeted therapeutic intervention in the future.

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Disclosure of conflict of interest

None.

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