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Review

NPM1 in Aging-Related Multi-System Diseases: Molecular Mechanisms and Therapeutic Implications

Jiayao Li[1, 2, 3#], Jiaqi Jin[1, 2, 3#], Xinyu Yang[1, 2, 3, 4], Wentao Gao[1, 2, 3], Haozhi Gong[1, 2, 3], Xvebing Feng[1, 2, 3], Huijie Fang[1, 2, 3], Rui Liu[1, 2, 3], Shihao Jiang[1, 2, 3], Yanping Shen[1, 5, 6, 7], Xiaoting Liang[1, 5, 6, 7], Yiming He[1, 7, 8, 9], Liqun Jiao[1,2, 3, 10*], Xiao Zhang[1, 2, 3*], Tao Wang[1, 2, 3*]

[1]Departments of Neurosurgery and Departments of Interventional Radiology, Xuanwu Hospital, Capital Medical University, Beijing, China. [2]China National Center for Neurological Disorders, Beijing, China. [3]China International Neuroscience Institute, Beijing, China. [4]Binzhou Medical University, Yantai, China. [5]Center of Cerebrovascular diseases and Department of Neurology, Jinan Hospital of Xuanwu Hospital, Jinan, Shandong, China. [6]Department of Neurology, Central Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China. [7]China National-level Regional Medical Centers, Jinan 250100, Shandong Province, China. [8]Center of Cerebrovascular diseases and Department of Stroke Center, Jinan Hospital of Xuanwu Hospital, Jinan, Shandong, China. [9]Department of Stroke Center, Central Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China. [10]Center of Cerebrovascular diseases and Department of Neurosurgery, Jinan Hospital of Xuanwu Hospital, Jinan, Shandong, China.

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ABSTRACT: The prevalence of aging-related diseases, including tumors, cardiovascular and cerebrovascular diseases, and fibrotic diseases, has been consistently increasing in the aging population. In these conditions, nucleolar stress response mechanisms, such as defective ribosome biogenesis and dysregulated DNA damage repair, play instrumental roles in disease initiation and progression. Nucleophosmin 1 (NPM1), a multifunctional nucleolar chaperone, helps maintain cellular homeostasis through these stress response pathways. Accumulating evidence reveals that NPM1 exhibits disease-type-specific, and sometimes dual, roles in tumorigenesis, vascular aging, and multi-organ fibrosis, positioning it as a central regulator of age-related pathological processes. This review summarizes the role of NPM1 in the pathogenesis and treatment of multi-system aging-related diseases. We explore NPM1-related signaling pathways that regulate nucleolar stress responses and cellular homeostasis, evaluate its potential as a predictive biomarker for aging-related diseases, and discuss therapeutic strategies targeting NPM1-associated signaling. Although growing evidence highlights the potential of NPM1 inhibitors to modulate signaling cascades and improve clinical outcomes, context-selective inhibition of NPM1 may unexpectedly worsen disease progression in certain settings, underscoring its functionally dual nature depending on the context of the disease. This review delineates NPM1 signaling as a central orchestrator in aging-related pathogenesis and supports its potential as a therapeutic target to enhance treatment efficacy.

Keywords: NPM1, vascular aging, DNA damage repair, senescence, nucleolar stress, therapeutic targeting

1. Introduction

Nucleophosmin 1 (NPM1 also known as B23 or Numartin) is a ubiquitously expressed nucleolar phosphoprotein that plays pivotal roles in diverse cellular processes, understanding the dynamic functions of NPM1 and its role in cellular regulation is crucial for elucidating

***Correspondence should be addressed to:** Dr. Tao Wang (Email: wangtao_dr@sina.com), Dr. Xiao Zhang (Email: zhangxiao_dr@sina.com), and Dr. Liqun Jiao (Email: liqunjiao@sina.cn), Department of Neurosurgery, Xuanwu Hospital of Capital Medical University, Beijing, China. # These authors contributed equally to this work.

its broader implications in both normal physiology and disease states [1–3].

1.1 NPM1 Involved in Cellular Regulation and Stress Response

NPM1, located on chromosome 5q35.1, is a multifunctional nucleolar chaperone essential for genomic integrity. By facilitating nucleosome assembly/disassembly through binding to H3-H4 histones, it maintains chromatin architecture, particularly in heterochromatic domains [4, 5]. Crucially, NPM1 integrates three functional axes: ribosome biogenesis, DNA damage response, and epigenetic regulation, collectively enabling its role as a central guardian of cellular homeostasis [6–19].

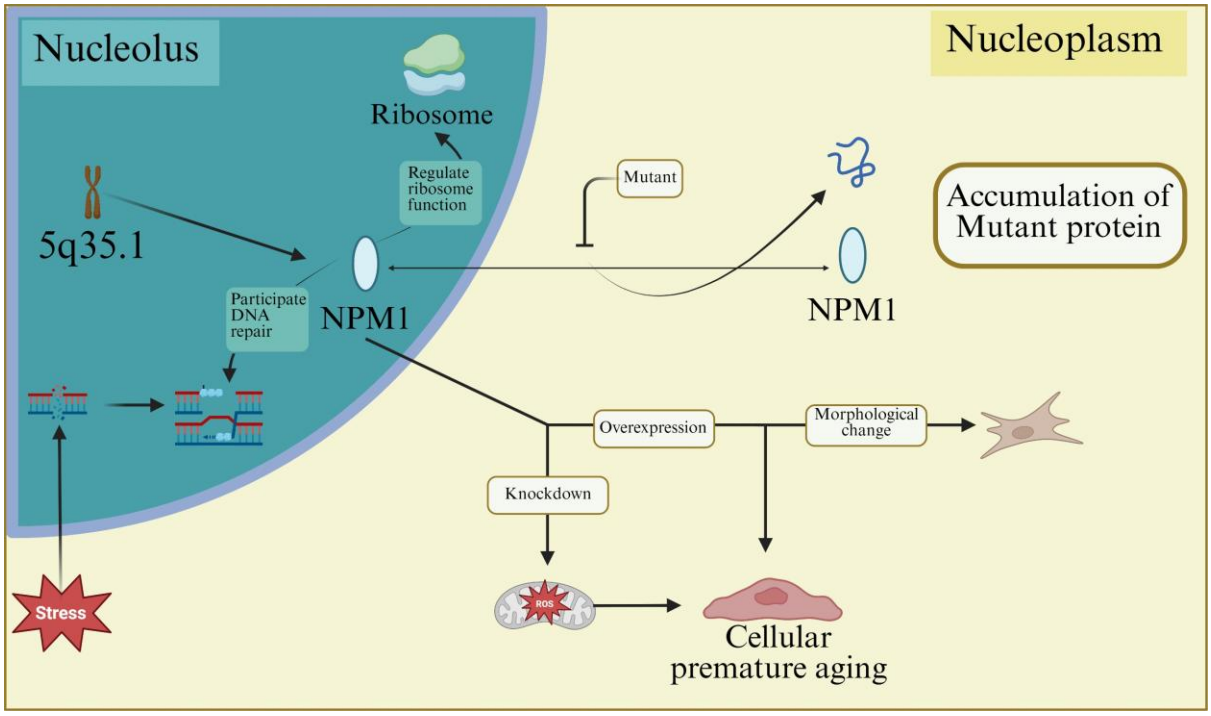

Figure 1. NPM1, Stress Response, and DNA Damage Repair in Senescence. NPM1 is involved in the bidirectional transport between the nucleolus and the cytoplasm, participating in the regulation of cellular stress, DNA damage repair, and the development of cellular premature aging. NPM1, Nucleophosmin 1; ROS, Reactive Oxygen Species.

1.2 Pathological Implications of NPM1

A variety of pathological conditions are related to NPM1. Disruptionof NPM1, including overexpression, interference, or deletion, influences DNA damage repair, organelle functions, apoptosis, and aging [13, 20, 21].
In murine primary fibroblasts, NPM1 overexpression induces morphological changes: cells become flatter, larger, and senescence-associated β -Galactosidase (SA-β-gal) positive. The senescence caused by overexpression is achieved by interaction between NPM1 and p53, which mainly depends on the heterodimerization domain (residues 186–259) [22].In mouse model, the conditional knockout of NPM1 leads to mitochondrial aberrant activation with increase of membrane potential and mitochondrial ROS increases, following increased overall pro-inflammatory trend and causing premature aging of hematopoietic stem cells and hematopoietic progenitor cells [23].

In summary, NPM1 plays a pivotal role in a variety of cellular processes. Perturbation of NPM1, including overexpression, interference with its expression, or deletion, can lead to severe pathological conditions. These conditions are specifically manifested as impaired DNA damage repair, altered organelle functions, cellular senescence, and premature aging—all of which are direct consequences of NPM1 dysfunction (Fig. 1). Meanwhile, based on the aforementioned roles, NPM1 is closely associated with the development and progression of multiple diseases, including acute myeloid leukemia (AML), various solid tumors, cardiovascular and cerebrovascular diseases, and fibrotic diseases [24–29] (Fig. 2). Integrated analysis of the differential regulatory mechanisms of NPM1 in these diverse diseases will provide a critical framework for defining future research directions, with a particular focus on the field of non-tumor diseases.

2. Molecular Mechanisms Underlying NPM1 Function

NPM1 orchestrates fundamental cellular homeostasis through the integration of ribosome biogenesis, programmed death pathways, and genome surveillance. As a nucleolar scaffold protein, it governs pre-rRNA processing and ribosomal subunit assembly while transducing oxidative and nucleolar stress signals via phosphorylation-dependent subcellular relocalization. During DNA damage response, NPM1 maintains genomic fidelity by recruiting repair complexes and modulating chromatin architecture. This multifunctional regulator further balances apoptosis-autophagy cascades to coordinate tissue microenvironment adaptation. The synergistic coordination of these mechanisms establishes a core regulatory framework for essential biological processes.

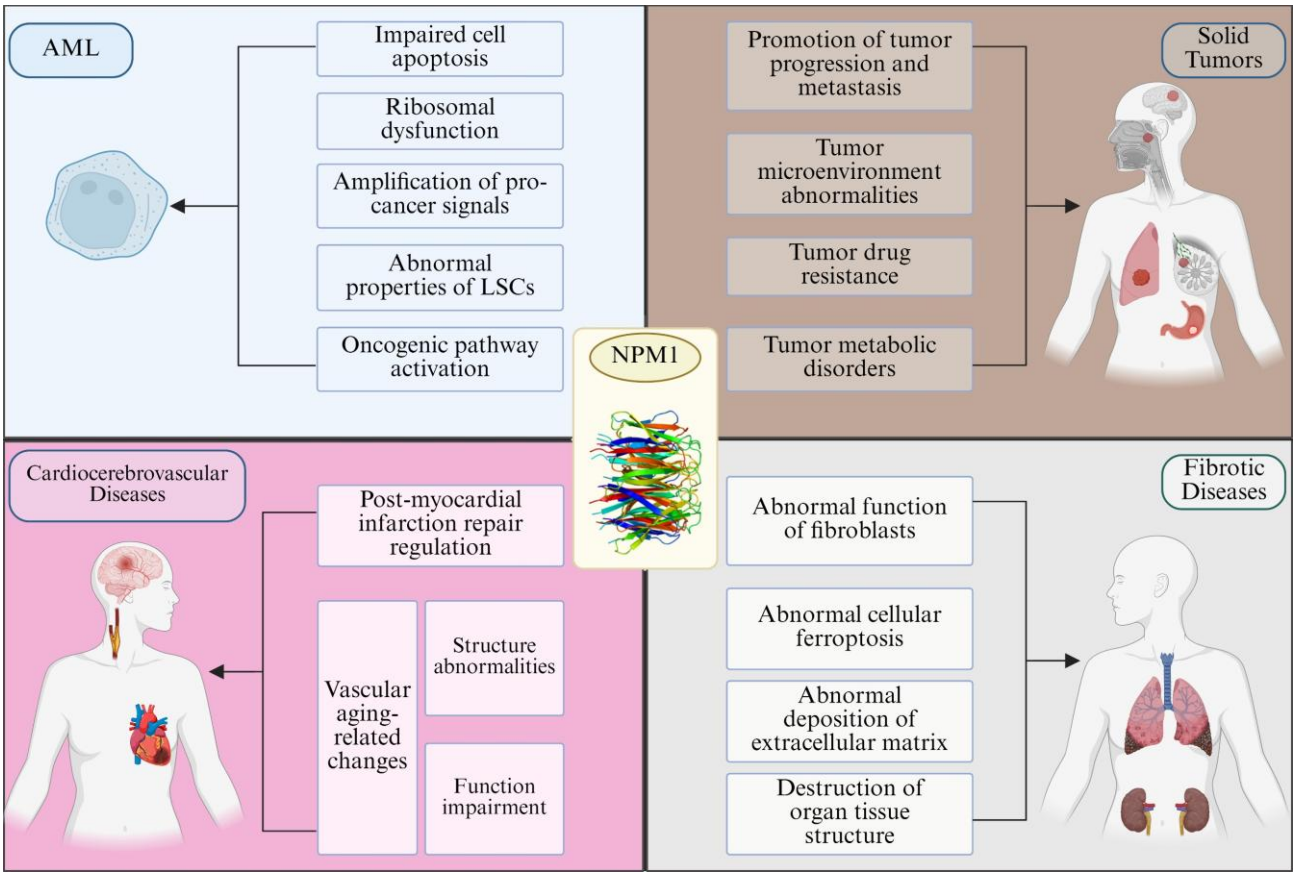

Figure 2. Pathological Regulatory Network of NPM1 in Multiple Diseases. NPM1 induces key pathological changes in AML, solid tumors, cardiocerebrovascular and fibrotic diseases through abnormal expression mutation or regulation of signaling pathways. AML, acute myeloid leukemia; LSCs, leukemia stem cells; NPM1, Nucleophosmin 1.

2.1 NPM1 regulates ribosome biogenesis

As a key player in ribosome assembly, NPM1 localizes to the nucleolus and coordinates ribosomal RNA (rRNA) processing. It binds C/D-box small nucleolar RNAs (snoRNAs) and recruits fibrillarin (FBL), the methyltransferase responsible for 2′-O-methylation of rRNA. This epitranscriptomic modification fine-tunes ribosomal function, ensuring translational fidelity and efficiency [30]. Disruption of NPM1-snoRNA-FBL interactions impairs rRNA methylation, leading to defective ribosome biogenesis and the altered translation of mRNAs with internal ribosome entry sites (IRES), such as CDKN1B and XIAP, which are critical for hematopoietic stem cell maintenance.

Notably, though NPM1 is mainly located in nucleolus, it transfers between the nucleus and cytoplasm, meaning a part of NPM1 constantly translocates to the nucleoplasm and inner nuclear membrane, and also to the cytoplasm and plasma membranes [5, 31, 32]. NPM1 relies on G-quadruplex and nucleolar localization signals for nucleolar targeting, while its dynamic shuttling between the nucleus and cytoplasm is regulated by nuclear export signals and nuclear localization signals [33, 34]. And mutation of NPM1 disrupts this transformation and given NPM1 acts as an endoribo-

nuclease at the specific site which located at the endonuclease activity at specific sites in the spacer region between 5.8S and 28S rRNA, playing a key role in the processing of ribosomal RNA precursors and the assembly of ribosomal subunits [35–39]. The interference of NPM1 shuttle can cause the mutant protein to accumulate in the cytoplasm instead of the nucleolus.

2.2 NPM1 Modulates Programmed Cell Death

NPM1 governs cell fate decisions through spatiotemporal regulation of programmed cell death modalities, primarily by modulating apoptosis and ferroptosis.

2.2.1 NPM1 & Apoptosis: Mechanisms and Pathways

In nucleus, NPM1 and PIP3 can bind with the c-terminus of NPM1 to form a complex suppressing the DNA fragmentation function of caspase-activated DNase (CAD), thus mediating the anti-apoptotic effects [13, 40]. Besides, anti-apoptotic efforts of NPM1 can be achieved by the interaction between NPM1 and p53 as well [41]. Although NPM1 and p53 binding is observed in vitro and their interaction persists in vivo, colocalization is not detected in staining studies. The absence is attributed to the predominant nucleolar localization of NPM1 with a limited nuclear diffuse fraction, whereas p53 is typically excluded from the nucleolar compartment [42, 43].

NPM1/Yes-associated protein 1 (YAP1) axis is involved in apoptosis resistances as well [44]. NPM1 physically binds with YAP1 ensuring the stability of YAP1. And knockdown of Aurora kinase A（AURKA）specifically resulted in a decrease in the phosphorylation level of Thr95 of NPM1 (p-NPM1 Thr95) that is important for binding of NPM1 to YAP1. Knockdown of either AUEKA or NPM1 significantly reduces YAP1 protein expression, impairing cell growth and inducing cell apoptosis [45]. Erythroid differentiation-associated gene (EDAG), a haematopoietic tissue-specific gene, binds to NPM1 (118–187), which contains the acidic domain/nuclear localization domains [46]. The colocalization of EDAG and NPM1 primarily occurs in the nucleoplasm. The overexpression of EDAG inhibits the polyubiquitination of NPM1 in a dose-dependent manner, thereby maintaining the stability of the NPM1 protein, which in turn prevents apoptosis induced by the increased activity of caspase-3 [47, 48] (Fig. 3).

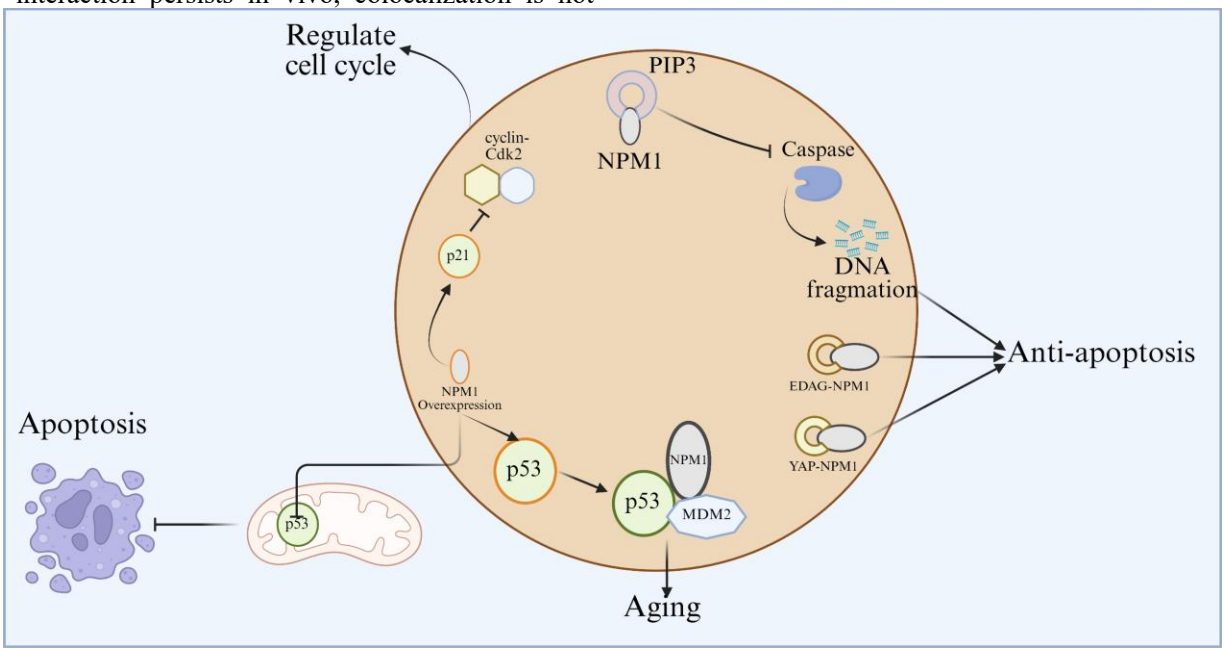

Figure 3. NPM1-mediated cell cycle control and anti-apoptotic pathways. NPM1 exerts its anti-apoptotic effects or regulates the cell cycle by binding to PIP3, EDAG, or YAP, or through its own overexpression or knockdown, subsequently affecting the levels of p53/p21. Cdk2, Cyclin-dependent kinase 2; EDAG, Erythroid differentiation-associated gene; MDM2, Mouse double minute 2 homolog; NPM1, Nucleophosmin 1; p21, cyclin-dependent kinase inhibitor 1A; p53, Tumor protein p53; PIP3, Phosphatidylinositol 3,4,5-trisphosphate; YAP1, Yes-associated protein 1.

2.2.2 NPM1 & Ferroptosis: Mechanisms and Pathways

NPM1 potentiates the inhibition of Bromodomain-containing protein 4 (BRD4), thereby suppressing its activity. This bidirectional regulatory mechanism concomitantly downregulates Kelch-like ECH-associated protein-1 (KEAP1) expression and facilitates nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2). Consequently, Nrf2 protein stability and

transcriptional activation are enhanced [49]. Activated Nrf2 binds to antioxidant response elements (AREs) in target gene promoters, inducing expression of core ferroptosis-suppressing genes including glutathione peroxidase 4 (GPX4) and solute carrier family 7 member 11 (SLC7A11) [28]. Functionally, GPX4 scavenges cytotoxic lipid peroxidation products, whereas SLC7A11 sustains glutathione synthesis through cysteine transport regulation. These effectors cooperatively suppress the lipid peroxidation-driven ferroptosis cascade [28].

2.3 NPM1 & DNA Damage Repair

NPM1 is involved in several pathways of DNA damage repair (DDR) including translesion synthesis (TLS), base excision repair (BER), homologous recombination (HR) (Fig. 4).

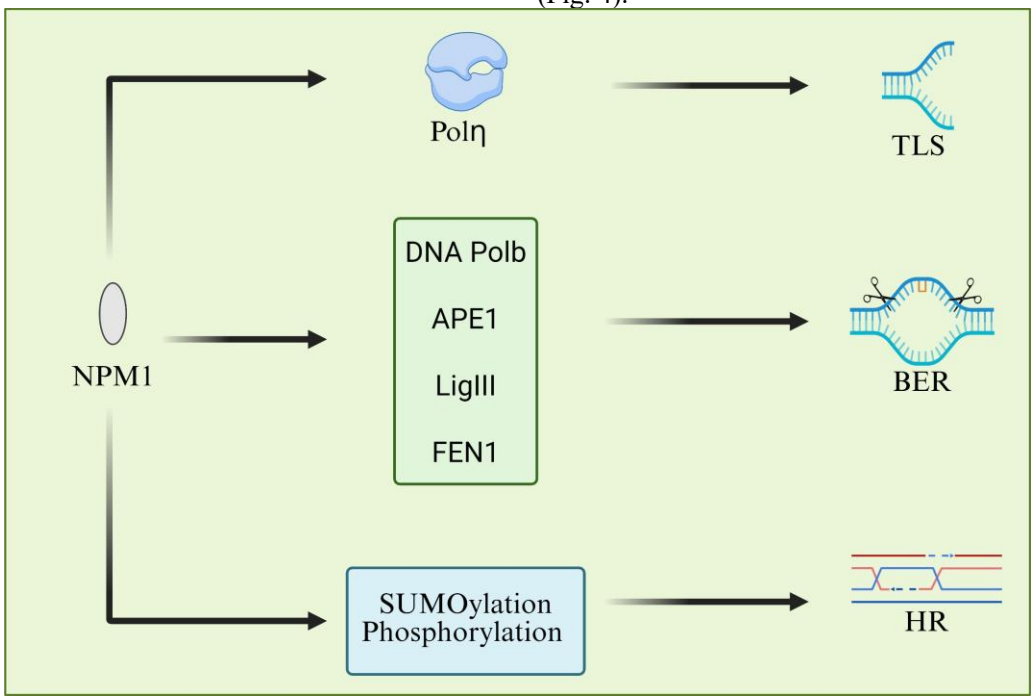

Figure 4. NPM1 modulates multiple DNA repair pathways. NPM1 participates in TLS, BER, and HR through cooperative interactions with enzymes required for DDR or through its own phosphorylation and SUMOylation. APE1, Apurinic/apyrimidinic endonuclease 1; BER, base excision repair; FEN1, Flap endonuclease 1; HR, Homologous Recombination; LigIII, DNA ligase III; NPM1, Nucleophosmin 1; Pol η , polymerase- η ; SUMOylation, Small Ubiquitin-like Modifier modification; TLS, translesion synthesis.

The TLS pathway involves the recruitment of specialized DNA polymerases. These polymerases can bypass inhibitory or non-informative DNA lesions on the parental strand, enabling them to incorporate nucleotides into the daughter strand and sustain the DNA synthesis process [50]. In terms of TLS, NPM1 is reported to regulate activity of polymerase-η (Polη) [51, 52], a major TLS DNA polymerase. In the process of TLS, Polη not only offers a sufficient space for thymine–thymine cyclobutane pyrimidine dimers (CPD) in a template strand but also immobilizes DNA templates in bulky lesions ensuring their straight and rigid [53]. A direct interaction between NPM1 and catalytic domain of Polη has been reported while Polη expression can be reduced by three-fourfold once NPM1 expression is interfered by siRNA [51]. The reduction of Polη is regarded as a result of proteasome-dependent degradation, but the mechanism remains unclear [54]. Notably, Polη participates in HR as well, extending DNA synthesis and interacting with RAD51 which increases Polη-mediated D loop extension [55]. Activity of Polη boosts HR repair of DNA double-strand breaks (DSBs) [56].

As for base excision repair, it bears repair responsibility for abasic sites, nucleobase damage, and single-stranded DNA (ssDNA) breaks [57, 58]. This requires lesion-specific DNA glycosylases, monofunctional glycosylases and separate lyases [59]. NPM1 regulates activities of several BER enzymes, for example, it increases activities of DNA Polb, Flap endonuclease 1 (FEN1), DNA ligase III (LigIII), and Apurinic/apyrimidinic endonuclease 1 (APE1) [21]. During the S phase of the cell cycle, the first 117 N-terminal amino acids of NPM1 bind to the 33 N-terminal amino acids of APE1 resulting in a threefold stimulation of the endonuclease activity of APE1 [39].

HR primarily occurs during the S and G2 phases, playing a crucial role in maintaining genomic integrity and initiating at DNA ends that feature 3′-overhanging ssDNA [60–62]. NPM1 needs phosphorylation at Thr199 in S, late G1 and G2 [63, 64], and SUMOylation at K263 to participate in HR [65–67]. Formation of DSBs leads to NPM1 SUMO-3 SUMOylation allowing NPM1 to interact with BRCA1-A complex [68], regulating BRCA1-A recruitment to DSBs and replication forks [65]. SUMOylated K263 NPM1 is reported to boost RAD51 foci formation at the sites of DSB in vivo and mutation of K263 NPM1 inhibits this ability [65].

In addition to the shared role of BER, HR and TLS in promoting aging through the accumulation of DNA damage, HR and TLS also drive aging via distinct mechanisms [69]. In cells with insufficient telomerase activity, HR-mediated alternative lengthening of telomeres serves as a means to maintain telomere length. Impairment of HR exacerbates telomere shortening, which itself is a classical trigger of replicative senescence [70]. The role of TLS in aging is more complex. On one hand, defects in TLS polymerases render cells highly sensitive to certain DNA lesions, causing frequent replication fork collapse and thereby accelerating cellular senescence [71]. On the other hand, excessive or erroneous activation of the TLS pathway, while conferring damage tolerance, substantially increases mutation rates due to its inherent error-proneness. These mutations may activate oncogenes, and oncogene activation itself is a potent trigger of senescence, a phenomenon termed “oncogene-induced senescence” [72].

In summary, NPM1 acts as a central coordinator across multiple DDR pathways by directly regulating the activity and stability of key repair factors, enhancing the function of core repair enzymes, and precisely orchestrating the recruitment of repair complexes to damage sites in a post-translational modification-dependent manner. Its functions span the continuum from damage tolerance to high-fidelity repair, which is crucial for maintaining genomic integrity. Consequently, by compromising the precise regulation of TLS, BER, and HR, disruption of NPM1 function may collectively exacerbate DNA damage accumulation and genomic instability. This positions NPM1 as a critical molecular node linking DNA repair deficiency to cellular senescence.

3. Pleiotropic Regulatory Mechanisms of NPM1 in Tumorigenesis

Emerging evidence highlights aberrant expression or mutations of NPM1 as pivotal drivers in diverse malignancies, spanning leukemia, lymphoma, and solid tumors [12]. The oncogenic mechanisms of NPM1 involve genetic mutations, fusion proteins, post-translational modifications, and epigenetic reprogramming, positioning it as a central node in tumor progression and therapy resistance [73, 74].

3.1 NPM1 Mutations and Leukemogenesis

In AML, NPM1 mutations represent one of the most frequent genetic alterations, recognized as a distinct entity in the WHO classification [24]. Over 50% of cytogenetically normal AML cases harbor cytoplasmic-localized NPM1 mutants, characterized by aberrant exon 12 frameshift mutations. These mutations disrupt the nucleolar localization signals, leading to abnormal cytoplasmic accumulation of NPM1 and loss of its native functions in ribosomal RNA processing [75]. Mechanistically, nucleophosmin 1 mutant c (NPM1c) activates oncogenic pathways such as AKT/NF-κB, promoting leukemic cell survival and chemoresistance. Notably, NPM1c stabilizes the homeobox genes/myeloid Ecotropic viral integration site genes (HOX/MEIS) transcriptional network, a hallmark of leukemia stem cells (LSCs). By enhancing chromatin accessibility at homeobox A cluster genes and homeobox B cluster genes (HOXA and HOXB) loci, NPM1c blocks myeloid differentiation and sustains LSCs self-renewal [75]. This epigenetic reprogramming blocks myeloid differentiation and sustains self-renewal, contributing to AML initiation and relapse. NPM1 cooperates with fms-like tyrosine kinase 3 - internal tandem duplication (FLT3-ITD) mutations exacerbating leukemogenesis. FLT3-ITD driven hyperactivation of signal transducer and activator of transcription 5 (STAT5) synergizes with NPM1c to amplify pro-survival signals, while dual inhibition of FLT3 and mitogen-activated protein kinase kinase/ extracellular signal-regulated kinase (MEK/ERK) pathways demonstrates therapeutic efficacy in preclinical models [73]. Furthermore, mutant NPM1 disrupts p53-mediated apoptosis by sequestering alternative reading frame (ARF) in the cytoplasm, enabling unchecked proliferation [76]. These findings underscore NPM1 mutations as central orchestrators of AML pathogenesis, offering actionable targets for precision therapy and given the important role of NF-κB and p53 in inflammation or aging, NPM1 owns a promising application prospect in non-tumor diseases.

3.2 NPM1 has Context-Dependent Regulatory Functions in Solid Cancers.

In solid tumors, NPM1 is frequently overexpressed and corelates with poor prognosis [77]. The overexpression of NPM1 may result from the oncogene c-MYC binding to

the NPM1 promoter and inducing its transcription [78]. Overexpression of NPM1 is associated with the promotion of tumor progression, induction of immune escape, enhancement of drug resistance, and facilitation of metabolic reprogramming [4, 79–81].

Take nasopharyngeal carcinoma (NPC) for example, NPM1 recruits the E3 ubiquitin ligase Mouse double minute 2 homolog (MDM2) to promote ubiquitination-mediated degradation of the tumor suppressor p53. This axis enhances epithelial-mesenchymal transition (EMT) and cancer stemness, facilitating metastasis [82]. The loss of p53 derepresses pro-metastatic genes, while NPM1 knockdown reverses these effects, underscoring its role in maintaining aggressive tumor phenotypes. In glioblastoma, NPM1 interacts with runt-related transcription factor 1 (RUNX1) to remodel the extracellular matrix (ECM) by enhancing FOS-like 2 (FOSL2)-mediated transcriptional activation of ECM-related genes. This process, dependent on histone H3K4me3 modifications, fosters an immunosuppressive microenvironment by upregulating programmed death ligand 1 (PD-L1) [29]. The RUNX1/NPM1 complex thus links ECM remodeling to immune evasion, highlighting NPM1's dual role in structural and immunological tumor adaptation. Besides, the regulation of PD-L1 extends beyond glioblastoma (GBM). In lung cancer, tobacco carcinogen-induced hyperglycemia reprograms tumor-associated macrophages (TAMs) to secrete insulin-like growth factor 2 (IGF2), activating insulin receptor (IR) signaling in cancer cells. Nuclear IR complexes with NPM1 to directly bind the CD274 (PD-L1) promoter, driving its expression and enabling immune escape [83]. Similarly, in triple-negative breast cancer (TNBC) and melanoma, NPM1 acetylation by N-acetyltransferase 10 (NAT10) enhances its transcriptional activation on PD-L1, which is abrogated by NAT10 inhibition [84]. These findings position NPM1 as a central mediator of PD-L1 upregulation across cancers, often via post-translational modifications.

However, it is noteworthy that in certain gastric cancer patients, NPM1 levels were significantly reduced compared to paired non-tumor tissues. Moreover, within this specific malignancy, the high-NPM1 expression group demonstrated significantly higher overall survival (OS) rates, disease-free survival (DFS) rates, and distant metastasis-free rates relative to the low-expression group. Notably, a negative correlation between NPM1 protein and mRNA expression levels was also observed in these patients [85, 86]. Upon infection, helicobacter pylori secrete the cytotoxin-associated gene a protein (CagA) virulence factor and mediates its injection into gastric epithelial cells via the type IV secretion system (T4SS). This process triggers phosphorylation of janus kinase (JAK) kinases, which subsequently induces phosphorylation of the STAT family of transcription factors [87, 88]. Specifically, phosphorylation of STAT5 at tyrosine residue Y694 (pY694-STAT5) exerts a dual regulatory effect on NPM1. Phosphorylation of STAT5 at Y694 upregulates NPM1 mRNA but destabilizes the protein by impairing the breast cancer susceptibility gene 1 - BRCA1-Associated Ring Domain (BRCA1-BARD1) E3 ubiquitin ligase complex [89]. While the CagA-JAK-pSTAT5 axis provides a mechanistic explanation for the observed decrease in NPM1 protein alongside increased mRNA levels in gastric cancer, it is important to note that CagA can also activate analogous pathways leading to STAT3 phosphorylation. Notably, studies in Jurkat T-cell leukemia models have demonstrated that STAT3 phosphorylation induces NPM1 upregulation in this cellular context [90].

In summary, the expression of NPM1 in tumors is regulated by highly complex network mechanisms. Its protein and mRNA levels are co-regulated by multiple factors, including the tumor microenvironment and epigenetic modifications, and sometimes exhibit inverse trends, suggesting the existence of post-transcriptional regulation. Moreover, it is particularly noteworthy that the expression changes of different family members at key nodes within the same pathway exert diametrically opposite effects on NPM1 levels, further highlighting the intricate and finely tuned nature of the NPM1 regulatory network. This multi-layered, dynamic, and highly context-dependent regulatory pattern results in significant cancer type-specificity in the prognostic value of NPM1, manifesting as a functional duality across different disease contexts: it functions as a tumor suppressor marker in certain cancers, while potentially acting as an oncogenic driver in others. Therefore, elucidating the precise regulatory mechanisms governing NPM1 and the molecular switches underlying its functional conversion within specific tumor types and microenvironmental contexts is critical for understanding its biological essence, developing precision diagnostic biomarkers, and designing effective targeted intervention strategies.

4. Regulatory Role of NPM1 in Cardiovascular and Cerebrovascular Diseases

NPM1 plays a complex role in cardiovascular and cerebrovascular diseases such as myocardial infarction and carotid atherosclerosis by regulating vascular aging, macrophage metabolism, and inflammatory responses.

4.1 NPM1 Regulates Immune Cell Phenotypic Transition to Mediate Cardiac Repair after Myocardial Infarction

Myocardial infarction (MI) is one of the leading causes of death and disability worldwide [91]. Since myocardial repair after MI profoundly affects patients' prognosis and quality of life, clarifying the regulation of immune cell differentiation is crucial [92]. Specifically, 30 minutes after MI onset, monocytes are recruited to the infarcted heart and persist for days to weeks; these cells then differentiate into M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages under the control of signaling pathways like type I interferon (IFN-1), Notch, hippo signaling pathway/yes-associated protein (Hippo/YAP), and TGF-β/SMAD—this phenotypic switch directly determines the efficiency of post-infarction repair [93]. NPM1 is expressed in both cardiomyocytes and cardiac immune cells, indicating its potential multi-faceted role in cardiac physiology and pathology. After the occurrence of MI, the expression level and subcellular localization of NPM1 undergo dynamic changes—for instance, NPM1 in cardiomyocytes may translocate from the nucleolus to the cytoplasm to respond to stress, while in cardiac macrophages, such changes are more pronounced [94]. Notably, the changes of NPM1 expression in cardiac macrophages play a crucial regulatory role in the myocardial repair process, as they are closely associated with macrophage phenotypic transition (from M1 to M2) and the secretion of repair-related cytokines [94]. In macrophages, elevated NPM1 recruits Histone Lysine Demethylase 5B (KDM5b) —a histone demethylase—to form a functional NPM1-KDM5b complex. This complex then specifically binds to the promoter region of Tuberous Sclerosis Complex 1 (TSC1), a key negative regulator of the mammalian target of rapamycin (mTOR) signaling pathway. As a result, the level of Trimethylation of Lysine 4 on Histone H3 (H3K4me3) in the TSC1 promoter region is significantly reduced, which decreases the transcription and expression of the TSC1 gene. Subsequent overactivation of mTOR Complex 1 (mTORC1) increases glycolysis levels in macrophages while inhibiting mitochondrial oxidative phosphorylation, thereby promoting the transition of macrophages to a pro-inflammatory phenotype, providing a novel therapeutic insight for the treatment of post-myocardial infarction [95, 96]. Beyond this, macrophages in the brain, including resident microglia and monocyte-derived macrophages recruited after injury, have been reported to be involved in neural repair after cerebral infarction by clearing necrotic tissue and secreting neurotrophic factors [97]. Notably, the regulatory role of NPM1 in macrophage phenotypic transition in the heart operates via modulating pathways such as mTOR and histone modifications. This role also provides a novel intervention strategy for the regulation of microglial phenotypic transition in the brain, suggesting a potential conserved role of NPM1 in immune cell-mediated repair across different organs [25].

4.2 Vascular Aging and the Potential Therapeutic Value of NPM1 in Cardiovascular and Cerebrovascular Diseases

A series of cardiovascular diseases with typical geriatric disease characteristics, represented by atherosclerosis, stroke and hypertension, show a significant increase in incidence as the population ages. Beyond classical chronological aging, vascular aging is another important pathogenic mechanism that warrants attention. Specifically, vascular aging refers to a condition where abnormal structural and functional degenerative changes occur in blood vessels with age or under pathological conditions [98–101]. And these degenerative changes leads to hemodynamic aging syndrome, which increases risk of a series of cardiovascular and cerebrovascular diseases, including atherosclerosis, hypertension, and stroke [26, 102–104].

4.2.1 Structure, functional and cellular changes with vascular aging

In the aspect of structural change, vascular aging is characterized by chaotic arrangement of vascular smooth muscle cells (VSMCs), elevated collagen deposition, disarrayed elastic fibers, thickened intima-media and calcification of vascular wall [105–109].

Intima media thickness (IMT), the distance between the lumen and the outer membrane interface, is an important index for assessing vascular aging, as its thickening is strongly correlated with age [110]. From the perspective of functional change, vascular aging results in augmented vascular stiffness, elevated secretion of inflammation factors, sensitivity change to vascular active factors and diminished angiogenesis capacity [105]. Pulse wave velocity (PWV) is the propagation speed of the blood pressure wave as it travels between two defined points in the arterial system. Vascular aging leads to increased arterial stiffness, reduced compliance, and diminished ability of the vessel wall to absorb pulse waves, resulting in accelerated PWV [111] .Increased vascular stiffness is often reflected by an increase in PWV on vascular ultrasound examinations, especially an increase in brachial-ankle pulse wave velocity (baPWV) [112].

Endothelial cell aging is associated with a decrease in nitric oxide (NO) release, which in turn results in impaired endothelial vasodilation function and weakened vascular relaxation ability [113–115].

As for cellular changes accompanied by vascular aging, flatter endothelial cells and hypertrophy of smooth

muscle cells are common [116]. As senescence of endothelial cells occurs, endothelial cells damage follows, interfering the regulation of endothelin-1 (ET-1), angiotensin II and NO levels then accelerates progression of atherosclerosis [117]. And autophagy deficiency in VSMC also causes calcification of arterial wall and facilitates age-related alterations in the vascular system [118].

In summary, vascular aging is characterized by both structural and functional degenerative changes in blood vessels, leading to hemodynamic aging syndrome and increasing the risk of various cardiovascular and cerebrovascular diseases, highlighting the importance of understanding the mechanisms of vascular aging for the prevention and treatment of these conditions.

4.2.2 Vascular aging in Cardiovascular and Cerebrovascular diseases

Vascular aging triggers a cascade of pathological changes across multiple organ systems through diverse mechanisms. In the cardiovascular system, reduced nitric oxide bioavailability and elevated oxidative stress promote vasoconstriction and arterial stiffness, contributing to hypertension development [119, 120]. Concurrent chronic inflammation exacerbates atherosclerotic progression [121], while these combined hemodynamic and structural alterations induce cardiac remodeling characterized by left ventricular hypertrophy and diastolic dysfunction, ultimately progressing to heart failure [122, 123].

Cerebrovascular complications emerge through distinct pathways: increased arterial stiffness and plaque instability heighten ischemic stroke risk, while chronic cerebral hypoperfusion and microvascular damage directly impair cognitive function [124]. Notably, blood-brain barrier disruption mediated by endothelial senescence and inflammatory damage precedes cognitive decline in Alzheimer's disease [125].

Systemic manifestations of vascular aging include microvascular dysfunction through oxidative-inflammatory mechanisms, manifesting as retinopathy, chronic kidney disease, and erectile dysfunction [119, 126]. Unique pathophysiological processes involve vascular calcification from abnormal VSMC osteogenic differentiation [127] and matrix metalloproteinase activation driving abdominal aortic aneurysm formation [121].

4.2.3 NPM1: A Dual-Function Target for Diagnostic and Therapeutic Advancement in Vascular Aging

Although the pathogenic role of vascular aging in cardiovascular diseases is well-established, significant diagnostic and therapeutic challenges persist. Current diagnostic approaches lack standardized, clinically feasible methodologies [128]. While PWV measurement represents the gold standard for vascular aging assessment, its clinical implementation faces substantial barriers: limited availability of validated instrumentation, technical complexity in obtaining reliable measurements using conventional ultrasound systems, and high operator dependency requiring specialized expertise [129]. In the therapeutic domain of vascular aging, lifestyle interventions demonstrate beneficial effects but their long-term efficacy is constrained by suboptimal patient adherence, while conventional pharmacotherapies such as statins and metformin require validation through large-scale clinical trials [123, 130]. NPM1 serves as a pivotal regulator of vascular aging through orchestrating critical processes including apoptosis, DNA damage repair, and nuclear stress response, revealing significant potential as a novel interventional target.

4.2.3.1 NPM1 as Anti-Apoptotic Regulator: Therapeutic Targeting for Senescent Cell Clearance

With NPM1 overexpression, p53 exhibits a pronounced tendency toward intranuclear redistribution, and the colocalization of p53 and NPM1 occurs concomitantly. This event facilitates the formation of the NPM1/p53/MDM2 ternary complex, thereby inducing cellular senescence. Notably, the efficient inhibition of NPM1 translocation can effectively abrogate the senescence phenotype triggered by NPM1-dependent p53 activation [22, 131–133]. The activation of p53 plays a pivotal role in mediating cellular apoptosis, a process that is highly dependent on the abundance of p53 localized in mitochondria. Under physiological conditions, NPM1 elevates the level of p53 in the nucleus while suppressing its accumulation in mitochondria, consequently exerting its anti-apoptotic effects [11]. Targeted modulation of NPM1 expression holds promise for enhancing the apoptosis of senescent cells, thereby alleviating the degree of vascular aging.

4.2.3.2 NPM1 & DNA Damage Repair

Stalling of DDR is regarded as a risky factor accelerating the cellular senescence [134]. NPM1 regulates DDR through its involvement in TLS, BER, and HR. In TLS, NPM1 directly interacts with the catalytic domain of Pol η to stabilize this key TLS polymerase: siRNA-mediated knockdown of NPM1 reduces Pol η expression by 3-4-fold via proteasome-dependent degradation, impairing its ability to bypass DNA lesions such as thymine-thymine CPD [51, 52, 54]. Notably, Pol η also contributes to HR

by extending DNA synthesis and interacting with RAD51 to facilitate DSB repair [55, 56]. For BER, NPM1 enhances the activities of core enzymes including APE1, DNA Pol β , FEN1, and LigIII, thereby improving the repair of base damage and single-strand breaks [21, 39]. In HR, DSB formation triggers SUMO-3 modification of NPM1 at K263, enabling its interaction with the BRCA1-A complex to promote RAD51 foci formation at damage sites; mutation of K263 abolishes this function [65–67]. Collectively, NPM1 coordinates multiple DDR pathways to maintain genomic integrity, and its dysfunction-induced repair deficiency directly accelerates cellular senescence.

4.2.3.3 NPM1 & Nucleolar Stress: Implications for Aging

Nucleolar stress response is commonly reported in age-related diseases [135]. This refers to a condition where ribosome biogenesis is disrupted while nucleolar architecture and function becomes aberrant [136]. Nucleolar stress can be regarded as early response to apoptosis and accumulation of free ribosomal proteins caused by nucleolar stress generally leads to premature aging [137]. In this process, the dislocation of NPM1 from nucleoli is generally regarded as a marker of nucleolar stress [138–140]. Avitabile et al. revealed nucleolar decondensation associated with reduced signal intensity for both nucleostemin and NPM1 [18]. By silencing NPM1, important alterations occurred to nucleolar structure including delocalization of nucleostemin and p19ARF as well as nucleolar fragmentation [141]. At the molecular level, the expression level of NPM1 has a bidirectional effect on the onset of aging. Both overexpression and inhibition of NPM1 lead to an increase in p21 expression. Downregulation of NPM1 results in inhibition of pre-rRNA synthesis and induced expression of p21, which suggesting occurrence of aging [18]. This biphasic effect suggests incomplete understanding of the functional mechanisms of NPM1 remains incomplete, and further experimental investigations are urgently required to address the limitations of NPM1 as a therapeutic target for vascular aging.

5. The Regulatory Role of NPM1 in Multi-Organ Fibrotic Diseases

Fibrosis represents a widespread age-associated disorder affecting virtually multi organ system [142]. The defining hallmark of fibrosis is aberrant ECM accumulation, resulting in progressive architectural distortion of affected tissues and destruction of organ structure [142, 143].

In clinical practice, there is still a lack of therapeutic approaches to reverse this fibrotic process, which largely drives the progression of the disease toward organ failure. This underscores the urgency to identify key regulatory molecules governing fibrotic progression, exemplified by NPM1, which modulates pathological fibrosis in prototypical fibrotic diseases including silicosis-induced pulmonary interstitial fibrosis and CKD-related renal tubular fibrosis [143].

In silicosis, inhalable crystalline silica (SiO_2) induces localized endothelial senescence, upregulating the secretory protein galectin-3 (Gal-3). Subsequent binding of Gal-3 to transforming growth factor beta receptor 1 (TGFBR1) on pulmonary fibroblasts drives their transdifferentiation into myofibroblasts [144, 145]. This process elevates expression of fibrotic markers, α-smooth muscle actin (α-SMA), fibronectin, and type I collagen, while enhancing fibroblast migration and collagen synthesis, ultimately leading to excessive extracellular matrix (ECM) deposition that forms silicotic nodules and pulmonary fibrosis [145, 146].

Concurrently, in CKD-related renal tubular fibrosis, accrual of senescent cells during aging propagates fibrogenesis through senescence-associated secretory phenotype (SASP)-mediated chronic inflammation, culminating in pathological tissue remodeling [147]. Meanwhile, renal macrophages develop pronounced iron accumulation, which triggers ferroptosis via pathological elevation of reactive oxygen species (ROS) and consequent lipid peroxidation. These ferroptotic macrophages enhance intercellular communication with renal tubular epithelial cells, inducing partial epithelial-mesenchymal transition (EMT) and upregulating pro-fibrotic genes that directly promote fibrotic pathogenesis [148].

NPM1 exhibits abnormal expression during the fibrotic stage of both diseases and participates in the formation of fibrosis through distinct mechanisms. In silicosis, interleukin 33 (IL33), whose level is elevated under the influence of silica, activates the ERK/AP-1/NPM1 signaling pathway, thereby further enhancing the activation, proliferation, and migration of pulmonary fibroblasts [27].

In CKD-related renal tubular fibrosis, NPM1 exerts its role by regulating ferroptosis and SASP-mediated chronic inflammation. NPM1 governs ferroptosis homeostasis in CKD-driven renal fibrosis. It leverages its mechanistically defined anti-ferroptosis program to mitigate oxidative parenchymal deterioration. This fundamentally intersects with IL33/Nrf2-mediated profibrotic signaling, cooperatively accelerating pathological matrix deposition that characterizes end-stage nephropathy [28]. Within the SASP milieu, NPM1 orchestrates dichotomous inflammatory responses

through dual molecular pathways. It potentiates NF-kB signaling via allosteric stabilization of p65, substantially enhancing kB-dependent transcriptional activation [149]. Conversely, NPM1 deficiency induces mitochondrial dysfunction that triggers NLRP3 inflammasome hyperactivation and pathological IL-1 β /IL-18 secretion [23]. This mechanistic duality necessitates context-specific therapeutic strategies to exploit NPM1's anti-fibrotic functions while mitigating inflammatory toxicity.

6. Therapeutic Targeting of NPM1 Dysregulation and Associated Networks in Oncology

The context-dependent duality of NPM1, which can function as an oncogene or a tumor suppressor in different malignancies, necessitates the development of precision therapeutic strategies. Current strategies focus on exploiting NPM1-centric regulatory vulnerabilities through three primary avenues: direct NPM1 inhibition, modulation of critical regulatory nodes, and microenvironment-directed normalization.

6.1 Direct NPM1 inhibition

In a range of solid tumors, including hepatocellular carcinoma (HCC), the level of NPM1 is elevated in cancerous tissues and is associated with poor prognosis [150]. In this context, where inhibition of nucleophosmin 1 (NPM1) has been shown to suppress the malignant proliferation of solid tumor cells such as HCC, NPM1 is expected to serve as a potential therapeutic target in the pan-tumor setting [150]. The function of NPM1, especially its mutant form, depends on oligomer formation mediated by a highly hydrophobic dimerization surface that acts as a hydrophobic interface within its N-terminal domain (NTD), and NSC348884 specifically binds to this interface to disrupt the hydrophobic interactions required for oligomerization, prevent proper NPM1 folding, abolish its molecular chaperone function, and ultimately compromise ribosome biogenesis, p53 stability and DNA damage repair [151]. In AML cell lines with NPM1 mutations, treatment with arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) induces proteasomal degradation of the mutant NPM1 protein [152].

6.2 Indirect Targeted Therapy through Downstream Regulation of NPM1

In NPM1-mutated AML, the mutant protein drives aberrant overexpression of HOX/MEIS genes [153], while concurrently conferring dependence on BCL-2-mediated anti-apoptotic pathways [154]. Consequently, multiple targeted agents have advanced into clinical development, including: (i) Menin-MLL inhibitors (e.g., Ziftomenib, SNDX-5613) [155] ; (ii) EPZ-4777, which suppresses HOXA/MEIS1 expression via inhibition of H3K79 methylation [154] ; and (iii) BCL-2 inhibitors exemplified by venetoclax.

6.3 Therapeutic Dilemma Posed by Drug Resistance and Toxicity in NPM1-Targeted Therapy

In the treatment of AML, young patients with NPM1 mutations eligible for intensive chemotherapy achieve complete remission (CR) rates of up to 85%, however, the 5-year overall survival (OS) rate remains only 40% – 50% [156]. This disparity suggests that current chemotherapy-centric regimens for NPM1-mutated AML may fail to eradicate LSCs. Additionally, chemotherapy-induced selective pressure drives leukemic clonal evolution and expansion of drug-resistant subclones, further compromising treatment efficacy.

Crucially, due to the pivotal role of NPM1 in cell cycle regulation, conventional chemotherapy exerts substantial non-selective cytotoxicity, leading to severe complications including myelosuppression, infections, hemorrhage, mucositis, and multi-organ (cardiac, pulmonary, hepatic, renal) dysfunction [157, 158]. These toxicities profoundly limit the therapy applicability in elderly patients. Thus, future strategies should prioritize: (1) developing targeted therapies against specific cell populations to reduce toxicity and expand eligibility for older adults; (2) designing combinatorial regimens to selectively eliminate malignant clones for sustained long-term efficacy; and (3) expanding the methodological repertoire for detecting NPM1 mutation status and expression levels to integrating biomarker-driven stratification, such as NPM1 mutation status and its molecular context, to guide precision therapy selection across different patient subgroups.

7. Conclusion

NPM1, a multifunctional nucleolar chaperone, has been extensively investigated in tumorigenesis, with its context-dependent duality (oncogenic or tumor-suppressive roles) well-characterized across malignancies. Such mechanistic insights have facilitated the development of targeted therapies, underscoring their translational significance in oncology. Beyond tumors, the conserved mechanisms of NPM1, which include DNA damage repair through TLS/BER/HR and apoptosis regulation through p53/YAP1, highlight immense research prospects in non-tumor diseases. In these diseases, NPM1 participates in core pathological processes by modulating cellular homeostasis and stress responses. Notably, vascular aging is a critical non-tumor

context. It is characterized by structural degeneration and functional decline, and it also serves as a key driver of cardiovascular diseases. NPM1 mitigates vascular aging by maintaining genomic stability, suppressing senescence, and preserving nucleolar integrity, while its aberrant functionality triggers accelerated aging. In summary, NPM1's tumor research underpins non-tumor exploration, with vascular aging a promising direction for mitigating age-related cardiovascular pathologies. Future integrated applications of multi-omics profiling, cross-linking mass spectrometry, and computational modeling may provide valuable insights into expanding the therapeutic potential of NPM1 in hematologic malignancies.

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