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Review

Decoding and Targeting the Tumor Ecosystem in Hematological Malignancies: Microenvironmental Cues, Epigenetic Landscapes and Systems Biology Insights

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Abstract

Hematological malignancies are not just beginning to be studied as being cell-autonomous, but rather as multi-cellular ecosystems in which malignant clones are able to usurp bone marrow and lymphoid niches to facilitate survival, immune evasion and resistance to treatment. Recent findings involve mutual interactions between stromal factors, immune subgroups, extracellular matrix, and tumor-produced extracellular vesicles as one of the key determinants of disease initiation, disease progression, and minimal residual disease. At the same time, epigenetic landscape perturbations, including DNA methylation, histone post-translational modifications, chromatin remodeling complexes, and non-coding RNAs, become the major regulators of malignant lineage identity, stemness and niche-guiding programs. These abnormalities in epigenetic regulations reflect and constitute microenvironmental conditions and hence they are modifiable therapeutic weaknesses. The current technological improvements in the fields of single-cell genomics, spatial transcriptomics, and integrative multi-omics have now rendered it possible to solve cellular phenotypes, signaling circuits, and epigenetic states on a tissue-scale level. These modalities, in combination with longitudinal sampling and liquid-biopsy designs, allow the reconstruction of clonal fates and niches remodelling underlying therapeutic failure. The use of such high-dimensional datasets necessitates systems-biology models and computational algorithms that can derive intercellular networks, predict ecosystem responses to perturbation and prioritize combination strategies that can effectively target malignant cells and supportive niches. Initial experiments with network biology and machine-learning-based biomarkers have the potential to allow the use of ecosystem-oriented and precision therapies, but clinical implementation is limited by spatial heterogeneity, model fidelity, and predictive validation. The review summarizes existing information about tumor-ecosystem biology in hematologic malignancies, identifies epigenetic processing that binds intrinsic and extrinsic disease advantages, surveys systems-level approaches to ecosystem decoding, and assesses new therapeutic approaches, which combines epigenetic, immune, metabolic and niche-guided methods. We conclude with a description of translational needs to achieve adaptive, ecosystem-directed interventions in clinical hematology.

Keywords

Hematology cancer, Tumor microenvironment, Bone marrow niche, Epigenetics, Systems biology, Single-cell multi-omics, Precision oncology, Immune evasion

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1. Introduction

Hematological malignancies are complicated illnesses that are influenced by interactions with their surroundings as well as innate genetic processes.The understanding of hematological malignancies has been traditionally classically characterized with a cell-centric view of disease origin and progression is mainly because of inherent genetic malfunctions of the hematopoietic cells [1]. This reductionist paradigm centered on chromosomal rearrangements, oncogenic mutations and dysregulation of intracellular signaling was central to the subtype classification of diseases and the development of specific therapy. But recent studies have radically changed this knowledge [2]. Hematologic cancers are now being regarded as evolving complex, adaptive tumor ecosystems where malignant clones are dependent upon, reshape and interactively evolve with the microenvironment surrounding them [3]. They are mesenchymal stromal cells, endothelial and osteolineage populations, immune subsets, extra-cellular matrix components and metabolic support systems all of which are in a continuous interaction with the malignant cells [4]. The lymphoid microenvironment and the bone marrow microenvironment actively influence the behavior of tumors by providing survival cues, maintaining the redox and metabolic conditions, controlling immune surveillance, and protecting malignant cells against immunogenic and chemotherapeutic cytotoxicity [5]. Simultaneously, these niches are, in turn, remodeled reciprocally by malignant cells with the help of cytokines, chemokines, exosomes, and metabolic reprogramming, which eventually form permissive habitats that ensure disease persistence, immune evasion, and resistance to therapy [6]. Bidirectional interactions of this nature underscore the inadequacy of cell-intrinsic models, and underscore the importance of considering hematological malignancies as the properties of dysregulated host-tumor ecosystems [7].

The other foundation of this ecosystem-based view is epigenetic reprogramming. Dysregulated DNA methylation, disturbed histone modification patterns, and disturbed positioning of the nucleosomes one after another reorganize transcriptional programs controlling differentiation arrest, stemness, lineage plasticity, and immune escape [8]. Notably, a significant number of these changes in epigenetics are triggered or maintained by microenvironmental signals, which pair extrinsic niche signals with intrinsic chromatin marks [9]. It is this merger of microenvironmental and epigenetic processes which, in turn, give rise to phenotypic plasticity, which supports clonal evolution, malignant adaptation, and is involved in minimal residual disease (MRD) and relapse [10]. These interactions are complex and need systems-level investigations in order to address them. Recent developments in the single-cell sequencing, spatial transcriptomics, chromatin-accessibility profiling, proteogenomics, and multi-omic integration have facilitated resolving cellular heterogeneity, niche architecture and intercellular communication circuits to a degree never achieved previously [11]. Signaling networks, ecological vulnerability prediction, and identification of determinants of therapeutic responses are now reconstructed with the aid of complementary computational tools, such as network biology, mathematical modeling, and machine learning [12]. The combination of these technologies lays the groundwork of the ecosystem-based view of the holistic approach to hematologic cancers [13]. This review article presents a concept of ecosystem-based precision oncology, which integrates tumor microenvironment (TME) biology, epigenetics, and systems biology. By using the example of hematologic malignancies, we discuss the molecular relationships underlying the development of the diseases, response to therapy, as well as potential therapeutic opportunities. It uses evidence from prominent research studies, including single-cell analysis in acute myeloid leukemia (AML) [14] and multi-omic approaches in multiple myeloma, illustrating how microenvironmental cues regulate cancer cell behavior and therapy resistance [15]. Next, it highlights a paradigm shift in thinking about hematologic malignancies, moving beyond a focus on cancer cells themselves, but considering these malignancies in terms of ecosystems in which bone marrow and lymphoid microenvironments, epigenetic factors, and tumor-host interactions all play a role in determining cancer outcomes. Finally, this review discusses new therapeutic approaches designed to disrupt cancer cells and their microenvironments, in order to develop guidelines for ecosystem-based cancer therapy in clinical practice.

2. Methods

This study was conducted as a narrative integrative review by utilizing the structured features available in the literature search to synthesize existing knowledge on TME dynamics, epigenetic regulation, and systems biology in the context of hematological malignancies. A comprehensive search of the literature was conducted by utilizing the PubMed/MEDLINE, Scopus, and Web of Science databases, with search terms ranging from 2010 to 2025, with an emphasis on recent breakthroughs. The search phrases included the following: "hematological malignancies", "leukemia", "lymphoma", "multiple myeloma", "tumor microenvironment", "bone marrow niche", "epigenetics", "DNA methylation", "histone modification", "systems biology", "multi-omics", "single-cell sequencing", "spatial transcriptomics", "therapy resistance", and "precision oncology". The reference section of the selected articles was also reviewed to obtain additional relevant articles.

Specific predetermined inclusion criteria were used to filter the studies. This included articles from peer-reviewed literature on topics such as hematologic cancers, TME, epigenetics, or systems biology approaches. Other studies included clinical, translational, or preclinical studies of high quality from English literature. Excluded studies included articles without any clinical or mechanistic relevance, non-peer-reviewed literature, or duplicate studies. The data was grouped based on theme domains such as microenvironmental architecture, epigenetic dysregulation, systems biology approaches, therapy resistance, and integrative therapeutic approaches. A qualitative synthesis technique was employed

to reveal key patterns, mechanisms, and clinical applications, keeping in mind limitations such as study heterogeneity, experimental model variability, and clinical application challenges.

3. Architecture of the TME in Hematological Malignancies

Despite the widely recognized role of the TME in controlling hematological malignancies, little is known about its functional role as shown in Figure 1 [16]. While the role of stroma, cytokine, and immune factors in promoting survival of malignant cells has been demonstrated, there are significant differences in the contribution of these factors to different malignancies [17]. For example, stroma-based survival in AML, versus immune escape in lymphoid malignancies. However, existing models have been criticized for being too simplistic, as they often fail to take into account the geographical and temporal complexity of the TME. Moreover, experimental data are mostly based on *in vitro* or murine studies [18]. Another mechanism of immune escape is the involvement of myeloid-derived suppressor cells (MDSCs), which do not only suppress the functioning of the T-cells, but also secret pro-tumorigenic factors. Another layer of complexity is that of the extracellular matrix (ECM) and the soluble factors [19]. Both physical and biochemical scaffolds are formed by matrix proteins, adhesion molecules and secreted chemokines and direct cell localization, proliferation and survival. Exosomes and microvesicles secreted by the tumor contain bioactive molecules which remodel the microenvironment, support angiogenesis and disseminate malignant phenotypes between spatially segregated niches [20]. Together, these structural and functional factors form a dynamic, reciprocal ecosystem where malignant and stromal cells co-evolve, resulting in therapy resistance, persistence, and relapse of the disease. Significantly, however, this dependence on structural and functional microenvironments may not be identical across various hematological malignancies. Hence, generalized statements regarding this aspect should be viewed with a degree of caution. For example, AML is highly dependent on bone marrow stromal connections and drug resistance via adhesion-mediated pathways, whereas chronic lymphocytic leukemia (CLL) is more reliant on immune-mediated survival signals within the microenvironments of the lymphoid tissues. Lymphomas exhibit a highly organized spatial architecture and immune checkpoint-mediated evasion within the microenvironments of the lymphoid tissues, whereas multiple myeloma is characterized by extensive interaction with the bone marrow microenvironment, including osteoblastic and osteoclastic activities, angiogenesis, and cytokine-mediated proliferation, especially via interleukin-6 (IL-6). These distinctions underscore the fact that TME interactions are disease-specific, and it is important to avoid extrapolating information without due consideration of context in order to avoid oversimplification of the biology. A nuanced view of disease-specific biology is critical in order to understand TME interactions in an accurate context [21].

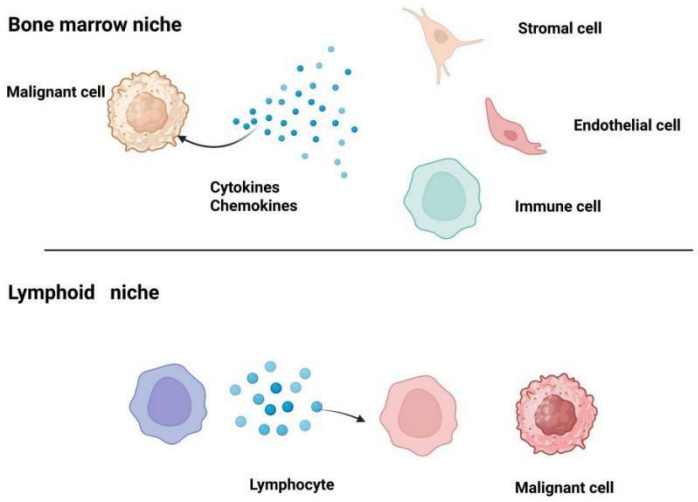

Figure 1. Architecture of the TME in hematological malignancies.

This figure shows the TME in hematological malignancies is depicted schematically, illustrating the dynamic interactions between malignant cells and surrounding components such as stromal cells, immune cell subsets, endothelial cells, ECM, and soluble factors like cytokines and chemokines. The picture depicts bidirectional signaling, niche modification, and the involvement of extracellular vesicles in tumor survival, immune evasion, and treatment resistance.

4. Functional Role of the TME

In hematologic malignancies, the TME influences immune suppression, metabolic reprogramming, and resistance to targeted therapy in addition to structural structure.The TME of hematological malignancies is not an inert scaffold, but rather an active receptor of malignancy cell behavioral features, including proliferation, survival, evasion of immune responses, and resistance to therapy [22]. The ability of the TME to signal pro-survival is one of its major functions that allow malignant clones to flourish [23]. Stromal cells, endothelial networks and osteolineage populations release cytokines, chemokines and growth factors such as IL-6, interleukin-10 (IL-10), tumor necrosis factor (TNF) and

vascular endothelial growth factor (VEGF) that interact with signaling pathways such as PI3K/AKT, JAK/STAT and NF-κB [24]. The pathways stimulate cell-cycle and suppress apoptosis, as well as, favor metabolic adaptation, to establish a laxative environment in disease progression. The TME also promotes immune evasion, which is also characteristic of hematological malignancies [25]. The malignant cells use the immune checkpoints, such as PD-1/PD-L1 and CTLA-4 and also alter the structure and action of the infiltrating immune populations [26]. Regulatory T cells are increased and cytotoxic T cells are dysfunctional or exhausted and natural killer (NK) cells have poor cytotoxicity [27]. M2-polarized macrophages, as well as MDSCs, achieve additional anti-tumor immunity suppression and release immunomodulative factors that strengthen tumor survival. Malignant cells can release extracellular vesicles and exosomes that include immunosuppressive microRNAs and proteins to cause dysfunction of the systemic immunity [28]. The other important role of the TME is that of resistance to therapy and MRD. Adhesion-mediated drug resistance (CAM-DR) is a condition whereby the malignant cells associate with stromal components through integrins and selectins, stimulating anti-apoptotic signal cascades that confer resistant neoplastic cells against chemotherapy, targeted agents, and immunotherapies [29]. Leukemic stem cells which remain unaffected by the cytotoxic assaults after being coated with the niche can be used as a reservoir of disease relapse. Also, the metabolic cross-talk between the malignant and stromal populations facilitates survival in conditions of nutrient limitation and antagonizes chemotherapy [30].

Malignant cells are not passive consumers of TME support, but rather they actively remodel their environments in order to increase survivability and growth. Angiogenesis and remodeling of the ECM as well as modification of stromal cell phenotypes are induced by tumor-derived cytokines and growth factors in a feedback mechanism that strengthens oncogenic niches [31]. Such a mutually adapted reciprocity makes sure that TME co-evolves with clonal selection, maintaining malignant populations and making them more difficult to eliminate. Overall, the TME serves as a refuge and as a means of facilitation of malignant hematopoietic cells. The need for ecosystem-focused solutions in hematological malignancies has been highlighted by its roles in proliferation, immune escape, drug resistance, and niche remodelling. The insight of these functional dynamics is an essential starting point in the establishment of interventions that can be used to breaktumor-stroma interaction and to sensitize malignant cells to treatment. Yet another level of complexity associated with the translation of ecosystem-based approaches to clinical practice is the high degree of heterogeneity among patients. For example, age, co-existing health problems, history of previous treatments, and genetic background are some of the factors that can play a crucial role in the biology of the tumor, TME, and responses to treatments. For example, elderly patients or those with co-existing health problems might have a compromised immune system and low tolerance to aggressive therapies, which can impact the course of the disease as well as the outcome of the treatments. In a similar manner, the history of previous treatments can impact the TME, which can, in turn, impact the outcome of subsequent treatments. The socioeconomic background of the patients, including access to healthcare resources and advanced diagnostic tools, can also play a crucial role in the feasibility of precision-based approaches to cancer treatments [32].

5. Epigenetic Alterations Driving Hematologic Malignancies

Epigenetic dysregulation is now recognized as a primary cause of human hematologic cancers, but this is more complex than a regulatory mechanism in gene expression control. Although epigenetic modifications in DNA methylation and histone modifications are recognized to play a part in cancer development, their significance is conditional and often reversible, leading to concerns about their viability as therapeutic targets [33]. Additionally, mutations in epigenetic regulator genes such as *DNMT3A*, *TET2*, and *IDH1/2* are not always predictive of disease outcome or response to treatment. Although epigenetic therapies aim to normalize gene expression control, clinical outcomes are still variable, suggesting that epigenetic modifications alone cannot account for disease outcome. Moreover, the complexity of epigenetic states and their response to their local environment is not yet well accounted for in current models [34]. Therefore, Figure 2 lists the main epigenetic processes that control gene expression and propel the course of disease, such as DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs.

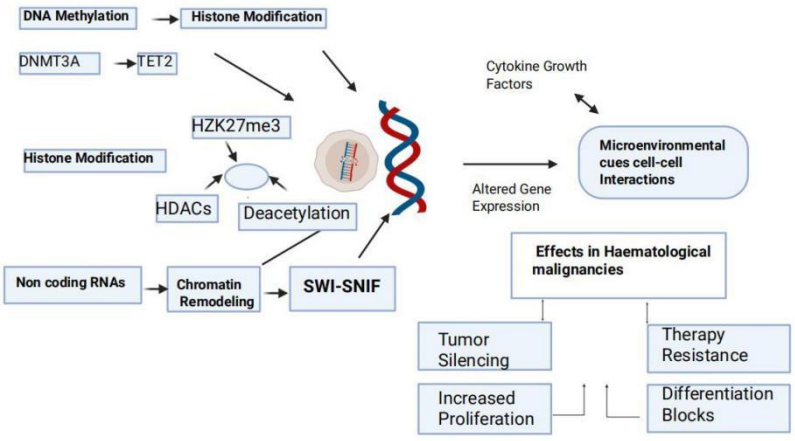

Figure 2. Epigenetic dysregulation in hematological malignancies.

5.1 DNA Methylation

One of the epigenetic mechanisms that have been examined most in the hematologic cancers is the DNA methylation. Aberrant hypermethylation of promoter CpG island can silence tumor suppressor genes, such as apoptosis, cell-cycle checkpoint and differentiation, and global hypomethylation may lead to genomic instability and oncogenic activities [35]. DNA methylation regulators mutations *DNMT3A*, *TET2*, and *IDH1/2* occur frequently in AML, myelodysplastic syndromes (MDS) and other hematologic malignancies, and hence are functionally important in the pathogenesis of diseases as well as potential therapeutic targets [36].

5.2 Histone Modifications

The chromatin accessibility and transcriptional results are controlled by histone modifications such as acetylation, methylation, phosphorylation, and ubiquitination. The pathogenesis of leukemia and lymphoma has been linked to dysregulation of histone-modifying enzymes, including EZH2, KMT2A (MLL) and histone deacetylases (HDACs) [37]. As an example of gain of function mutations, EZH2 gain-of-function mutations contribute to H3K27 trimethylation that causes transcriptional repression of differentiation-associated genes, maintaining a progenitor-like malignant state. On the other hand, HDAC overexpression has the potential to impose chromatin compaction, silence tumor suppressors and play a role in drug resistance [38].

5.3 Chromatin Remodeling Complexes

Remodeling complexes of chromatins which include the SWI/SNF family are often deregulated in hematologic malignancies leading to distorted nucleosome positioning and transcriptional regulation failures [39]. The inability of hematopoietic cells to retain the lineage fidelity and support malignant transformation have been compromised due to mutations or loss-of-function of these complexes. The dynamic interaction between the chromatin remodeling and the transcription factor further increases the sensitivity of the tumor cells to both environmental conditions and therapeutic cues [40].

5.4 Non-Coding RNAs

Non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are epigenetic regulators, which target mRNAs to cause degradation, chromatin regulation, and transcriptional-network regulation [41]. Abnormal miRNAs are capable of enhancing oncogenic signaling, silencing apoptotic signaling and immune surveillance, and regulating immune surveillance, whereas lncRNAs play a role in stemness, differentiation inhibition, and niche communication. Exosomal non-coding RNAs also allow the malignant cells to interact with stromal and immune elements, which strengthens the tumor ecosystem [42].

It represents a general overview of the key epigenetic modifications such as DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA involvement in the development of hematological malignancies. The image depicts the role of these systems in the development and progression of tumors and drug resistance through the regulation of gene expression, differentiation, and stemness, as well as their integration of microenvironmental signals.

Collectively, these epigenetic alterations establish a flexible regulatory network that integrates intrinsic oncogenic programming with microenvironmental signals, enabling malignant clones to survive, adapt, and evolve [34]. Understanding the spectrum of epigenetic dysregulation provides a foundation for the development of targeted therapies, including DNMTis, HDAC inhibitors, and emerging epigenetic modulators that aim to restore normal transcriptional landscapes and sensitize tumor cells to conventional and immune-based therapies [43]. However Table 1 outlines key epigenetic changes in hematological malignancies, including related genes, functional effects, and therapeutic targets.

Table 1. Key epigenetic alterations in hematological malignancies.

Epigenetic Mechanism	Key Regulators /Mutated Genes	Hematologic Malignancy Association	Functional Consequence	Therapeutic Targeting	References
DNA methylation	*DNMT3A*, *TET2*, *IDH1/2*	AML, MDS, chronic myelomonocytic leukemia (CMML)	Silencing tumor suppressors, genomic instability	DNMT inhibitors (azacitidine, decitabine)	[44]
Histone methylation	*EZH2*, *KMT2A* (MLL)	B-cell lymphoma, AML	Repression of differentiation genes	EZH2 inhibitors	[44]
Histone acetylation	*HDAC1/2/3*, *SIRT1*	Multiple myeloma, T-cell lymphoma	Chromatin compaction, apoptosis resistance	HDAC inhibitors	[45]
Chromatin remodeling	*SWI/SNF* complex (ARID1A/B)	AML, lymphomas	Altered nucleosome positioning, lineage plasticity	Experimental inhibitors	[46]
Non-coding RNAs	miRNAs, lncRNAs	AML, CLL, lymphomas	Gene silencing, immune modulation	RNA therapeutics, exosome-targeted strategies	[46]

6. Epigenetic Control of the Tumor Ecosystem

Hematological malignancies have more than intrinsic cellular programs and regulate epigenetics to mediate interaction of malignant cells with surrounding microenvironment. Epigenetic modulation of gene expression can be used as a dynamic interface between tumor-intrinsic and extrinsic niche-derived signals by regulating these processes [47]. This crosstalk allows the malignant cells to evolve to environmental pressures, avoid immune surveillance, and take advantage of stromal support, and strengthens the ecosystem of the tumor. The regulation of immune evasion is one of the bright features of epigenetic influence. When major histocompatibility complex (MHC) molecules and antigen-processing genes are underexpressed by aberrant DNA methylation and histone modify, the tumor immunogenicity is reduced and cytotoxic T lymphocytes are unable to recognize these targets [48]. At the same time, epigenetic regulators regulate the expression of the immune checkpoint molecules including PD-L1, CTLA-4 ligands, CD47 and enable the formation of immunosuppressive niches. Such alterations tend to be specific to the context, where stromal-derived cytokines and chemokines cause dynamic chromatin remodeling of malignant cells in order to maximize immune evasion [49]. Another area that is regulated by epigenetics is the cytokine and chemokine signaling [50]. The transcriptional responsiveness of tumor cells to microenvironmental signals, such as IL-6, IL-10, TGF-b and CXCL12 is determined by histone changes and chromatin accessibility. Stronger reciprocal stromal-tumor interactions can be reinforced by the epigenetic reprogramming to increase production of these factors or their receptors and improve survival, proliferation and niche retention [51]. In addition to this, non-coding RNAs, including intracellular and exosomal, mediate intercellular communication and relay epigenetically imprinted signals to adjacent stromal and immune cells. Epigenetic processes among malignant cells also regulate the modulation of stromal and niche components [52].

As an illustration, epigenetic regulation of matrix metalloproteinases, angiogenic factors, and adhesion molecules by leukemia and lymphoma cells can be used to remodel the extra-cellular matrix, support angiogenesis, and strengthen protective niches. Correspondingly, epigenetically regulated exosome secretion of miRNAs, lncRNAs, and regulatory proteins has the potential to cause changes in the phenotype of stromal and immune cells to form a self-sustaining, pro-tumorigenic ecosystem [53]. These observations demonstrate the duality of epigenetic modifications in hematological malignancies: epigenetic modifications do not only determine intrinsic malignant behavior but also actively regulate the surrounding microenvironment. The role of *DNMT3A* or *TET2* mutations is related to immune cell infiltration and stromal support in AML. This is according to experimental studies that used patient-derived xenografts and organoid models. The clinical implications of epigenetic control in the tumor ecosystem were demonstrated in studies that used HDAC or DNMT inhibitors. These studies showed alterations in cytokine signaling. The coordination of epigenetic processes by the combination of signals in the niche and their translation into transcriptional and post-transcriptional responses enable a highly-tuned ecosystem, which promotes persistence of disease, resistance to therapy and clonal evolution. In turn, attack on epigenetic regulators presents an invigorating approach to disrupt tumor-stroma communication, repair immune surveillance, and sensitize malignant cells to the traditional and novel treatments [54].

7. Epigenetic Therapeutics

Epigenetic therapeutics the identification of epigenetic dysregulation as a primary cause of hematological malignancies has sparked the invention of targeted therapies, the goal of which is to normalize abnormal chromatin states and transcriptional programs [33]. Despite the fact that epigenetic drugs, such as DNA methyltransferase inhibitors (DNMTis) and histone deacetylase (HDAC) inhibitors, are clinically effective, their therapeutic potential is limited. In addition, the effectiveness of these drugs may differ in various patients. Although these drugs are capable of causing partial remission and increasing survival rates in patients, these drugs are not curative and are associated with drug resistance and relapse. Moreover, the action of these drugs is not limited to epigenetic regulation. These drugs also affect immunological activation and cellular metabolism. This makes the results obtained from these drugs clinically challenging. In summary, although epigenetic drugs are an alternative, their integration into existing drug regimens requires more specificity in the categorization of patients [55].

7.1 DNMTis

Some of the most clinically developed epigenetic therapies are the DNMTis, including azacitidine and decitabine [56]. These agents cause global and locus-specific hypomethylation by incorporating into DNA and inhibiting the DNMT activity and reactivating silenced tumour suppressor genes, as well as regulating immune recognition [57]. MDS, AML, and CMML have shown degree of clinical studies that showed enhanced survival especially in patients who are not viable to undergo effective chemotherapy [58]. There is also emerging evidence to indicate that DNMTis may be able to remodel the TME by improving antigen presentation and facilitating the T-cell-mediated anti-tumor immunity [59].

7.2 HDAC Inhibitors

Vorinostat, panobinostat and romidepsin are histone deacetylation inhibitors (HDACis) that target the enhancement of histone acetylation, chromatin relaxation, and transcriptional regulation of tumor suppressor genes [60]. Hdaciis have demonstrated clinical activity in hematologic malignancies including cutaneous T-cell lymphoma, peripheral T-cell

lymphoma and multiple myeloma, and have been used to treat hematologic malignancies in conjunction with proteasome inhibitors or immunomodulatory drugs [45]. The non-histone targets of HDAC inhibition are also involved, affecting apoptosis, cell-cycle regulation, and immune modulation, which is why their mechanism of action is multifaceted [61].

7.3 Emerging Epigenetic Modulators

Innovative epigenetic regulators attack histone methyltransferases, demethylases, and bromodomains-based proteins. EZH2 is a histone methyltransferase which is commonly mutated in B-cell lymphomas, and its inhibitors have been shown to reverse aberrant H3K27 trimethylation and revert differentiation programs [62]. The inhibition of bromodomain-recognition of acetylated histones, through the use of BET inhibitors, disrupts oncogenes transcriptional activation of the Myc protein, providing a way to intervene and target epigenetic drivers of malignancy [63]. Simultaneously, KDM inhibitors, as well as agents of other chromatin remodelers, are in preclinical and early clinical development, which widens the therapeutic pipeline. Epigenetic agents are increasingly being used as combination modalities with other therapeutic modalities [64].

7.4 Combination Strategies

DNMTis and HDACis have been shown to be effective in reinstating anti-tumor immunity by combining with immune checkpoint inhibitors, and reinstating microenvironment-mediated drug resistance by combining epigenetic drugs with targeted kinase inhibitors [65]. Multi-modal strategies are intended to concomitantly interfere with malignant signaling, reprogram supportive niches, as well as to increase immunogenicity, and this will target both intrinsic and extrinsic disease dynamics. Although these progresses have been made, there are still difficulties, such as inter-patient differences in epigenetic topography, drug side effects, and lack of knowledge on how microenvironmental crosstalk works [66]. The current research aims to achieve patient stratification with predictive biomarkers, especially optimizing dosing schedules, and incorporating epigenetic treatments into precision oncology systems based on ecosystem directions. Taken together, these efforts make epigenetic modulation a pillar of modern hematologic cancer therapy, which can be used to redefine the pathways of the disease by remodelling the malignant cells and their natural environments [67].

7.5 Safety and off-target Considerations

The concerns regarding toxicity, off-target effects, and long-term safety are major obstacles in the clinical translation of epigenetic and TME-targeted therapeutics, despite the fact that these agents have the potential to offer opportunities for the development of precision cancer therapies. Clinical trials have demonstrated that epigenetic agents, including DNA methyltransferase (DNMT) inhibitors and HDAC inhibitors, have the capacity to cause hematologic, hepatic, and gastrointestinal toxicities through the interference of regular gene function. In addition, the combination of agents, especially immunotherapy agents and agents with the capacity to modulate multiple pathways, has the capacity to cause off-target effects and untoward interactions. This demonstrates the need for meticulous preclinical evaluation. In spite of this, there are few data on the long-term exposure and the possibility of adverse effects, and the long-term safety of these agents is not well established. In order to achieve the balance between the efficacy of the treatment and the safety of the patient, these factors demonstrate the need for meticulous toxicity evaluation, targeted approaches, and monitoring [68].

8. Systems-Level Approaches to Decode the Tumor Ecosystem

Understanding the complex interplay between malignant cells and their microenvironment requires integrative, systems-level approaches that transcend traditional single-dimensional analyses. Hematological malignancies are characterized by heterogeneous cell populations, dynamic epigenetic states, and intricate intercellular signaling networks [69]. In addition, Table 2 summarizes essential systems biology techniques, data sources, and applications for studying tumor ecosystem dynamics in hematologic malignancies. Systems biology methodologies–including single-cell genomics, spatial transcriptomics, multi-omics integration, and computational modeling–offer unprecedented resolution to map these tumor ecosystems, identify regulatory nodes, and predict therapeutic vulnerabilities as shown in Figure 3 [69]. Figure 3 illustrates System-level approaches for analyzing tumor ecosystems in hematological malignancies, such as single-cell sequencing, spatial transcriptomics, multi-omics integration, and computational modeling. The image depicts how these methodologies allow for cellular heterogeneity mapping, intercellular communication networks, and therapeutic response prediction modeling.

Table 2. Systems biology tools for tumor ecosystem analysis.

Technology /Approach	Purpose	Data Type	Key Insights in Hematologic Malignancies	References
Single-cell RNA-seq	Cellular heterogeneity	Transcriptomics	Clonal diversity, stem-like populations, therapy-resistant subclones	[70]
ATAC-seq/scATAC	Chromatin accessibility	Epigenomics	Epigenetic regulatory states, transcription factor activity	[70]
Spatial transcriptomics	Niche organization	Spatial gene expression	Microanatomical mapping, immune-suppressive niches	[71]
Proteomics/Mass cytometry	Protein expression	Proteomics	Signaling pathway activation, immune phenotype	[71]
Multi-omic integration	Systems-level understanding	Multi-layer (RNA, protein, epigenome, metabolome)	Network modeling, regulatory nodes, therapeutic vulnerabilities	[72]
Computational modeling & AI	Predictive and network analysis	Integrative datasets	Therapy response prediction, clonal evolution modeling	[72]

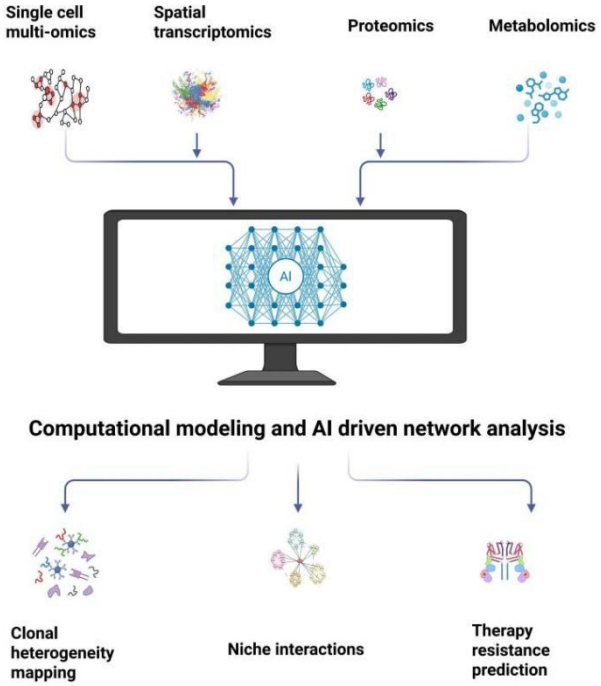

Figure 3. Systems biology approaches to decoding the tumor ecosystem.

8.1 Single-Cell Sequencing Technologies

Single cell sequencing technologies have transformed the characterization of cellular heterogeneity in the hematologic cancers. Single-cell RNA sequencing (scRNA-seq) can be used to distinguish between different malignant subclones, stromal populations and immune subsets in bone marrow and lymphoid niches [73]. Using scRNA-seq to identify transcriptional states on a single-cell basis, clonal hierarchies, differentiation blockades, and niche-sensitive transcriptional programs are revealed that are frequently blurred when using bulk methods. Combination with single-cell ATAC-seq offers complimentary data on chromatin accessibility by attributing epigenetic regulation to transcriptional performance and cellular phenotype [74].

8.2 Spatial Transcriptomics and Proteomics

Spatial transcriptomics and proteomics also provide a higher resolution in ecosystems due to the maintenance of spatial context of cellular interactions. These methods chart the physical structure of tumor and stromal compartments, identify pathways of cell-cell communication and show microenvironmental gradients of cytokines, chemokines and metabolic factors [75]. Spatial profiling in lymphomas and leukemias has demonstrated the existence of localized immunosuppressive niches, angiogenic microdomains, and areas rich in therapy-resistant stem-like cells, and topographical organisation has been shown to play a role in disease progression and therapeutic response [76].

8.3 Multi-omic Integration

A combination of genomics, epigenomics, transcriptomics, proteomics and metabolomics, will offer a very big picture

of the tumor ecosystem. By comparing DNA mutations, epigenetics alterations, RNA expression, protein abundance, and metabolic flux, researchers have the ability to create global maps of signaling network, regulatory networks and intercellular dependencies. This method allows unearthing vulnerabilities in the ecosystem at the level of key stromal support pathways or epigenetically regulated immune checkpoints, which can be targeted as therapeutic targets [77].

8.4 Network Biology and Computational

Modeling are used as a complement to experimental systems to predict through high-dimensional data translating and convert it into predictive frameworks. Intercellular communication can be reconstructed by use of network analysis, machine learning, and dynamic modeling; regulatory hubs identified; and perturbations induced by therapy simulated. Such computational approaches can assist in predicting the malignant clone responses to microenvironmental constraints as well as predict the drug resistance mechanisms and prioritize multi-modes of combination therapies which can target the tumor-intrinsic and extrinsic nodes within the ecosystem [78]. The combination of systems level approaches offers an overall viewpoint of deciphering the tumor ecosystem in hematological malignancies. These approaches combine cellular heterogeneity, spatial structuring and regulation of epigenetics and network dynamics, shedding light on the multi-dimensional dynamics that race the disease process and therapeutic resistance, which form the basis of the precision, ecosystem-guided interventions [79]. Whilst concepts like ecosystem-guided precision oncology and systems-level decoding offer a useful paradigm for understanding the integration of complex biological interactions, it is important to note that the level of evidence varies significantly. Established concepts like the role of the TME in immune evasion, survival signaling, and drug resistance are well substantiated by experimental and clinical data. In contrast, integrative approaches like multi-omics analysis, network-based models, and artificial intelligence-based predictions are still in their infancy. These emerging concepts have several limitations, including data reliability, lack of established frameworks, and limited prospective validation. Thus, these methods should be regarded more as "hypothesis-generating" than "definitive clinical tools." Clearly, it is important to distinguish between established mechanisms and conceptual models to avoid over-interpretation and to correctly state the state of the art. There are tremendous technical and analytical challenges to the application of the systems biology and artificial intelligence-based approaches, which have tremendous revolutionary potential but are currently limited by the technical challenges to their clinical application [80]. There is a concern about bias and reproducibility of results, which can arise from batch effects, sample processing, and noise, especially in high-dimensional multi-omics data. The heterogeneous nature of the data, including proteomics, transcriptomics, genomics, and epigenomics, makes it challenging to integrate the data, and the lack of a widely accepted standard framework for integrating multi-omics data increases the likelihood of errors in integrating the data, which can lead to conflicting results from different studies. Furthermore, a large number of machine learning algorithms, which are used for predictive modeling, are essentially "black boxes" and therefore lack transparency, which can create a lack of trust among clinicians and provide little insight into the results obtained from the models, which are likely to fail to generalize to other populations than those included in the training dataset, thereby creating a problem of reproducibility of results obtained from the models [81].

9. Systems Biology of Therapy Resistance

The problem of therapy resistance is one of the main concerns in the treatment of hematological malignancies, and it is frequently associated with multi-layered interactions within the tumor ecosystem. The systems biology approaches offer a platform to comprehend the set of molecular, cellular and microenvironmental processes that promote resistance, and therefore, identify actionable vulnerabilities and create adaptive therapy options [82].

9.1 Signaling Network Plasticity

Signaling network plasticity is one of the mechanisms of resistance. The malignant cells have the ability to rearrange intracellular pathways in reaction to treatment, frequently via feedback and cross-talk between indicators cascades, including PI3K/AKT, JAK/STAT, NF-κB, and MAPK. Systems-level studies indicate that such adaptive responses are not only intrinsic to tumor cells but also niche-inspired, i.e. depend on cytokines, growth factors, and adhesion-mediated cues [83]. And as an example, stromal support through integrin-mediated adhesion may stimulate anti-apoptotic signaling in leukemic cells, which lead to chemoresistance and MRD [84].

9.2 Clonal Heterogeneity and Evolution

Another important aspect of resistance that is critical is clonal heterogeneity and evolution. It has been demonstrated by single-cell multi-omics and spatial transcriptomics that therapy can selectively stress subclones that already have or can acquire survival benefits, which increase the size of resistant populations. Modeling systems at the systems level can be used to recreate clonal dynamics and predict the response of separate subpopulations to treatment, and the appearance of relapses and maintenance of MRD [85].

9.3 Therapeutic Protection and Immune Escape

TME has also a crucial role in therapeutic protection and immune escape. In the niche regions, there is an abundance of immune suppressive cells, including the regulatory T cells, M2-polarized macrophages, and the myeloid-derived

suppressive cells, which can suppress the action of cytotoxic therapies as well as immunotherapies [86]. This protective environment is further enhanced by exosomal signaling and metabolic competition. Systems biology solutions incorporate spatial, transcriptional, and epigenetic measurements to find these ecosystem-wide obstacles and propose treatments that have the potential to kill malignant cells and their niche [87].

9.4 Predictive Modeling of Therapeutic Response

The use of predictive modeling of therapeutic response is becoming more and more useful in predicting precision treatment. Computationals take multi-omic data sets and overlay this information on network models to find key regulatory nodes whose suppression can break resistance pathways. ML algorithms are able to make patient-specific predictions, recreate combination therapies and rank interventions that address tumor-intrinsic and extrinsic bedroom reliance [88]. These integrative strategies are required in creating adaptive therapies that are sufficient to surmount dynamic resistance mechanisms in hematologic malignancies. To conclude, clonal heterogeneity, signaling plasticity of the network, and protective interactions with the microenvironment are the factors that contribute to therapy resistance in hematological cancers. Systems biology is able to help decode these intricate processes on a multifaceted basis with predictive information and rational combination methods of interfering with both the cancerous cells and their supportive ecosystems to increase the possibility of long-term remission and lasting responses [89].

9.5 Operationalizing Ecosystem-Guided Precision Oncology

To apply the ecosystem-guided precision oncology concept, experimental and clinical studies are needed. Preclinical studies, including patient-derived organoids and xenografts, could be used to test drugs that are tailored to a specific tumor ecosystem. Multi-omics and geo-profiling may be used to guide the selection of the most appropriate treatment and to monitor the tumor response, as well as the changes in the ecosystem and the survival of the patients in the clinical studies that stratify patients according to the biomarkers used in the ecosystem-guided approach [90].

10. Microenvironment-Targeted Therapeutics

The addressing of the TME has become a potential approach to adjunct standard therapies in hematological malignancies. As conventional therapies are mainly geared towards the destruction of malignant events, microenvironment-targeted therapies are designed to destabilize the supportive niches, immune-suppressive networks, and signaling that enable bacteria to survive, grow and develop resistance to therapy [91]. As Table 3 summarizes therapeutic methods for the tumor ecology, including modes of action, targets, and clinical relevance.

Table 3. Therapeutic strategies targeting the tumor ecosystem.

Therapeutic Approach	Mechanism of Action	Target	Clinical/Preclinical Status	Combination Potential	References
DNMT inhibitors	DNA hypomethylation, gene reactivation	Malignant cells, immune checkpoints	FDA-approved for AML/MDS	With immune checkpoint blockade or CXCR4 inhibitors	[99]
HDAC inhibitors	Histone acetylation, chromatin relaxation	Malignant cells, stromal interaction	Approved in T-cell lymphomas, multiple myeloma	With proteasome inhibitors or immunotherapy	[99]
CXCR4/adhesion inhibitors	Mobilize tumor cells from niches	Stromal–malignant interactions	Clinical trials	With chemotherapy or epigenetic therapy	[100]
Immune checkpoint inhibitors	Restore T-cell cytotoxicity	PD-1/PD-L1, CTLA-4	Approved for select lymphomas	With DNMT/HDAC inhibitors, CAR-T therapy	[100]
Anti-angiogenic agents	Inhibit VEGF signaling	Vascular niche	Preclinical / clinical trials	Combined with chemotherapy or epigenetic agents	[101]
CAR-T/CAR-NK therapy	Immune-mediated cytotoxicity	Malignant cells	FDA-approved for B-ALL, B-cell lymphomas	Enhanced by epigenetic modulation and niche disruption	[101]

10.1 Stromal-tumor Interaction Modulation

A major approach includes the stromal-tumor interaction modulation. Is it common that in malignant cells adhesion molecules and chemokine gradients like the CXCL12/CXCR4 axis are used to position themselves in protective niches? Plerixafor, a CXCR4 antagonist, transfers leukemic and lymphoid cells in such sanctuary locations to more exposure to cytotoxic agents. On the same note, integrin, selectin and other adhesion molecule inhibitors disorient cell-matrix and cell-cell interactions, decreasing niche-mediated cell survival signaling and increasing chemosensitivity [92].

10.2 Immune Microenvironment Modulation

Another major therapeutic approach is through immune microenvironment modulation. PD-1, PD-L1, and CTLA-4 immune checkpoint inhibitors have shown effectiveness in subsets of lymphomas especially in disease relapse or resistance [93]. In addition to the use of checkpoint blockade, re-population of immunosuppressive cells (e.g., M2 macrophages and MDSCs) or the increase in cytotoxic T-cell and NK cell numbers are under consideration [94]. DNMTis and HDAC inhibitors are epigenetic modulators that have been shown to act synergistically with each other to increase antigen presentation and co-stimulatory molecules effectively exposing malignant cells to host immunity [95].

10.3 Immune Microenvironment Modulation

Other modalities in microenvironment-directed therapy are immune microenvironment modulation. The anti-angiogenic agents also interfere with vascular assistance that supports tumor growth and nutrient supply, such as VEGF inhibitors. Simultaneously, metabolic interventions also strive to take advantage of the metabolic addicts of the malignant cells and their niche partners (e.g., glucose, amino acid metabolic dependencies, etc.), and thus disrupt the ecosystem that supports the survival of tumors [96].

10.4 Combination Strategies

The idea of combination strategies is being identified as a critical factor in effective disruption of the ecosystem. Combining the use of microenvironment-targeted agents with conventional chemotherapy, targeted kinase inhibitors, or immunotherapies can both simultaneously target the malignant cells with support niches and destroy them [97]. Although such combinatorial methods are still in preclinical studies and initial clinical trials have yet to be completed, they have shown the ability to overcome therapy resistance, reduce MRD and provide durable responses. In general, microenvironment-based therapeutics highlight the shift toward an ecosystem-guided precision oncology. These methods provide a complementary treatment to current therapy options, enhancing the chances of long-lasting remission and better patient outcomes by targeting cellular and molecular networks that support malignancy in hematological cancers [98].

11. Integrative Strategies: Combining Epigenetic and Microenvironmental Targeting

Interactions of epigenetic dysregulation with the TME in hematological malignancies have provided a rationale of combinatoric, ecosystem-guided therapeutic strategies. Epigenetic remodeling and adaptation of malignant cells to their niches are used by the cells, whereas the microenvironment also affects epigenetic states. The identification of this bidirectional crosstalk has prompted the emergence of integrative strategies that, in combination, attack inherent tumor weaknesses and extrinsic niche-based support [102].Therefore figure 4 depicts integrative therapy techniques that target both malignant cells and the TME using epigenetic, immunological, and microenvironment-directed therapies.

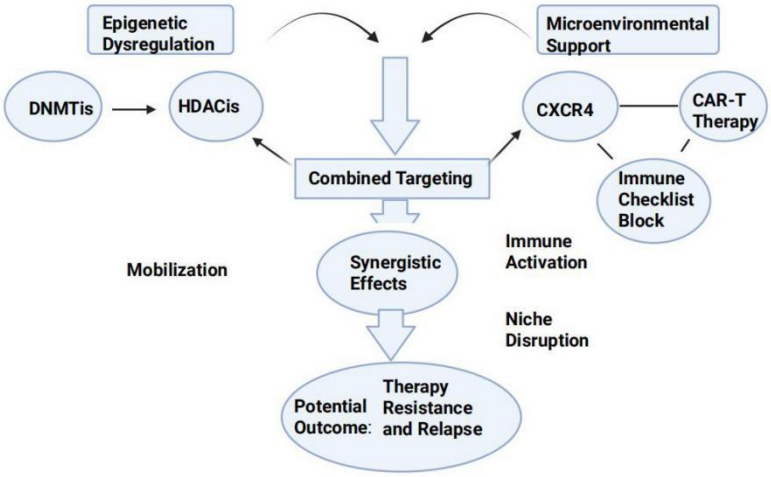

Figure 4. Integrative therapeutic strategies targeting malignant cells and microenvironment.

This figure shows the conceptual framework for integrative therapy techniques to target cancer cells and their surroundings. In the illustration, the application of epigenetic medicines, immune checkpoint inhibitors, microenvironment-targeted agents, and metabolic therapies is demonstrated to disrupt the interactions of cancer cells with their niche, evade the development of resistance, and enhance the effectiveness of treatment.

11.1 Synergizing of Epigenetic Modulators with Microenvironment-Targeted Agents

Among the strategies, there is the synergizing of the epigenetic modulators with microenvironment-targeted agents. The DNMTis and HDACis are known to reorganize both transcriptional and chromatin states in the malignant cells, in

addition to increasing the immune recognition through the up-regulation of antigen presentation machinery and co-stimulatory molecules [103]. In combination with immune checkpoint blockade, these agents may enhance immunosuppression induced by the microenvironment and enhance cytotoxic T-cell and NK cell responses. Likewise, epigenetic therapy can make tumor cells responsive to either CXCR4 or integrin blockers and attentuate their enclosure by protective niches as well as make them more vulnerable to cytotoxic drugs [104].

11.2 Combination of Metabolic and Signaling Dependencies in the Ecosystem and Increased Combinatorial Efficacy

The epigenetic reprogramming usually overlaps with the metabolic pathways and stress-response programs which are supported by the stroma [105]. By blocking essential metabolic enzymes or signaling nodes, e.g. PI3K/AKT, JAK/STAT or NF-κB, but at the same time using epigenetic modulators, can interfere with the adaptive potential of tumor cells, destabilize niche interactions, and lower resistance to therapy. In preclinical studies in the area of AML, CLL, and multiple myeloma, these dual-targeting strategies have been shown to eliminate resistant subclones and block relapses [106].

11.3 Rational design of Combination Therapies

Systems biology and computational modeling are becoming an important influence in rational design of combination therapies. High-resolution maps of tumor ecosystems obtained with multi-omic profiling, single-cell analyses, and spatial transcriptomics can be used to gain a better understanding of essential regulatory centers and cellular interactions. With machine-learning algorithms and network analysis, one can figure out what combinations of epigenetic and microenvironment-targeted agents will have the highest effect in disrupting the ecosystem, and reduce off-target toxicity to a minimum [69]. This accuracy system enables patient-specific therapy plans that consider the heterogeneity of clonal clustered subsets (niches), the complexity of niche, and adaptive resistance mechanisms. In general, integrative approaches can be considered a paradigm shift with the goal of holistic, ecosystem-oriented treatment in hematological malignancies. These methods, which simultaneously suppress epigenetic drivers and support microenvironments, will destroy the protective niches, re-establish immune surveillance, and sensitize malignant cells to therapy, and will have the potential to provide the ability to achieve lasting remission and better long-term outcomes [107].

12. Emerging Technologies and Future Directions

Technological innovations which allow the widespread mapping and manipulation of the tumor ecosystem are changing the hematological malignancies landscape at a very rapid pace. New tools such as high-resolution multi-omics, spatial profiling, single-cell studies, and artificial intelligence (AI)-based modeling are offering new information on cellular heterogeneity, microenvironment, and epigenetic processes. Such innovations will transform the perspectives of the biology of the disease and precision, ecosystem-directed treatment [108].

12.1 Single-Cell and Spatial Multi-Omics

High-resolution characterization of malignant subclones, stromal cells, and immune populations can be done using such techniques as scRNA-seq, ATAC-seq, and mass cytometry. Spatial transcriptomics and proteomics retain the tissue architecture, and the physical arrangement and networks of communication within niches. By combining these modalities, it will be possible to discover new previously unknown cellular interactions, discover treatment-resistant subpopulations, and track epigenetic states in spatially resolved micro environments [109]. Computational Modelling and Artificial Intelligence are in growing use to combine and analyse the huge datasets of multi-omic technologies. Machine-learning systems have the potential to discover predictive biomarkers of therapeutic response, learn the dynamics of signaling networks, and predict responses to therapeutic perturbations of an ecosystem [110]. The solutions of network biology help to reveal essential nodes and intercellular interactions and allow the rational design of combination therapies that act on malignant cells and supportive microenvironment [111].

12.2 Next-Generation Approaches With These Technological Advances

Next-Generation Approaches to therapy are being developed. CAR-T and CAR-NK cell-based precision immunotherapies are being fine-tuned to conquer immune-suppressive niches and take advantage of microenvironmental weaknesses [112]. The combination of epigenetic drugs with microenvironment-targeted therapies, metabolic modulators, and checkpoint inhibitors are aimed at becoming effective to produce multi-level disruption of tumor ecosystems [113]. Also, emerging modalities that include targeted protein degradation, RNA therapeutics and nanomedicine have potential to provide highly specific interventions to malignant cells and malignant cell niches at reduced systemic toxicity [114].

12.3 Clinical and Translational Priorities

As creation of patient-specific ecosystem maps, adaptive therapy strategies, and real-time monitoring of MRD are

developed. The implementation of multi-omic profiling in clinical processes could allow assessing the development of tumors dynamically, resistance to therapy, and adaptation to niches and using the information to take practical steps to support individual therapy [115]. Moreover, a set of standardized systems to incorporate computational prediction with experimental and clinical data are needed in order to translate ecological-scale knowledge into effective and precision-directed therapies. To conclude, the integration of developed multi-omics, analytics powered by AI, and the next-generation therapeutics is a revolutionary change in the field of hematological oncology. These innovations hold promise to holistically decode tumor ecosystem dynamics, forecast therapeutic outcomes and apply adaptive, precision therapies to malignant cells and their home niches to ultimately enhance patient outcomes and long-term disease control [116]. While advances have been made in the development of multi-omics and spatial profiling methods, a number of systemic and operational barriers remain to be addressed for these methods to be implemented at the clinical level. One such barrier is that access to these methods is limited by the cost of data storage, computing facilities, and sequencing instruments, especially in environments that are less resourced. Moreover, access to appropriate laboratory facilities, sophisticated bioinformatics expertise, and standard operating procedures for implementing these methods is lacking in most healthcare centers. Another barrier to implementing these methods is related to ethical and legal considerations, including data protection, standardization of diagnostic standards, and approval of computational tools.Furthermore, the time required for the analysis of multi-omics data may not match the urgent need for decision-making in cases of aggressive hematological malignancies. These challenges demonstrate that, despite the technological potential, the routine application of ecosystem-level profiling into the clinic will be challenging and will require concerted efforts to improve infrastructure, reduce costs, and harmonize regulations [117].

13. Conclusion

It is now being acknowledged that hematological malignancies are complicated, dynamic ecosystems of malignant cells, stromal elements, immune populations, and extra-cellular matrices that interact dynamically to affect disease progression, therapeutic reaction, and clinical outcomes. This review has noted the changing paradigm of the classical, cell-centric view of hematologic cancer to an ecosystem-driven paradigm integrating microenvironmental signatures, epigenetic controls and system-level understanding. Strategic and biochemical support of bone marrow and lymphoid niches helps keep malignant clones alive, whereas the dysregulation of the epigenetic processes enables these cells to alter their environment and survive the pharmacological treatment. Approaches of systems biology such as single-cell and spatial multi-omics, network modelling, and computational analytics have started to demystify the complexity of such interactions revealing key regulatory nodes and therapeutic vulnerabilities. The combination of epigenetic modulators, microenvironment-directed agents, immunotherapy, and next-generation modalities provides the possibility to surmount drug resistance, reduce relapse and provide long-term remission due to its ability to target both malignant cells and their supportive ecosystems.

Although there have been improvements, there are still major challenges. The interpatient variability and the heterogeneity of tumor ecosystems, as well as dynamic adjustment of malignant cells and niches, require the precision-directed and adaptive therapy. The future directions of research are the incorporation of high-resolution multi-omic profiling to clinical practice, the use of AI-based predictive models, and the development of combination therapies that simultaneously deter intrinsic and extrinsic malignancy drivers. To summarize, ecosystem-oriented precision oncology is a paradigm shift to hematologic cancer. The paradigm includes combining the contribution of microenvironmental biology, epigenetics and the study of systems, which allows developing the rational design of therapies that view the tumor as a dynamic interdependent ecosystem, which gives a new reason to hope that more patients will be saved and diseases controlled over time.

Conflict of Interest

The authors declare no conflicts of interest.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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