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Review Article

Dyskerin dysfunction in cancer development: from telomere dysregulation to immune deficiency

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Abstract: Dyskerin, encoded by the dyskerin pseudouridine synthase 1 (DKC1) gene, is a core component of the H/ACA ribonucleoprotein complex and plays essential roles in telomerase activity maintenance, rRNA pseudouridylation, and ribosome biogenesis. Loss of DKC1 function represents a major pathogenic basis of dyskeratosis congenita (DC) and is associated with a markedly increased risk of malignancy, particularly head and neck squamous cell carcinoma and oral squamous cell carcinoma. Traditionally, cancer susceptibility in DC has been largely attributed to telomere shortening and the resulting genomic instability; however, this explanation does not fully account for the heterogeneity observed across different genetic subtypes and clinical phenotypes. In this review, we systematically integrate three key mechanisms through which dyskerin dysfunction contributes to DC-associated carcinogenesis: disruption of telomere homeostasis, defects in selective translation regulation dependent on RNA pseudouridylation, and progressive impairment of T-cell-mediated immune surveillance. We highlight how DKC1 deficiency leads to insufficient rRNA pseudouridylation, selectively affecting the translation of internal ribosome entry site (IRES)-dependent transcripts, thereby attenuating the stress-induced expression of critical tumor suppressor proteins. In parallel, evidence from patient cohort studies is discussed to support a potentially dominant role of immunodeficiency in tumor development. Finally, we propose that future studies on DC and short telomere syndromes should emphasize genetic stratification and long-term clinical outcomes to refine cancer risk assessment and optimize preventive and therapeutic strategies.

Keywords: Dyskerin, DKC1, dyskeratosis congenita, telomere dysfunction, selective translation, cancer susceptibility

Introduction

Dyskeratosis congenita

DC is a rare inherited multisystem disorder caused by mutations in genes involved in telomere biology. Previous studies have estimated its overall incidence to be approximately 1 per 1,000,000 live births; however, this figure is largely derived from early case compilations and single-center studies and is therefore subject to under-ascertainment and reporting bias [1]. Among reported patients, males substantially outnumber females, with some studies describing a male-to-female ratio as high as 13:1. This skewed sex distribution is generally attributed to the high prevalence of X-linked DC caused by DKC1 mutations [1], whereas no significant sex difference has been observed in autosomal dominant or autosomal recessive subtypes [2-4].

The clinical phenotype of DC is highly heterogeneous, with disease severity and progression varying according to the causative gene, inheritance pattern, and extent of telomere shortening. Several studies have reported that the average age at death in DC clusters within the third to fifth decades of life [5]. In contrast, patients with severe disease - particularly those with childhood onset or those diagnosed with Hoyeraal-Hreidarsson syndrome - may have a life expectancy of less than 20 years [2, 6-11]. These apparent discrepancies primarily reflect differences in cohort composition and follow-up duration rather than true epidemiological

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Table 1. Diagnostic criteria and commonly used tools for DC

Diagnostic domain	Key points
Key points	• Classic mucocutaneous triad (reticular skin pigmentation, nail dystrophy, and oral leukoplakia); • May be accompanied by bone marrow failure, pulmonary fibrosis, liver disease, and immunodeficiency; • Marked heterogeneity in phenotype and age at onset
Telomere length assessment	• Flow-FISH analysis of peripheral blood leukocytes; • Results should be interpreted with age adjustment; • Telomere length markedly below age-matched controls (particularly in the lowest percentiles) is suggestive of a telomere biology disorder
Molecular genetic testing	• Targeted gene panels including ACD, TINF2, CTC1, DCLRE1B, NHP2, NPM1, POT1, RPA1, STN1, TCAB1, PARN, RTEL1, DKC1, TERT, TERC and NOP10; • Whole-exome or whole-genome sequencing should be considered in cases with high clinical suspicion but negative targeted testing
Diagnostic principles	• Diagnosis should be based on an integrated assessment of clinical phenotype, telomere length, and genetic findings; • No single parameter is sufficient to confirm or exclude DC

Table 2. Practical differential diagnosis of dyskeratosis congenital

Disease category	Representative conditions	Key distinguishing features
Other telomeropathies	Adult-onset short telomere syndromes; Telomere-associated pulmonary fibrosis	• Marked telomere shortening, but often lacking the complete mucocutaneous triad; • Clinical manifestations are frequently limited to one organ system
Inherited bone marrow failure syndromes	Fanconi Anemia	• Defect in DNA interstrand crosslink repair; • Positive chromosomal breakage test
Ribosomopathies	Diamond-Blackfan Anemia	• Predominantly hematopoietic abnormalities; • Telomere length is usually not markedly shortened; • Distinct underlying molecular mechanisms
Acquired disorders	Acquired aplastic anemia; Acquired immunodeficiency	• Absence of identifiable germline mutations; • Differentiation relies on clinical history and genetic testing

contradictions. Bone marrow failure (BMF) represents the leading cause of death in DC, accounting for approximately 67%-70% of fatalities [12]. During the first two decades of life, infections [6, 7] and bleeding [8] also constitute major causes of mortality, while pulmonary disease contributes to approximately 15%-18% and malignancy to 8%-10% of deaths [9].

Given the marked heterogeneity in age at onset, extent of organ involvement, and genetic background, reliance on the classic mucocutaneous triad alone is no longer sufficient for contemporary clinical diagnosis. It is now widely accepted that the diagnosis of DC should be established within an integrated framework combining clinical phenotype assessment, telomere length measurement, and molecular genetic testing, rather than depending on any single criterion [1, 2, 13-15] (**Table 1**). In terms of differential diagnosis, DC must be distinguished from a range of inherited bone marrow failure syndromes and telomere-related disorders (**Table 2**). For example, Fanconi anemia shares features such as bone marrow failure, mucocutaneous abnormalities, and cancer susceptibility, but is fundamentally a disorder of DNA interstrand crosslink repair and can be differentiated by chromosomal breakage testing [2, 16, 17]. Other telomere-related disorders, including adult-onset short telomere syndromes, typically lack the classic mucocutaneous triad and exhibit distinct patterns of systemic involvement and inheritance. Certain ribosomopathies may also present with early hematologic abnormalities; however, their underlying mechanisms are unrelated to telomere dysfunction and require integrated clinical and genetic evaluation for accurate distinction [2].

DC is associated with a markedly increased susceptibility to cancer. Data from multiple registry-based cohorts and referral-center studies indicate an approximately 11-fold increased overall cancer risk compared with the general population, with malignancies typically emerg-

Table 3. Quantitative cancer risk profile in patients with DC and related short telomere syndromes

Cancer type	Median/mean age at diagnosis	Cumulative risk before age 50	Cumulative risk before age 50	Inheritance pattern/ genotype association
HNSCC	Young to middle adulthood (30-40 years)	Markedly increased (contributing to an overall cumulative cancer risk of ~40%-50%)	Substantially elevated (O/E >> 1)	Highest risk in X-linked DC (DKC1)
OSCC	30-40 years	High	Significantly elevated	Predominantly observed in DKC1-associated DC
Tongue SCC	Predominantly young to middle adulthood	--	Extremely high (reported O/E ratios in the hundreds to thousands)	Frequently associated with DKC1 and TINF2
Myelodysplastic syndrome	Young to middle adulthood	--	Markedly elevated	Associated with critically short telomeres
Acute myeloid leukemia	Young to middle adulthood	--	Elevated	DC/telomeropathy spectrum
Gastrointestinal adenocarcinoma	adulthood	--	Elevated	DC/telomeropathy spectrum
Laryngeal/ bronchogenic carcinoma	adulthood	--	Elevated	--

Patients with dyskeratosis congenita exhibit a substantially higher overall risk of malignancy than the general population, with solid tumors predominated by HNSCC. Cancer risk varies markedly across genetic subtypes, with X-linked DC caused by DKC1 mutations conferring the highest risk of solid tumors, whereas autosomal dominant or recessive telomeropathies display a more heterogeneous tumor spectrum. Most risk estimates are derived from registry-based cohorts or referral-center populations and should be interpreted with consideration of potential ascertainment bias.

ing around 30 years after birth and cumulative incidence reaching 40%-50% before the age of 50 years [18, 19]. Solid tumors predominate and include squamous cell carcinoma, Hodgkin lymphoma, gastrointestinal adenocarcinoma, laryngeal cancer, and genitourinary malignancies [19, 20]. Among these, head and neck squamous cell carcinoma (HNSCC) is the most frequent, with oral squamous cell carcinoma (OSCC) being particularly prominent and accounting for approximately 40% of DC-associated secondary solid tumors [21-23]. It should be noted that these risk estimates are largely derived from registries and referral populations enriched for severe cases and may therefore overestimate the true cancer burden in the overall DC population.

Given the variability in tumor spectrum and risk magnitude across different telomere biology disorders, we performed a structured comparison of cancer susceptibility among patients with DC and related short telomere syndromes (**Table 3**) [2, 3, 18, 19, 24-26]. Overall, patients with X-linked DC exhibit the highest risk of solid tumors, whereas those with autosomal dominant or recessive telomeropathies display a more heterogeneous distribution of tumor types. Evidence regarding the role of human papillomavirus (HPV) in telomere-related squamous cell carcinomas remains limited, and systematic data are lacking for DC-associated tumors. Accordingly, HPV status was not incorporated into the quantitative cancer risk analysis in this review [27].

From a genetic perspective, DC may follow X-linked recessive, autosomal dominant, or autosomal recessive inheritance patterns [2, 28], with X-linked recessive disease being the most common. Mutations in the X-linked DKC1 gene lead to reduced telomerase activity and progressive telomere shortening [3], with patients typically presenting in childhood [29] and exhibiting more severe clinical phenotypes than those with autosomal forms of the disease [30]. As of the current release of the NCBI ClinVar database, 19 pathogenic genes associated with DC have been identified, among which telomerase reverse transcriptase subunit (TERT) is the most frequently reported, while DKC1 harbors the largest number of pathogenic or likely pathogenic variants [31, 32]. A recent analysis by Schratz et al. of 226 patients with short telomere syndromes diagnosed between 2003 and 2022 further demonstrated that HNSCC was the most common invasive solid tumor, and that male patients carrying X-linked DKC1 mutations exhibited the highest cancer risk [32]. This strong genotype-

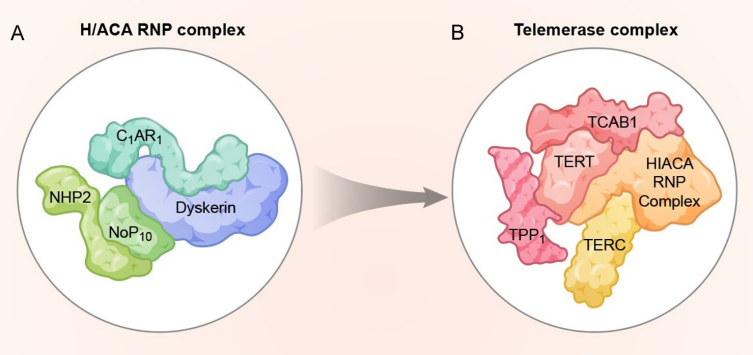

Figure 1. Schematic diagram of dyskerin's role in maintaining telomerase complex activity. A: Dyskerin, along with GAR1, NOP10, and NHP2 proteins, forms the H/ACA ribonucleoprotein complex. B: The H/ACA ribonucleoprotein complex, along with the telomerase RNA component, the telomerase reverse transcriptase subunit, TPP1, and TCAB1 proteins, collectively form the telomerase complex.

tumor spectrum association suggests that dyskerin dysfunction may selectively promote the development of squamous cell carcinomas such as OSCC through specific molecular mechanisms, providing a critical epidemiological and genetic foundation for the subsequent mechanistic discussion of DKC1-driven carcinogenesis.

Dyskerin is a key enzyme for maintaining telomere length

Dyskerin is an essential nucleolar protein encoded by the DKC1 gene located on the X chromosome. Its functions are closely associated with the proteins GAR1, NOP10, and NHP2, as well as H/ACA box guide RNAs [33]. Together, these components form the H/ACA ribonucleoprotein (H/ACA RNP) complex (**Figure 1A**), which participates in ribosome biogenesis and catalyzes pseudouridylation at specific residues of newly synthesized ribosomal RNA(rRNA) and small nuclear RNA(snRNA). This complex predominantly localizes to the nucleolus and Cajal bodies [34, 35].

In addition to its role in RNA modification, dyskerin is an integral component of the telomerase holoenzyme complex. It binds specific H/ACA RNAs, most notably the telomerase RNA component (TERC), thereby maintaining telomerase activity and enabling telomere elongation [36, 37] (**Figure 1B**). Telomerase synthesizes telomeric TTAGGG repeats at the ends of eukaryotic chromosomes using the intact RNA template provided by TERC in conjunction with the TERT [38]. Loss of dyskerin function destabilizes TERC, reduces telomerase activity, and leads to premature telomere shortening. Consequently, dyskerin plays a central role in multiple cellular processes, including ribosome biogenesis, snRNA maturation, telomere maintenance, and additional cellular functions that remain incompletely characterized [37]. The pathogenic significance of dyskerin dysfunction in DC has therefore attracted considerable attention.

Collectively, although prior studies have examined the relationship between dyskerin dysfunction and cancer susceptibility from the perspectives of telomere biology defects, ribosome dysfunction, or immune dysregulation, these mechanisms have largely been discussed in isolation. The unique contribution of this review lies in the integrated analysis of three interrelated pathways - telomere dysregulation, pseudouridylation-dependent selective translation defects, and impaired T-cell-mediated immune surveillance - through which dyskerin dysfunction may promote carcinogenesis in the context of DC. Furthermore, we specifically address ongoing controversies regarding the relative contributions of tumor-intrinsic genomic instability versus systemic immunodeficiency to cancer development and seek to delineate these mechanisms based on emerging evidence. Through this integrative framework, we aim to provide a clearer conceptual basis for understanding DC-associated cancer pathogenesis (**Figure 2**) and to inform future efforts in risk stratification and the development of targeted preventive and therapeutic strategies.

Carcinogenic mechanisms associated with dyskerin dysfunction

Telomerase dysfunction

As a component of the telomerase holoenzyme complex, dyskerin binds specific H/ACA RNAs, most notably the TERC [39]. Dyskerin plays a critical role in regulating TERC accumulation and stability, thereby contributing to the maintenance of telomerase activity [36]. In patients

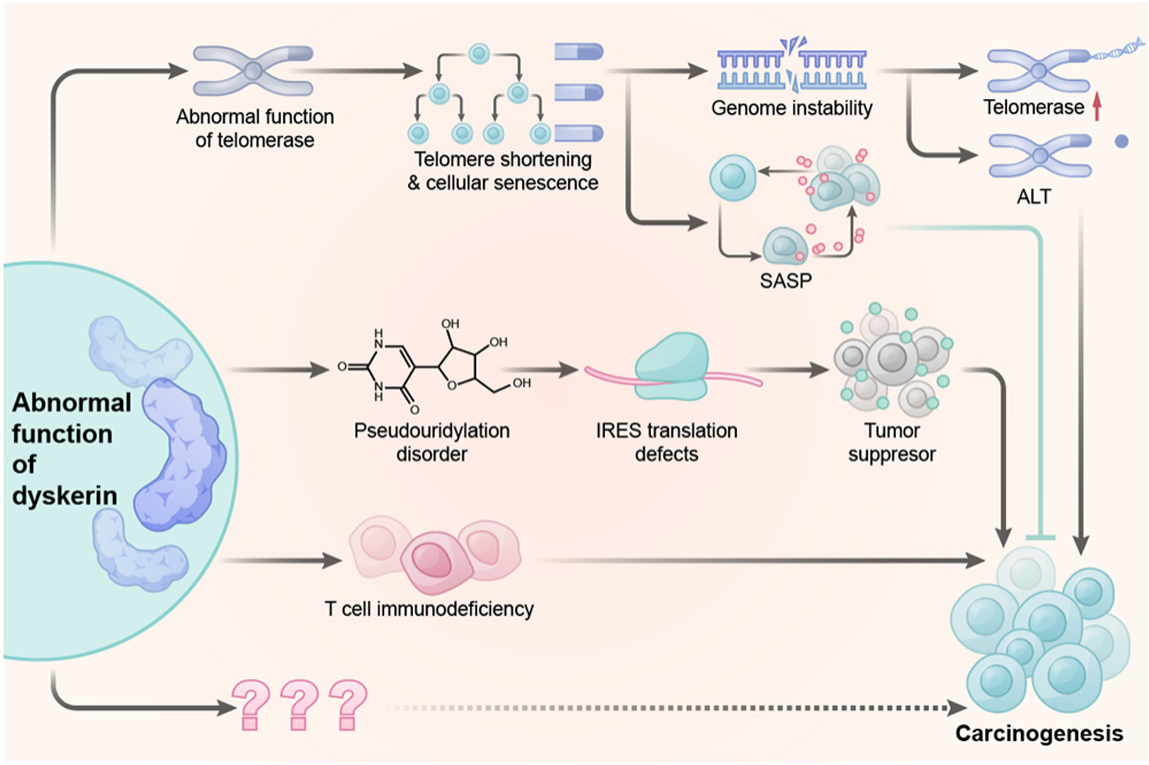

Figure 2. Carcinogenic mechanisms of dyskerin dysfunction. Dyskerin is involved in various cellular processes, and its functional abnormalities can promote tumor formation and cancer progression through telomerase dysfunction, dysregulation of RNA pseudouridylation, T-cell immunodeficiency, and other pathways that remain unclear or unknown.

with X-linked DC, mutations in the DKC1 gene result in dyskerin dysfunction, leading to reduced telomerase activity and progressive telomere shortening. When telomeres erode to a critical length, cells typically undergo replicative senescence or apoptosis [40].

Genomic instability: Excessive telomere shortening may give rise to genomic instability in a subset of cells, primarily as a consequence of telomere-telomere fusion and chromosome breakage during cell division [41, 42]. Under such conditions, cells may attempt to circumvent the detrimental consequences of telomere attrition by upregulating factors such as RB, TP53, or telomerase itself [43, 44]. Genomic instability is a hallmark of cancer and promotes tumor heterogeneity, facilitates cellular adaptation to stress, and ultimately contributes to malignant behavior and therapeutic resistance. The acquisition of oncogenic driver mutations and the inactivation of DNA repair genes represent early events in malignant transformation and constitute core mechanisms of tumorigenesis [45]. More than 75% of human cancers maintain telomere length (TL) through telomerase upregulation, thereby enabling continued proliferation [46]. In contrast, other malignancies - particularly those of mesenchymal origin, such as sarcomas - extend telomeres in the absence of telomerase via recombination-based alternative lengthening of telomeres(ALT) pathways [43, 44]. Both mechanisms facilitate the accumulation of somatic mutations, ultimately leading to uncontrolled cell division and tumor formation (**Figure 3**). Consistent with these observations, mouse models have demonstrated that telomere shortening can drive genomic instability through end-to-end chromosome fusions [47], and increased chromosomal rearrangements and mutation rates have also been observed in telomerase-deficient yeast [48].

Because of the intrinsic limitations of DNA replication, linear DNA molecules cannot be fully replicated, resulting in progressive telomere shortening with each round of cell division and

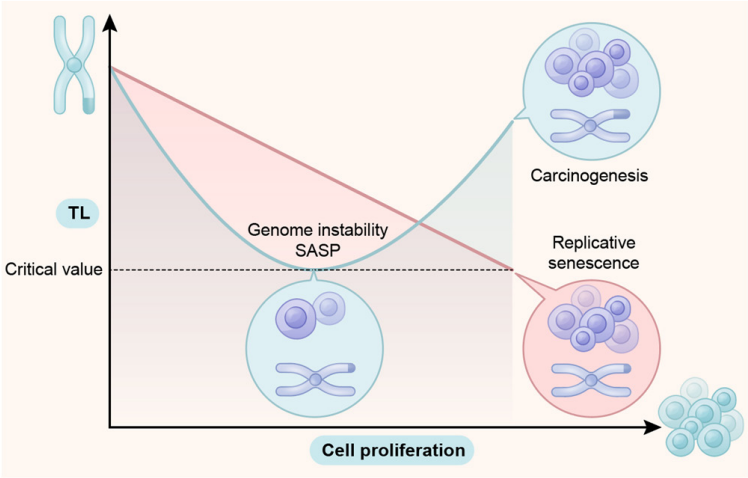

Figure 3. Abnormal elongation of telomere length. Normally, as cells proliferate, telomere length gradually shortens, and when telomere length reaches a critical threshold, apoptosis occurs. However, when telomeres are excessively short, some cells may experience genomic instability, leading to the ongoing accumulation of mutations and resulting in abnormal telomere elongation, which in turn causes uncontrolled cell division and carcinogenesis.

thereby imposing a replicative limit on normal somatic cells [49]. At the 3' end of double-stranded telomeric repeats, a G-rich single-stranded overhang of approximately 100-300 base pairs is formed, which folds back and invades adjacent telomeric repeats to generate a branched structure known as the telomeric loop(t-loop) [50]. With continued cell proliferation, the binding of protective proteins and the formation of t-loops become progressively compromised. This loss of telomere protection leads to telomere dysfunction and ultimately triggers cellular senescence or apoptosis [44]. Telomere maintenance mechanisms (TMMs) confer replicative immortality to cancer cells [44]. TMMs can be broadly categorized into two types: telomerase-dependent mechanisms, primarily mediated by the TERT [51, 52], and telomerase-independent mechanisms that rely on homologous recombination repair (HDR), collectively referred to as the ALT pathway [53, 54].

ALT is a recombination-based telomere maintenance mechanism analogous to break-induced replication (BIR) [55], enabling telomere elongation through HDR in the absence of telomerase. ALT activity is detected in approximately 10%-15% of human cancers and is often associated with poorer clinical outcomes [56]. Accordingly, ALT-positive cells are capable of maintaining telomeres without telomerase activity. Due to extensive homologous recombination (HR), ALT-positive cells exhibit pronounced telomere length heterogeneity and an increased frequency of telomeric sister chromatid exchange events [56]. Activation of the ALT mechanism involves a transition of telomeres into a recombination-prone state, which is closely linked to alterations in telomeric chromatin structure and elevated replication stress [44]. ALT telomeres display high levels of replication stress and DNA damage [57], attributable to disorganized chromatin architecture, telomeric sequence variants, and aberrant protein binding [58, 59]. If such stress cannot be alleviated through replication fork reversal and restart, replication fork stalling may be exacerbated, resulting in double-strand breaks (DSBs). Subsequently, DSB ends promote homology-directed search, allowing single-stranded DNA to invade homologous double-stranded DNA and complete telomere synthesis through BIR-like mechanisms [60-63].

Senescence-associated secretory phenotype: In cancer biology, cellular senescence represents a double-edged sword. During the early stages of tumorigenesis, senescent cancer cells can be eliminated through activation of the adaptive immune system [64]. Senescent cells undergo characteristic morphological changes, chromatin remodeling, and metabolic reprogramming, while simultaneously secreting a complex mixture of pro-inflammatory factors collectively termed the senescence-associated secretory phenotype (SASP) [65, 66]. SASP plays a critical role in cancer initiation and progression [64, 67, 68]. Accumulating evidence indicates that alterations in the secretory activity of senescent cells can modulate the tissue microenvironment, weaken control over cellular behavior, and promote tumorigenesis [69].

SASP comprises a broad array of factors secreted by senescent cells, including cytokines, che-

mokines, extracellular matrix proteases, growth factors, and other signaling molecules [70]. Senescent cells can influence neighboring cells through multiple mechanisms, such as juxtacrine NOTCH/JAG1 signaling [71], increased production of reactive oxygen species (ROS) [72, 73], or transfer via cytoplasmic bridges and extracellular vesicles, including exosomes [73, 74]. In vitro, SASP reinforces senescence-associated growth arrest through autocrine positive feedback loops. Indeed, downregulation of IL-6R, insulin-like growth factor binding protein 7 (IGFBP7), or IL-8 and its associated chemokine receptor CXCR2 can prevent the establishment of senescence [74, 75]. This autocrine circuitry contributes to the tumor-suppressive effects of senescence. Notably, SASP can also induce senescence in neighboring non-malignant proliferating cells, a phenomenon known as paracrine senescence [76, 77], suggesting that senescent cells may enhance antitumor responses by limiting the proliferation of adjacent cells within the same microenvironment.

Conversely, senescence-associated secretory programs may also promote tumor development. A substantial body of evidence from animal models demonstrates that selective elimination of senescent cells significantly improves healthspan in mice and ameliorates outcomes in age-related diseases as well as responses to cancer therapy [78-83]. SASP is inherently pro-inflammatory, and inflammatory mediators are well-recognized drivers of tumor progression. Early studies showed that SASP secreted by senescent fibroblasts promotes the proliferation and invasion of premalignant epithelial cells and enhances vascularization of xenograft tumors [69, 84]. Similarly, SASP derived from senescent hepatic stellate cells has been shown to promote proliferation and malignant transformation of neighboring hepatocytes in obese mice exposed to chemical carcinogens [85]. Importantly, senescence-associated secretory factors mediate the deleterious effects of senescent cell accumulation during chemotherapy in vivo, and clearance of senescent cells in this context can prevent tumor recurrence [81].

The interplay between SASP and immune responses is complex and context dependent. On the one hand, SASP is initially thought to facilitate immune-mediated clearance of senescent cells. During early tumorigenesis, SASP-dependent recruitment of Th1 cells, natural killer (NK) cells, and macrophages is critical for eliminating early premalignant cells and restraining the progression of hepatocellular carcinoma (HCC) [64, 86]. On the other hand, SASP may exert immunosuppressive effects under certain conditions [87-89]. For example, Eggert et al. reported that when premalignant senescent hepatocytes coexist with hepatocellular carcinoma cells, SASP-dependent recruitment of immature myeloid cells impairs NK cell function and thereby promotes HCC progression, highlighting the multifaceted interactions among SASP, immune cells, and cancer development [90].

Taken together, these findings support a model in which DKC1 mutations lead to reduced telomerase activity and progressive telomere shortening, thereby inducing genomic instability and cellular senescence, which may ultimately contribute to carcinogenesis.

Defective translational regulation: selective effects on IRES-dependent transcripts and potential biomarkers

Although the clinical manifestations of DC have long been primarily attributed to defects in telomere maintenance, accumulating evidence indicates that abnormalities in RNA pseudouridylation caused by DKC1 dysfunction, and the resulting defects in selective translation, exert an independent contribution to cancer susceptibility [35, 91, 92]. As the core component of the H/ACA ribonucleoprotein complex, dyskerin catalyzes pseudouridylation at multiple sites within rRNA, a process that is essential for ribosomal conformational stability and efficient assembly of the translation initiation complex [93, 94]. Impairment of DKC1 function reduces rRNA pseudouridylation levels, thereby weakening ribosome-mRNA and ribosome-tRNA interactions and reshaping selective translational output [95].

A consistent finding across multiple DKC1 mutant models and cells derived from patients with X-linked DC is that DKC1 deficiency does not cause global translational repression. Instead, it preferentially affects transcripts that rely on IRESs for translation initiation [96, 97]. In these contexts, IRES-dependent translation

is selectively compromised, whereas cap-dependent translation is relatively preserved under basal conditions [86, 97]. Affected transcripts include key tumor suppressors (such as p53 and p27) as well as survival-associated factors (including XIAP and Bcl-xL) [97-100]. Bellodi et al. further demonstrated that insufficient DKC1-dependent rRNA pseudouridylation interferes with pre-initiation complex assembly and limits ribosome loading onto IRES-rich transcripts, such as p27 [99].

IRES-dependent translation becomes particularly critical under cellular stress conditions, including hypoxia, DNA damage, and cell cycle arrest, during which cap-dependent translation is broadly suppressed [101, 102]. Consequently, in the setting of DKC1 deficiency, cells may fail to appropriately upregulate essential tumor suppressor proteins in response to stress or genotoxic insults, thereby facilitating checkpoint escape and conferring a survival advantage [98]. Notably, these translational defects can arise prior to overt telomere shortening, suggesting that impaired IRES-dependent translation may represent an early pathogenic event in DC-associated tumorigenesis [97].

At the mechanistic level, recent studies have revealed that DKC1-mediated regulation of IRES-dependent translation is both transcript-specific and context dependent. Gupta et al. systematically characterized a MYC/MYCN-activated DKC1-hnRNP A1 axis, in which dyskerin maintains the translation of hnRNP A1 by catalyzing pseudouridylation at specific sites within 28S rRNA (Ψ4331 and Ψ4966). This, in turn, enhances IRES-dependent translation and amplifies ATF4-driven metabolic adaptation and the integrated stress response [96]. Importantly, ribosomes isolated from familial DC patients exhibit significantly reduced pseudouridylation at these sites [103], providing direct evidence for the relevance of this mechanism in human disease. These findings support the concept of “specialized ribosomes”, whereby ribosomal modification states determine translational preferences for subsets of mRNAs harboring regulatory elements such as IRESs or upstream open reading frames (uORFs) [104-106].

Consistent with this model, regulation of IRES-dependent translation is not uniformly suppressive. Rocchi et al. reported that DKC1 knockdown in breast cancer cells enhances IRES-dependent translation of VEGF mRNA and promotes an invasive phenotype [107], indicating that defects in dyskerin-mediated rRNA pseudouridylation may exert directionally distinct effects on different IRES elements [107]. From a tumor-suppressive perspective, Bellodi et al. further demonstrated that loss of DKC1 function directly promotes tumorigenesis by disrupting IRES-dependent translation of p27. In both animal models and human pituitary adenomas, DKC1 abnormalities were associated with reduced p27 protein levels [86]. Collectively, these observations indicate that dyskerin-mediated translational control constitutes a substantive tumor-suppressive barrier.

From a methodological and translational perspective, ribosome profiling and high-throughput Ψ mapping represent powerful tools for dissecting selective translational alterations associated with DKC1 dysfunction. However, in human samples and disease models of dyskeratosis congenita or DKC1 deficiency, integrated, system-level studies jointly interrogating selective translation and Ψ landscapes remain limited. Current evidence is therefore largely derived from analyses of alterations at specific rRNA Ψ sites and validation of impaired translation of key IRES-dependent transcripts [108, 109]. Accordingly, rRNA pseudouridylation signatures, together with reduced protein - but not transcript - levels of IRES-dependent tumor suppressors such as p53 and p27, may serve as candidate biomarkers for evaluating dyskerin functional status and cancer risk [98, 99]. Given that distinct IRES-containing transcripts may be regulated in opposite directions (e.g., p27/p53 versus ATF4/VEGF) [86, 96, 107], future studies in genetically stratified cohorts of DC and short telomere syndrome patients that integrate rRNA Ψ profiling with assessment of key IRES-dependent proteins may enable the development of more actionable strategies for risk stratification and longitudinal monitoring.

T-Lymphocyte immunodeficiency

Although telomere shortening can lead to end-to-end chromosome fusion and genomic instability and is widely regarded as an important facilitating factor in tumorigenesis [41, 42, 88,

110-112], increasing evidence suggests that impaired host immune surveillance - particularly T-lymphocyte immunodeficiency - may play a more fundamental role in shaping cancer susceptibility in DC and related short telomere syndromes [113-115]. This perspective does not negate the pathogenic significance of telomere dysfunction but rather emphasizes the central position of immune impairment within the natural history of DC.

Findings from clinical registries and long-term follow-up studies indicate that the tumor spectrum observed in patients with short telomere syndromes more closely resembles that seen in states of immunodeficiency than that typically driven by pronounced genomic instability [91]. For example, the markedly increased incidence of solid tumors such as head and neck squamous cell carcinoma in these patients parallels patterns observed in chronically immunosuppressed organ transplant recipients or individuals with HIV/AIDS [2]. At the time of cancer diagnosis, most patients already exhibit overt immune abnormalities, including reduced T-lymphocyte counts, restricted T-cell receptor repertoires, and functional T-cell exhaustion [2]. It should be noted, however, that many of these cohort studies are derived from referral populations, and their interpretation must take into account potential confounding factors such as selection bias, prior therapeutic interventions (e.g., hematopoietic stem cell transplantation), and the use of immunosuppressive agents.

In contrast, direct evidence supporting a dominant role for tumor-intrinsic genomic instability in DC-associated solid tumors remains limited. Although telomere shortening is theoretically expected to increase the likelihood of chromosomal abnormalities, existing studies have not systematically demonstrated that DC-associated solid tumors universally harbor highly complex chromosomal rearrangements or markedly elevated mutational burdens. Consequently, the available tumor genomic data are insufficient to support a unifying model in which genomic instability serves as the primary driver of carcinogenesis in DC [2]. This notion is further supported by animal studies showing that, in telomerase-deficient mice engineered to possess telomere lengths comparable to those of humans, telomere shortening alone does not spontaneously confer a strong cancer predisposition [116, 117].

Importantly, a substantial body of clinical and experimental evidence indicates that immunodeficiency in DC and related short telomere syndromes can arise as an early event, in some cases preceding the development of classic clinical features [2, 118]. Case reports describe patients who initially present in childhood with isolated humoral immunodeficiency and are diagnosed with common variable immunodeficiency (CVID), while the characteristic mucocutaneous manifestations and other features of DC emerge only years later [118]. These observations suggest that immune dysfunction is not merely a secondary consequence of DC but may constitute an early and integral component of its disease trajectory.

Systematic reviews and registry-based analyses further support this conclusion. Patients with DC and related phenotypes exhibit a broad spectrum of immunological abnormalities, including dysregulated immunoglobulin levels, reduced B-cell and/or NK cell populations, and varying degrees of quantitative and functional T-lymphocyte impairment. Notably, these abnormalities can occur in the absence of overt bone marrow failure [119]. Immunodeficiency is particularly pronounced in severe phenotypes such as Hoyeraal-Hreidarsson syndrome or Revesz syndrome, as well as in specific genetic subtypes, including variants in DKC1, RTEL1, and TINF2 [2, 120].

Further cohort studies have explicitly characterized short telomere syndromes as primary T-lymphocyte immunodeficiency disorders. In this context, carriers of telomerase gene mutations may develop severe immunodeficiency in adulthood - often characterized by marked $CD4^+$ T-cell depletion - even in the absence of bone marrow failure, and experience a high incidence of potentially fatal opportunistic infections [115]. Notably, in some patients, opportunistic infections precede the onset of bone marrow failure or other canonical DC manifestations [115], underscoring the fundamental role of disrupted T-cell homeostasis in disease progression.

Taken together, these observations allow the formulation of testable predictions to further distinguish the relative contributions of immu-

nodeficiency and genomic instability to DC-associated tumorigenesis. If impaired immune surveillance is the dominant driver, DC-associated head and neck squamous cell carcinomas would be expected to exhibit relatively modest mutational burdens accompanied by reduced numbers or functional impairment of tumor-infiltrating T lymphocytes. Conversely, if genomic instability predominates, one would anticipate widespread chromosomal abnormalities and highly unstable tumor genomic architectures. Future integrative studies combining tumor genomics, immune microenvironment profiling, and detailed immunophenotyping of patients will be essential to resolve this issue.

Other possible mechanisms

An increasing body of evidence suggests that telomere dysfunction alone may be insufficient to fully account for the phenotypic spectrum of X-linked DC [121-124]. In our preliminary studies using OSCC cell lines overexpressing mutant DKC1, we observed a marked upregulation of SOX2 expression accompanied by enhanced tumor sphere-forming capacity (unpublished data). These findings raise the possibility that dyskerin dysfunction may promote OSCC progression, at least in part, through activation of SOX2-dependent pathways.

Extensive studies have demonstrated that SOX2 gene amplification and overexpression contribute to cancer progression [125-127], including in OSCC, breast cancer, colorectal cancer, and hepatocellular carcinoma, and that elevated SOX2 levels are associated with poor clinical outcomes [128]. SOX2 regulates a wide range of cancer cell properties, including proliferation, epithelial-mesenchymal transition (EMT), migration, invasion, metastasis, sphere and colony formation, tumor initiation, cancer stem cell (CSC) formation, as well as apoptosis resistance and drug tolerance [125, 129-131]. Given that CSCs share self-renewal capacity with normal stem cells and that SOX2 is a central regulator of pluripotency, numerous studies have implicated SOX2 in CSC regulation. For example, SOX2 cooperates with protein kinase C iota (PKCι) to induce and maintain interactions between stem cells and their microenvironment [108]. SOX2 also promotes EMT by activating the transcription of Snail, Slug, and Twist, while repressing epithelial markers such as E-cadherin and ZO-1 [132-134].

While the majority of studies support a protumorigenic role for SOX2, context-dependent effects have also been reported. In gastric cancer, for instance, SOX2 expression has been found to be lower than in normal gastric mucosa. Otsubo et al. demonstrated that SOX2 can inhibit gastric cancer cell proliferation by inducing proliferation of normal cells, thereby leading to cell cycle arrest [21]. Another study showed that SOX2 suppresses migratory and invasive potential in gastric cancer cells through upregulation of p21 [135]. These findings underscore the complex and context-specific functions of SOX2 in tumorigenesis and highlight the need for further mechanistic investigation.

Taken together, dyskerin dysfunction caused by DKC1 mutations likely shapes cancer susceptibility in DC and related short telomere syndromes through multiple, interrelated mechanisms. Disruption of telomere homeostasis and imbalances in selective translation create a permissive background characterized by impaired tissue renewal and attenuated tumor suppressive responses. In contrast, clinical evidence more consistently supports the notion that impaired T-lymphocyte-mediated immune surveillance emerges prior to, or independently of, overt tumor-intrinsic chromosomal instability in short telomere syndrome-associated solid tumors, particularly head and neck squamous cell carcinoma. In addition, dyskerin dysfunction may further amplify oncogenic risk in specific tissue contexts by aberrantly activating stemness-associated pathways, such as SOX2 signaling, thereby reprogramming tumor cell plasticity and adaptive phenotypes.

Discussion and outlook

An intriguing paradox has been noted in DC, wherein reduced cellular proliferative capacity coexists with an increased susceptibility to cancer [123]. Defects in telomerase function and ribosome biogenesis are sufficient to account for impaired proliferation. Proliferating cells require enhanced protein synthesis to meet increased biosynthetic demands, which in turn necessitates robust ribosome biogenesis [136]. Accordingly, cells with impaired or slowed ribosome production - such as those with dyskerin dysfunction - generally exhibit

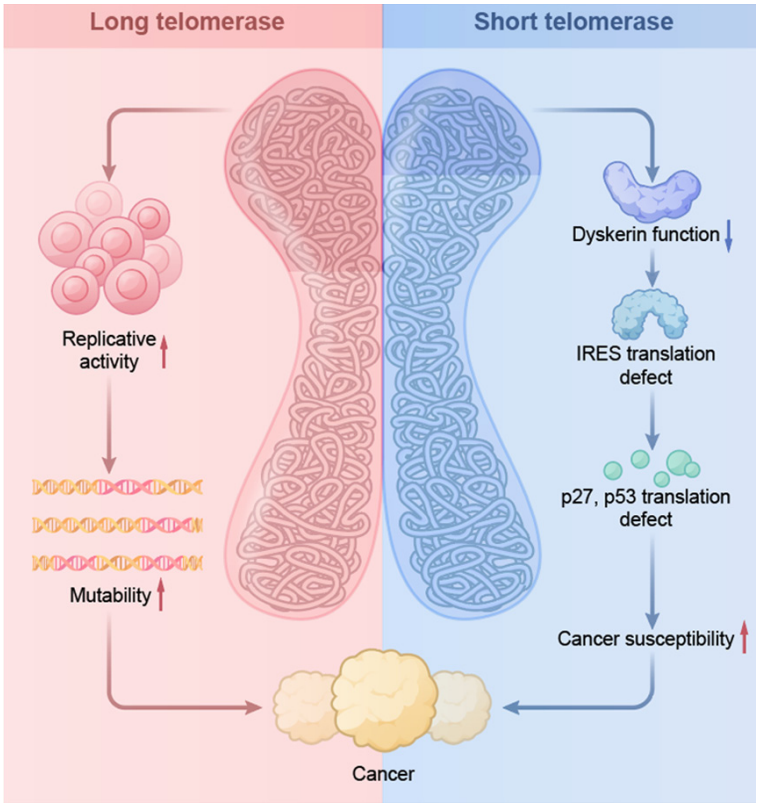

Figure 4. The "paradox" of dyskeratosis congenita - reduced cell proliferation and increased cancer susceptibility. Telomere length plays a "double-edged sword" role in cancer development, with both excessively long and excessively short telomeres potentially leading to uncontrolled cell division and tumor formation.

reduced proliferative capacity [137]. From this perspective, dyskerin dysfunction in X-linked DC may restrict self-renewal in highly regenerative and unstable tissues. Paradoxically, however, patients with DC display a markedly increased risk of malignancy.

Telomeres exert dual roles in carcinogenesis, with both excessively short and excessively long telomeres being associated with cancer development [40, 51, 138]. Cells harboring longer telomeres possess enhanced proliferative potential, as they typically lack telomere length-dependent signals that trigger senescence or apoptosis, thereby permitting sustained cell division and increasing the opportunity for accumulation of oncogenic DNA mutations [128]. The contribution of short telomeres to tumorigenesis has been discussed above. Beyond its role in maintaining telomerase activity and telomere stability, dyskerin also mediates post-transcriptional rRNA modification, a function that is increasingly recognized as being critical for tumor suppression. When dyskerin function is compromised, defects in IRES-dependent translation attenuate the synthesis of key tumor suppressive and survival-associated proteins, including p27, p53, and the anti-apoptotic factors XIAP and Bcl-xL, thereby contributing to increased cancer susceptibility (**Figure 4**).

DC is a multisystem disorder, with BMF occurring in approximately 80%-90% of patients and representing the leading cause of mortality [139, 140]. Pulmonary fibrosis and malignant transformation constitute additional severe complications during disease progression. At present, management of DC and related short telomere syndromes remains largely supportive and symptom oriented, with a primary focus on addressing hematopoietic failure and severe immunodeficiency rather than correcting the underlying molecular defects. Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only intervention capable of reversing BMF and partially restoring immune function. However, HSCT does not correct telomere-associated multisystem abnormalities, and both transplant-related mortality and long-term complication rates are substantially higher in DC than in other inherited BMF syndromes [2]. In recent years, fludarabine-based reduced-intensity conditioning regimens have improved transplant outcomes to some extent, yet pulmonary complications and secondary malignancies remain major limiting factors [141].

For patients who are not candidates for transplantation or prior to HSCT, androgen therapy - such as danazol - has been widely employed to improve peripheral blood counts, potentially through indirect enhancement of telomerase activity [142, 143]. Nevertheless, this approach remains supportive rather than curative, as it neither halts progressive telomere shortening nor reduces long-term cancer risk. Looking for-

ward, emerging therapeutic strategies may include TERC supplementation and telomerase activation, senescent cell clearance or senescence-modulating approaches, and interventions targeting translational control pathways. Rigorous evaluation of these strategies will require careful consideration of genotype-specific effects, long-term safety - particularly oncogenic risk - and clinically meaningful endpoints in well-stratified patient cohorts.

TERC supplementation and telomerase activation

Level of evidence: preclinical studies with limited human cell-based or case observations.

Multiple studies have demonstrated that exogenous supplementation of the TERC can restore telomerase activity and elongate telomeres in cells harboring DKC1 or TERC mutations [2, 135, 144, 145]. In addition, inhibition of PAPD5 stabilizes mature TERC levels and has been shown to improve hematopoietic function in cellular and animal models, highlighting a potentially promising molecularly targeted strategy [145, 146]. However, telomerase activation is intrinsically associated with oncogenic risk, particularly in patients with DC, who already exhibit a heightened predisposition to malignancy. Accordingly, future clinical investigations should place particular emphasis on long-term cancer incidence, genotype-specific risk stratification (e.g., DKC1 versus TERT/TERC mutations), and careful control of treatment timing and dosing.

Senescent cell clearance and senescence modulation (senolytics/senomorphics)

Level of evidence: preclinical studies.

Telomere dysfunction induces cellular senescence and promotes the development of a pro-inflammatory SASP, which plays an important role in tissue dysfunction and remodeling of the tumor microenvironment [147, 148]. In animal models, selective elimination of senescent cells has been shown to improve multisystem function and delay disease progression [110]. Although this strategy may theoretically alleviate systemic manifestations of DC, its safety in immunocompromised populations remains uncertain. Moreover, senescence also exerts tumor-suppressive effects during the early stages of carcinogenesis, raising concerns that indiscriminate senescent cell clearance could compromise these protective mechanisms. At present, senolytic and senomorphic approaches in DC remain confined to mechanistic exploration rather than clinical application.

Targeting translational regulation (modulation of IRES-dependent translation)

Level of evidence: mechanistic studies.

Abnormal rRNA pseudouridylation resulting from DKC1 dysfunction selectively affects IRES-dependent translation and thereby attenuates the expression of key tumor suppressors such as p53 and p27 [86, 96, 105, 149]. While this mechanism provides an important conceptual framework for understanding cancer susceptibility in DC, there are currently no established clinical interventions capable of specifically modulating this translational pathway. Translation of these insights into therapeutic strategies will require deeper mechanistic studies and the identification of robust biomarkers to enable patient stratification and treatment monitoring.

Overall considerations for future clinical studies

Based on the available evidence, future clinical trials in DC and related short telomere syndromes should prioritize: (i) clear delineation of evidence levels and rigorous assessment of risk-benefit ratios to avoid premature clinical implementation; (ii) stratified trial designs according to genotype and inheritance pattern (e.g., DKC1 versus TERT/TERC); and (iii) selection of clinically meaningful endpoints focused on long-term safety, cancer incidence, and immune function, rather than hematologic improvement alone. Only through careful integration of evidence strength, genetic background, immune status, and cancer risk into a unified evaluative framework can these emerging interventions be translated into safe, reproducible, and clinically meaningful applications.

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Disclosure of conflict of interest

None.

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