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REVIEW ARTICLE

THE ROLE OF CHROMOSOMAL TRANSLOCATIONS IN HEMATOLOGIC MALIGNANCIES: MECHANISTIC INSIGHTS AND CLINICAL CORRELATES

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Abstract

Chromosomal translocations are central drivers of hematologic malignancies, reshaping gene regulation, altering epigenetic states, and generating oncogenic fusion proteins that initiate and sustain malignant transformation. Advances in whole-genome sequencing, long-read mapping, and single-cell multiomics have expanded the catalog of recurrent and cryptic rearrangements while illuminating mechanisms such as enhancer hijacking, 3D chromatin architecture disruption, aberrant V(D)J recombination, and defective DNA repair. These insights reveal how translocations activate lineage-specific oncogenic programs across leukemias, lymphomas, and plasma-cell neoplasms. Clinically, translocations refine diagnostic classification, guide prognostic stratification, and increasingly direct targeted therapy, with fusion-specific agents, epigenetic modulators, and kinase inhibitors transforming outcomes for select subtypes. Their role in measurable residual disease (MRD) monitoring further enhances treatment precision. This review synthesizes recent mechanistic and clinical advances, emphasizing how an improved understanding of translocation biology is reshaping precision medicine in hematologic oncology.

Keywords: chromosomal translocations, hematologic malignancies, leukemia, lymphoma, molecular mechanisms.

INTRODUCTION

Hematologic malignancies arise from a complex interplay of genetic, epigenetic, and micro-environmental factors that disrupt normal blood cell development and function. Among the most defining genetic abnormalities in these cancers are chromo-somal translocations structural rearrangements that juxtapose segments of different chromosomes, frequently creating novel fusion genes or aberrantly regulating protooncogenes. Since the discovery of the Philadelphia chromosome in chronic myeloid leukemia (CML), chromosomal translocations have become central to understanding the biology, classification, and clinical behavior of leukemias, lymphomas, and plasma-cell neoplasms[1-3]. Translocations occur in up to two-thirds of hematologic malignancies, underscoring their pivotal role in pathogenesis. Their mechanistic consequences are diverse. Classical translocations generate fusion oncogenes, such as BCR-ABL1, PML-RARA, KMT2A fusions, and RUNX1-RUNX1T1, which promote malignant transformation through constitutive signaling, transcriptional dysregulation, or epigenetic reprogramming. Others lead to enhancer hijacking, whereby potent immunoglobulin or super-enhancers are repositioned near oncogenes like MYC, BCL2, and CCND1, driving uncontrolled proliferation without producing fusion transcripts. Recent advances in chromatin topology research further reveal that some translocations disrupt topologically associated domains (TADs), rewiring 3D genome architecture and enabling inappropriate gene activation[4,5].

Technological advances over the past decade have substantially reshaped our understanding of these events. High-throughput sequencing, whole-genome mapping, long-read technologies, and single-cell multiomics now uncover cryptic or complex rearrange-ments previously undetectable by conventional cyto-genetics. These tools have expanded the repertoire of known translocations and revealed new mechanisms of break formation, including RAG-mediated aberrant recombination, AID-induced mutagenesis, replication stress, R-loop accumulation, and defects in DNA damage response pathways. Such mechanistic insights

provide a more refined framework for understanding lineage-specific susceptibility to translocations, particularly in rapidly dividing or actively recombining hematopoietic compartments[6,7].

Clinically, the relevance of translocations is equally profound. The most recent WHO 5th Edition and International Consensus Classification (ICC) place translocation-defined entities at the core of hematologic cancer taxonomy. Translocations now serve as diagnostic hallmarks, prognostic biomarkers, and therapeutic targets. For example, identification of BCR-ABL1, PML-RARA, KMT2A fusions, and FGFR1 rearrangements directly guides treatment selection, enabling the use of tyrosine kinase inhibitors, ATRA/arsenic regimens, menin inhibitors, and FGFR inhibitors. In lymphoid malignancies, IGH-driven translocations and double-hit signatures inform risk stratification and dictate the intensity of therapy. In addition, fusion transcripts have become essential tools for measurable residual disease (MRD) monitoring, allowing real-time quantification of disease burden and improved therapeutic decision-making[8,9].

The aim of this narrative review is to synthesize the most recent discoveries on chromosomal translocations in hematologic malignancies, focusing on their mechanistic underpinnings, including fusion oncogenes, enhancer hijacking, 3D genome disruptions, and epigenetic reprogramming, and to examine their clinical relevance in diagnosis, prognosis, measurable residual disease monitoring, and therapeutic intervention. By integrating contemporary molecular insights with translational and clinical perspectives, this review seeks to provide a comprehensive understanding of how translocations drive disease biology and inform precision medicine strategies in hematologic oncology.

METHODS

This narrative review was conducted through a comprehensive search of the scientific literature to capture contemporary insights on chromosomal translocations in hematologic malignancies. Relevant publications were identified using PubMed, Scopus, Web of Science, and Google Scholar, focusing on articles published between 2015 and 2025 to ensure inclusion of the most recent mechanistic and clinical discoveries. Search terms included combinations of: "chromosomal translocations," "fusion oncogenes," "enhancer hijacking," "super-enhancer rewiring," "3D genome," "topologically associated domains," "epigenetic reprogramming," "hematologic malignancies," "leukemia," "lymphoma," and "myeloma."

Inclusion criteria were original research articles, systematic reviews, meta-analyses, and high-quality preclinical studies providing mechanistic insights, clinical correlations, or therapeutic implications of chromosomal translocations. Exclusion criteria included studies lacking relevance to hematologic malignancies or those with insufficient methodological detail.

Articles were screened by title and abstract, followed by full-text review. Data extraction focused on:

1. Mechanisms of translocation formation and genome regulation,
2. Functional consequences of fusion oncogenes and regulatory rewiring,
3. Epigenetic alterations associated with translocations,
4. Clinical relevance, including diagnosis, prognosis, measurable residual disease (MRD), and therapeutic strategies.

Findings were synthesized in a narrative format, integrating molecular mechanisms with translational and clinical insights. Emphasis was placed on emerging technologies, including high-throughput sequencing, long-read genome mapping, and 3D chromatin profiling, to contextualize novel discoveries within current and evolving clinical practice.

Mechanistic insights into chromosomal translocations

Chromosomal translocations in hematologic malignancies are not random events; rather, they arise from intricate biological processes that reflect both the intrinsic vulnerabilities of hematopoietic cells and errors in DNA maintenance mechanisms. At the core of these rearrangements are DNA double-strand breaks (DSBs), which can result from physiological processes, replication stress, or exogenous insults. Hematopoietic cells, especially progenitors in the bone marrow, are uniquely susceptible to DSBs due to their high proliferative rate and lineage-specific recombination programs. In B and T lymphoid cells, programmed genomic rearrangements, such as V(D) J recombination, provide essential diversity for antigen receptor formation but simultaneously create hotspots for translocation formation. Misrecognition of recombination signal sequences by the RAG1/2 complex can lead to illegitimate joining of chromosomal segments, explaining the recurrent emergence of fusions such as ETV6-RUNX1 in pediatric acute lymphoblastic leukemia (ALL) and TCF3-PBX1 in B-cell malignancies[10,11].

Beyond recombination errors, the activity of activation-induced cytidine deaminase (AID) has emerged as a major contributor to chromosomal instability. Initially characterized for its role in somatic hypermutation and class switch recombination, AID can inadvertently induce off-target DNA lesions at proto-oncogenes such as MYC, BCL2, and BCL6, particularly in germinal center B cells. These lesions, when improperly repaired, provide substrates for oncogenic translocations, offering a mechanistic link between normal lymphoid physiology and malignancy. Recent studies have further revealed that R-loop structures RNA-DNA hybrids formed during transcription can exacerbate DNA fragility at these loci, creating additional opportunities for erroneous chromosomal joining[12,13].

The repair of DSBs is equally central to translocation formation. While the classical non-homologous end joining (c-NHEJ) pathway efficiently repairs breaks under normal circumstances, defects in NHEJ components such as LIG4, XRCC4, or DNA-PKcs can redirect repair toward alternative, error-prone mechanisms. These aberrant pathways often join distant chromosomal ends, fostering the creation of

novel fusion genes or juxtaposing proto-oncogenes with active regulatory elements. This mechanistic interplay explains the diversity and lineage specificity observed in hematologic translocations[14,15].

Emerging research has highlighted the importance of three-dimensional genome architecture in facilitating translocations. Chromatin is organized into topologically associated domains (TADs), which constrain interactions between enhancers and promoters. Disruption of TAD boundaries by DSBs or pre-existing structural variants can allow enhancers to ectopically activate oncogenes, a phenomenon termed *enhancer hijacking*. This mechanism underlies translocations such as IGH-MYC in Burkitt lymphoma and IGL-MYC in multiple myeloma, where strong immunoglobulin enhancers are repositioned to drive uncontrolled oncogene expression without producing fusion proteins. Similarly, super-enhancer rewiring has been implicated in several newly described pediatric and adult leukemias, reflecting a shift in understanding from purely fusion-driven pathogenesis to regulatory element misappropriation[16,17].

While fusion proteins remain a classical consequence of translocations, their functional impact is multifaceted. Fusions such as BCR-ABL1, KMT2A rearrangements, and PML-RARA alter cellular signaling, transcription, and epigenetic landscapes. Recent discoveries reveal that many fusions act as epigenetic modulators, recruiting chromatin modifiers, altering histone methylation, or perturbing transcription factor networks to maintain a self-renewal program and block differentiation. For instance, KMT2A fusions recruit DOT1L-mediated H3K79 methylation, reactivating stem-cell-like gene expression, while PML-RARA remodels histone acetylation patterns to impede myeloid differentiation, a defect reversed by targeted therapy with ATRA and arsenic trioxide (Table 1)[18,19].

Table 1: Mechanistic insights into chromosomal translocations in hematologic malignancies.

Translocation / Fusion	Mechanistic Features	Molecular Consequences	Representative Malignancies
BCR-ABL1 (t(9;22)(q34;q11))	Fusion of BCR dimerization domain to ABL1 kinase; constitutive tyrosine kinase activity	Uncontrolled proliferation, inhibition of apoptosis, altered microenvironment signaling	Chronic myeloid leukemia (CML), Ph+ ALL
PML-RARA (t(15;17)(q24;q21))	Fusion disrupts retinoic acid receptor signaling; recruits HDAC complexes	Differentiation block, transcriptional repression, reversible epigenetic silencing	Acute promyelocytic leukemia (APL)
KMT2A (MLL) fusions (t(11q23))	Recruitment of DOT1L and other epigenetic modifiers	H3K79 methylation, activation of HOXA stemness maintenance	Infant and adult AML, ALL
RUNX1-RUNX1T1 (t(8;21)(q22;q22))	Recruitment of transcriptional repressors and HDACs	Differentiation arrest, altered hematopoietic gene expression	AML (favorable-risk subtype)
CBFB-MYH11 (inv(16)/t(16;16))	Disrupts core-binding factor function	Impaired differentiation, aberrant myeloid proliferation	AML (inv16 subtype)
IGH-MYC (t(8;14)(q24;q32))	Enhancer hijacking; relocation of IGH super-enhancers near MYC	Constitutive MYC overexpression, enhanced proliferation	Burkitt lymphoma, multiple myeloma
IGH-BCL2 (t(14;18)(q32;q21))	IGH enhancer-driven overexpression of anti-apoptotic BCL2	Apoptosis resistance, prolonged cell survival	Follicular lymphoma
NUP98 fusions (e.g., NUP98-NSD1)	Recruitment of epigenetic modifiers	Dysregulated transcription, stem-cell like program activation	AML (pediatric and adult)
BCR-FGFR1/PCM1-FGFR1	Constitutively active kinase fusions	Activation of RAS-MAPK, PI3K-AKT, and JAK-STAT signaling	Myeloproliferative neoplasms, AML
EP300-ZNF384	Altered enhancer promoter interactions; transcriptional dysregulation	Blocked differentiation, stemness gene activation	B-cell precursor ALL

3D Genome architecture and TAD disruptions

The spatial organization of the genome has emerged as a critical determinant of chromosomal translocation susceptibility and oncogene dysregulation in hematologic malignancies. Chromatin is not randomly arranged within the nucleus; instead, it is partitioned into topologically associated domains (TADs) self-interacting genomic regions that constrain enhancer-promoter contacts and preserve proper gene regulation. Disruption of these domains can profoundly alter gene expression, creating opportunities for malignant transformation even in the absence of traditional fusion proteins[20]. Recent studies using high-resolution Hi-C, single-cell ATAC-seq, and chromatin conformation capture techniques have revealed that translocations frequently exploit the 3D genome architecture. Double strand breaks occurring near TAD boundaries can induce misfolding of chromatin loops, enabling enhancers from one domain to aberrantly activate oncogenes in an adjacent domain a phenomenon referred to as *enhancer hijacking*. In B-cell malignancies, for example, immunoglobulin enhancers are often translocated into proximity with proto-oncogenes such as MYC, BCL2, and CCND1, leading to their sustained overexpression. Similarly, in multiple myeloma, IGH-MYC and IGL-MYC translocations reposition MYC near highly active super-enhancers, amplifying its transcription and promoting rapid proliferation[21,22].

Beyond enhancer hijacking, TAD disruptions can also influence susceptibility to DNA damage and recombination errors. Regions at TAD boundaries are enriched in transcriptionally active, open chromatin and often coincide with early replicating domains, making them inherently fragile. These structural vulnerabilities, when combined with replication stress or aberrant recombination machinery, create hotspots for translocation formation. Recent work in pediatric

acute lymphoblastic leukemia (ALL) has highlighted cases where TAD boundary disruptions facilitate ectopic interactions between transcription factors and oncogenes, driving lineage-specific leukemogenesis even without conventional fusion events[23,24]. Importantly, understanding 3D genome organization has reshaped the perception of translocations from merely linear genomic rearrangements to multi-dimensional regulatory disruptions. While traditional fusion oncogenes remain critical drivers, TAD boundary perturbations explain how some translocations activate oncogenes purely through regulatory rewiring. This mechanistic insight has practical implications: therapies targeting super-enhancers, transcription factor cooperativity, or chromatin architectural proteins are being explored as ways to counteract the oncogenic consequences of TAD disruptions (Table 2)[25].

Table 2: 3D Genome architecture and tad disruptions in hematologic malignancies.

Mechanistic Feature	Description	Impact on Gene Regulation	Representative Examples / Malignancies
Topologically Associated Domains (TADs)	Self-interacting chromatin domains that constrain enhancer-promoter interactions	Maintain lineage-specific gene expression; disruption can allow ectopic gene activation	Disrupted TAD boundaries facilitating MYC overexpression in multiple myeloma
TAD Boundary Disruption	Structural changes near TAD borders due to translocations or deletions	Permits enhancers to contact previously insulated proto-oncogenes	IGH-MYC translocations in Burkitt lymphoma; IGH-CCND1 in mantle cell lymphoma
Enhancer Hijacking via TAD Rewiring	Relocation of potent enhancers across disrupted TADs	Constitutive oncogene activation without fusion proteins	IGH-BCL2 in follicular lymphoma; IGH-MYC in multiple myeloma
Super-Enhancer Relocation	Translocations place super-enhancers adjacent to oncogenes	Amplifies transcriptional output, drives proliferation and stemness	NKX2-1 activation in pediatric ALL; MYC overexpression in aggressive myeloma subtypes
3D Chromatin Looping Alterations	Loss or gain of chromatin loops connecting enhancers and promoters	Alters transcriptional programs, can reinforce stem-cell–like states	EP300-ZNF384 fusion in B-ALL; HOXA cluster activation in KMT2A-rearranged AML
Replication Timing and Fragile Sites	Early replicating TADs with open chromatin are prone to DNA breaks	Increases susceptibility to translocations and enhancer-promoter miswiring	Pediatric ALL and adult B-cell lymphomas with cryptic translocations

Enhancer hijacking and super-enhancer rewiring

Chromosomal translocations in hematologic malignancies do not always create fusion proteins; many instead drive malignancy by repositioning powerful regulatory elements, a process known as *enhancer hijacking*. Enhancers especially super-enhancers, which are clusters of highly active regulatory elements play a central role in determining cell identity by driving high-level transcription of key genes. When translocations relocate these elements near proto-oncogenes, they can trigger sustained oncogene activation, circumventing normal regulatory controls[26]. Recent genomic studies have revealed that enhancer hijacking is a prevalent mechanism in both lymphoid and myeloid malignancies. Classic examples include IGH-MYC translocations in Burkitt lymphoma, where the immunoglobulin heavy chain (IGH) enhancer is repositioned adjacent to MYC, leading to its uncontrolled transcription. Similarly, in follicular lymphoma, BCL2 is brought under the control of IGH enhancers, conferring apoptosis resistance. In multiple myeloma, MYC overexpression is frequently driven by the juxtaposition of IGH or IGL enhancers to the oncogene, highlighting that regulatory rewiring can occur independently of coding sequence changes[27].

Super-enhancer rewiring represents a more recently recognized layer of complexity. Super-enhancers are especially sensitive to genomic rearrangements because of their strong transcriptional activity and open chromatin state. Novel translocations in pediatric and adult acute leukemias have been shown to reposition super-enhancers near oncogenes such as NKX2-1, HOXA9, and ETV6, thereby activating stem-cell–like transcriptional programs that sustain malignant proliferation. Unlike conventional fusion-driven malignancies, these rearrangements act primarily at the level of gene regulation, making them less apparent to traditional fusion-detection methods and underscoring the value of whole-genome and 3D genomics approaches[28]. Mechanistically, enhancer hijacking and super-enhancer rewiring exploit the spatial organization of the genome. By altering chromatin looping and bypassing TAD boundaries, translocations bring distal regulatory elements into contact with previously insulated protooncogenes. This creates a transcriptionally permissive environment, amplifying oncogene expression in a manner analogous to fusion protein-driven signaling. Importantly, these regulatory rearrangements often cooperate with additional genomic lesions, such as mutations in epigenetic modifiers, to reinforce malignant programs[29]. From a clinical perspective, enhancer hijacking has significant implications. It explains why certain translocations confer aggressive phenotypes even in the absence of novel fusion proteins, and why some tumors respond to therapies targeting transcriptional dependencies, such as BET inhibitors or other agents modulating super-enhancer function[30].

Fusion oncogenes and aberrant signaling

While enhancer hijacking highlights the regulatory consequences of translocations, many chromosomal rearrangements in hematologic malignancies produce fusion oncogenes chimeric proteins that directly alter cellular signaling, transcription, and differentiation

programs. These fusions represent some of the earliest and most well-characterized drivers of leukemia, lymphoma, and plasma-cell disorders, and they remain central to both mechanistic understanding and therapeutic targeting[31]. Fusion oncogenes typically combine the functional domains of two separate proteins, endowing the resulting chimeric protein with constitutive activity, altered localization, or aberrant interactions. A classic example is BCR-ABL1 in chronic myeloid leukemia (CML), where the breakpoint cluster region (BCR) dimerization domain constitutively activates the ABL1 tyrosine kinase. This persistent signaling drives unchecked proliferation, inhibits apoptosis, and remodels the hematopoietic niche. Similarly, the PML-RARA fusion in acute promyelocytic leukemia (APL) interferes with retinoic acid receptor-mediated transcription, blocking differentiation and establishing a reversible pre-leukemic state that responds exquisitely to differentiation therapy with all-trans retinoic acid (ATRA) and arsenic trioxide[32].

KMT2A (MLL) fusions exemplify another dimension of fusion oncogene biology. These rearrangements, which can involve over 100 distinct partner genes, recruit epigenetic modifiers such as DOT1L to ectopically methylate H3K79, reactivating stem-cell like transcriptional programs in committed progenitors. Similarly, fusions like RUNX1-RUNX1T1 in acute myeloid leukemia (AML) tether transcriptional repressors to promoters of differentiation genes, effectively freezing hematopoietic cells in an immature state. These mechanisms demonstrate that fusion proteins act not only as drivers of proliferation but also as master regulators of cell identity, altering lineage commitment and epigenetic landscapes[33]. The functional consequences of fusion oncogenes often extend beyond transcriptional regulation. Certain fusions, such as BCR-FGFR1 and PCM1-FGFR1, generate constitutively active kinases that promote survival and proliferation via canonical signaling cascades like RAS-MAPK, PI3K-AKT, and JAK-STAT. Novel FGFR1 fusions identified in myeloproliferative neoplasms are now therapeutically actionable with targeted inhibitors like pemigatinib, highlighting how mechanistic insights can directly inform precision medicine[34]. Recent discoveries have also revealed that fusion oncogenes may co-opt the tumor microenvironment, influencing stromal interactions, angiogenesis, and immune evasion. For instance, BCR-ABL1–driven leukemic cells secrete cytokines that remodel the bone marrow niche, supporting their own survival while suppressing normal hematopoiesis. Similarly, KMT2A-rearranged leukemias exploit inflammatory and epigenetic circuits to sustain leukemic stem cells[35].

Epigenetic reprogramming by fusion oncogenes

Beyond their direct effects on signaling and transcription, many fusion oncogenes drive hematologic malignancies by rewiring the epigenetic landscape, reshaping chromatin states to favor self-renewal, proliferation, and lineage arrest. This layer of regulation has emerged as a critical mechanism through which translocations induce malignant transformation, offering both mechanistic insights and therapeutic opportunities[36]. Fusion proteins such as KMT2A (MLL) rearrangements exemplify the epigenetic impact of chromosomal translocations. KMT2A fusions recruit histone methyltransferases, most notably DOT1L, leading to persistent H3K79 methylation at promoters of genes involved in stemness and proliferation, including HOXA cluster genes and MEIS1. This aberrant chromatin modification maintains leukemic progenitors in an undifferentiated, self-renewing state. Preclinical and clinical studies have shown that targeting this epigenetic dependency with DOT1L inhibitors selectively impairs leukemic growth without affecting normal hematopoiesis[37].

Similarly, the PML-RARA fusion in acute promyelocytic leukemia (APL) remodels the chromatin landscape by recruiting histone deacetylases (HDACs) and other corepressors to retinoic acid responsive elements. This epigenetic repression silences genes necessary for myeloid differentiation, creating a block that can be overcome by all-trans retinoic acid (ATRA) and arsenic trioxide, which degrade the fusion protein and restore permissive chromatin marks. This example highlights the therapeutic potential of targeting fusion-driven epigenetic alterations rather than the fusion protein alone[38]. Other notable fusions, such as RUNX1-RUNX1T1 and CBFB-MYH11, also leverage epigenetic mechanisms to maintain a leukemogenic state. These fusions recruit repressor complexes, including HDACs and polycomb proteins, to promoters of differentiation genes, reinforcing lineage arrest. Emerging studies suggest that combining HDAC inhibitors with conventional chemotherapy may sensitize these leukemias to differentiation and apoptosis, providing a rationale for epigenetic combination therapies[39,40]. Interestingly, fusion-driven epigenetic reprogramming often interacts with other genomic and regulatory aberrations, such as enhancer hijacking and TAD disruptions. For example, a KMT2A fusion may simultaneously modify histone marks and co-opt distal enhancers, creating a synergistic network of transcriptional and epigenetic dysregulation that locks cells into a malignant phenotype. These multilayered mechanisms underscore why some translocations are particularly aggressive and why their clinical outcomes often remain poor without targeted intervention[41].

Clinical correlates of chromosomal translocations

Chromosomal translocations are not only central to the pathogenesis of hematologic malignancies but also serve as critical clinical biomarkers that influence diagnosis, prognosis, and therapeutic decision-making. The identification of specific translocations has revolutionized hematology by linking precise genetic alterations to disease subtypes, risk stratification, and treatment responsiveness[42]. From a diagnostic perspective, many translocations define disease entities. The presence of BCR-ABL1 establishes chronic myeloid leukemia (CML), while PML-RARA confirms acute promyelocytic leukemia (APL). Similarly, rearrangements such as KMT2A fusions, RUNX1-RUNX1T1, and CBFB-MYH11 are hallmarks of distinct acute myeloid leukemia (AML) subtypes, and IGH-MYC, IGH-BCL2, and IGH-BCL6

translocations define high-grade B-cell lymphomas. Advances in next-generation sequencing (NGS), long-read genome mapping, and fluorescence in situ hybridization (FISH) have enhanced the detection of cryptic or complex translocations that were previously undetectable by conventional cytogenetics, thereby refining diagnostic accuracy and informing precision medicine[43].

Translocations also carry strong prognostic significance. Certain rearrangements are associated with favorable outcomes: t(15;17) PML-RARA, t(8;21) RUNX1-RUNX1T1, and inv(16)/t(16;16) CBFB-MYH11 predict high response rates to standard therapy and favorable long-term survival. Conversely, other translocations confer adverse risk: KMT2A rearrangements, particularly in infant leukemias; t(6;9) DEK-NUP214; BCR-ABL1–like acute lymphoblastic leukemia (ALL); and double-hit lymphomas with concurrent MYC and BCL2/BCL6 rearrangements. In multiple myeloma, IGH-MAF and IGH-FGFR3 translocations correlate with aggressive disease and poor prognosis, highlighting the utility of translocation profiling in risk-adapted therapeutic strategies[44]. From a therapeutic standpoint, translocations increasingly guide treatment selection. Fusion proteins such as BCR-ABL1 are effectively targeted by tyrosine kinase inhibitors (TKIs), while PML-RARA fusions are exquisitely sensitive to differentiation therapy with ATRA and arsenic trioxide. Novel fusion targets, including FGFR1 rearrangements and KMT2A fusions, are being exploited by FGFR inhibitors, menin inhibitors, and DOT1L inhibitors, respectively. Even regulatory rearrangements resulting from enhancer hijacking or super-enhancer rewiring are becoming actionable, with BET inhibitors and transcriptional modulators under clinical investigation. Importantly, translocations often coexist with secondary mutations or epigenetic alterations, requiring integrated therapeutic approaches that consider the full molecular context[45,46]. Chromosomal translocations also play a pivotal role in measurable residual disease (MRD) monitoring. Fusion transcripts provide sensitive and specific biomarkers for detecting minimal disease burden, guiding treatment intensification or de-escalation. For instance, BCR-ABL1 transcript quantification in CML informs TKI dosing and treatment discontinuation decisions, while PML-RARA MRD predicts relapse risk in APL. Similarly, monitoring RUNX1-RUNX1T1 and CBFB-MYH11 transcripts in AML refines consolidation therapy strategies, demonstrating the translational relevance of translocations beyond initial diagnosis[47].

Role in Measurable Residual Disease (MRD) monitoring

Chromosomal translocations serve as highly specific molecular markers for measurable residual disease (MRD) in hematologic malignancies, enabling the detection of low-level disease that is otherwise undetectable by conventional morphologic assessment.

The persistence of residual malignant cells after therapy is a major predictor of relapse, and fusion transcripts derived from translocations provide sensitive, quantitative tools to guide treatment decisions, risk stratification, and prognostication[48]. Fusion transcripts such as BCR-ABL1 in chronic myeloid leukemia (CML) exemplify the clinical utility of MRD monitoring. Quantitative PCR of BCR-ABL1 allows precise measurement of leukemic burden, guiding tyrosine kinase inhibitor (TKI) dosing and enabling informed decisions regarding therapy discontinuation. Similarly, in acute promyelocytic leukemia (APL), serial assessment of PML-RARA transcripts identifies patients at risk of relapse and informs the timing and intensity of consolidation therapy with ATRA and arsenic trioxide. In acute myeloid leukemia (AML), transcripts such as RUNX1-RUNX1T1 and CBFB-MYH11 provide MRD readouts that refine consolidation and maintenance strategies, particularly in patients with favorable-risk cyto-genetics[49-51].

Advances in high-sensitivity methods, including digital droplet PCR (ddPCR) and next-generation sequencing (NGS)-based MRD assays, have pushed detection limits to as low as one leukemic cell per million normal cells (10^{-6}), enabling earlier intervention and improved outcomes. These technologies are particularly valuable in cases with cryptic or complex translocations that may escape standard FISH or conventional PCR detection. Moreover, NGS-MRD approaches can simultaneously detect multiple fusion transcripts or subclonal variants, capturing the heterogeneity of residual disease and informing adaptive treatment strategies[52-54]. MRD monitoring based on translocation-derived markers not only predicts relapse but also provides a dynamic measure of therapeutic response. Rapid clearance of fusion transcripts correlates with favorable prognosis, whereas persistence or re-emergence signals resistance, disease evolution, or impending relapse. This real-time feedback allows clinicians to adjust therapy proactively, including escalation to intensive chemotherapy, targeted agents, or hematopoietic stem cell transplantation in high-risk cases[55-57]. By integrating translocation-based MRD monitoring into routine practice, clinicians can optimize treatment intensity, minimize toxicity, and improve long-term survival, illustrating how mechanistic insights into chromosomal translocations directly translate into clinical utility[58].

CONCLUSIONS

Chromosomal translocations remain a cornerstone of hematologic malignancy biology, integrating genetic, epigenetic, and regulatory mechanisms to drive malignant transformation. Recent technological advances including high-resolution sequencing, long-read genome mapping, and 3D chromatin profiling have expanded our understanding of both classical and cryptic translocations, uncovering novel mechanisms of formation and regulatory impact. As research continues to unravel the complexity of translocation biology, integrating mechanistic insights with clinical application will remain essential. Future directions include development of therapies targeting regulatory rewiring, exploiting fusion-driven epigenetic vulnerabilities, and combining MRD-guided approaches with precision interventions.

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AUTHOR'S CONTRIBUTIONS

Obeagu EI: conceptualization, methodology, literature review, supervision, writing original draft. **Chuwkwuebuka AJ:** methodology, literature search, manuscript drafting. **Abdalhabib E:** methodology, Literature review, editing, critical review. Final manuscript was checked and approved by all authors.

DATA AVAILABILITY

The related author can provide the empirical data supporting the study's conclusions upon request.

CONFLICT OF INTEREST

There are no conflicts of interest in regard to this project.

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