REVIEW

The significance of CUX1 and chromosome 7 in myeloid malignancies

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Purpose of review

Loss of chromosome 7 has long been associated with adverse-risk myeloid malignancy. In the last decade, *CUX1* has been identified as a critical tumor suppressor gene (TSG) located within a commonly deleted segment of chromosome arm 7q. Additional genes encoded on 7q have also been identified as bona fide myeloid tumor suppressors, further implicating chromosome 7 deletions in disease pathogenesis. This review will discuss the clinical implications of del(7q) and *CUX1* mutations, both in disease and clonal hematopoiesis, and synthesize recent literature on *CUX1* and other chromosome 7 TSGs.

Recent findings

Two major studies, including a new mouse model, have been published that support a role for *CUX1* inactivation in the development of myeloid neoplasms. Additional recent studies describe the cellular and hematopoietic effects from loss of the 7q genes *LUC7L2* and *KMT2C/MLL3*, and the implications of chromosome 7 deletions in clonal hematopoiesis.

Summary

Mounting evidence supports *CUX1* as being a key chromosome 7 TSG. As 7q encodes additional myeloid regulators and tumor suppressors, improved models of chromosome loss are needed to interrogate combinatorial loss of these critical 7q genes.

Keywords

7q, contiguous gene syndrome, CUX1, monosomy 7, myeloid neoplasia

INTRODUCTION

Loss of all or part of chromosome 7 [-7/del(7q)] is among the most common chromosomal abnormalities in high-risk myeloid disease [1]. The high frequency of -7/del(7q) suggests chromosome 7 harbors tumor suppressor genes (TSGs) important to disease pathogenesis, and -7/del(7q) has therefore been the subject of intense investigation. However, a major challenge in the identification of candidate tumor suppressors is the lack of recurrent second-hit mutations on the remaining allele [2,3]. These observations suggest that chromosome 7 TSGs likely act in a haploinsufficient manner, whereby single-copy loss of a gene produces a mutant phenotype, in contrast to Knudson's classical two-hit hypothesis of tumor suppressors [4].

In an alternative attempt to map candidate TSGs, minimally deleted regions (MDR) have been identified at the cytogenetic bands 7q22, 7q34, and 7q35–36 by aligning commonly deleted segments of 7q [2,3]. In 2013, *CUX1* was identified as one of the most significantly differentially expressed genes within the 7q22 MDR in -7/del(7q) leukemias, with ~50% expression compared to cases with both copies of *CUX1* [5]. CUX1 is a nonclustered homeobox transcription factor, and knockdown of the ortholog of *CUX1* in *Drosophila melanogaster* leads to myeloid cell hyperplasia [5]. In addition to *CUX1*, 7q contains multiple additional TSGs and myeloid regulators (Table 1) [6,7▪,8–12,13▪,14,15,16▪,17,18▪▪,19–21,22▪,23–52,53▪,54▪,55–58,59▪,60–64,65▪,66▪▪,64–71,72▪,73▪▪,74–77]. In this review we focus on recent findings regarding *CUX1* and other 7q-encoded genes, including the splicing factor *LUC7L2* and the histone lysine methyltransferase *KMT2C/MLL3*. We discuss chromosome 7 deletions in clonal hematopoiesis of indeterminate potential (CHIP),

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KEY POINTS

- Chromosome 7 alterations are early, driving events in myeloid disease pathogenesis.
- *CUX1* mutations also occur early in myeloid disease, and sustained CUX1 loss is necessary for disease maintenance.
- Chromosome arm 7q encodes multiple myeloid TSGs and regulators, suggesting the existence of contiguous gene syndrome region(s).

briefly review approaches to model del(7q), and endorse the concept of 7q as a contiguous gene syndrome (CGS) region in which combined loss of multiple dose-sensitive TSGs contributes to disease.

CLINICAL FEATURES AND IMPLICATIONS OF -7/del(7q)

Chromosome 7 alterations in hematologic malignancies are almost always deletions or copy-neutral loss of heterozygosity (LOH), in contrast to solid tumors where amplifications are observed [78]. -7/del(7q) occurs in a wide range of myeloid diseases, including 5–10% of acute myeloid leukemias (AML) and adult myelodysplastic syndromes (MDS), 40% of pediatric MDS, 40% of myeloid neoplasms arising from cancer predisposition syndromes, and 50% of therapy-related myeloid neoplasms (t-MN) [9,79–81]. -7/del(7q) is associated with higher-risk MDS, faster time to transformation to AML, and poor overall survival in AML, and is therefore considered an adverse prognostic event [3,79]. Within these diseases, chromosome 7 deletions often co-occur with 5q deletions and gains of chromosome 8, but also frequently occur as isolated cytogenetic events [9,79–81]. Together, these findings strongly suggest a role for chromosome 7 deletions in disease pathogenesis.

A major unanswered question is to what degree −7/del(7q) influences disease initiation and pathogenesis. Analyses of clonal hierarchies in AML, t-MN, and CHIP suggest chromosome 7 alterations are early events [82–87]. In CHIP, seemingly healthy individuals with no history of hematologic malignancy harbor low-frequency alterations in genes associated with leukemia in their blood; these individuals are at an increased risk of development of a hematologic malignancy, but it remains unclear why only some individuals progress to disease [84]. Two recent studies by Gao *et al.* and Saiki *et al.* examined the combined landscape of somatic variants and copy number alterations in CHIP in large cohorts from Memorial Sloan Kettering and BioBank Japan, respectively [65▪,66▪▪]. Both studies identified chromosome 7 deletions and LOH at similar levels as previous CHIP studies [84–87]. Saiki *et al.* further found that individuals with del(7q) and 7q LOH had significantly increased risk for the development of hematologic malignancy, particularly myeloid disease [66▪▪]. The risks associated with chromosome 7 abnormalities were similar to those of 17p deletions or LOH, the chromosome arm encoding *TP53*, indicating that del(7q) is a biomarker for risk of disease progression that warrants close monitoring [66▪▪].

There is also evidence that -7/del(7q) functions as a driver event in disease. In a study of pediatric MDS, 30% of patients with -7/del(7q) had no other detectable cytogenetic or molecular abnormalities in the coding region of the genome [9]. Though it is possible that noncoding changes were present but not detected, it is compelling evidence that -7/del(7q) alone may be sufficient to promote MDS. Spontaneous remission of monosomy 7 has also been observed in children with MDS, albeit rarely, with subsequent resolution of disease, further suggesting -7 is critical for enabling the disease state [88]. In addition to occurring alone, -7/del(7q) can coexist with other somatic and karyotypic alterations, most commonly complex karyotypes or RAS pathway mutations [75,89]. Although RAS pathway mutations function as oncogenic drivers in a number of other cancer types, RAS pathway mutations typically arise late in AML development [79,90,91]. Additionally, RAS mutations are not typically observed in CHIP, and, in contrast to -7/del(7q), do not have prognostic impact in MDS and AML [65▪,66▪▪,92,93]. Therefore, even in the context of additional mutations, multiple lines of evidence point to -7/del(7q) as a driver of disease.

Cell extrinsic factors likely also influence cells with -7/del(7q). -7/del(7q) is found in up to 50% of t-MNs, second cancers arising after treatment for a primary malignancy, and is particularly associated with prior alkylating agent therapy [81]. -7/del(7q) is also found in hematopoietic cells of benzene-exposed workers as well as AML in elderly patients, which often resembles t-MNs [94,95]. These data suggest -7 may be selected for in the context of environmental exposures and aging, similar to *PPM1D* and *TP53* mutations promoting fitness during chemotherapy [96,97]. Identifying the mechanism by which loss of chromosome 7 genes increases fitness in response to different environmental pressures remains an outstanding question.

Whether the effects of -7 and del(7q) are equivalent remains an open question. Monosomy 7 and del(7q) are often grouped together clinically despite differing mechanisms of occurrence: monosomy 7 results from a chromosome segregation failure, whereas del(7q) results from chromosomal breakage

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Table 1. 7q genes implicated in myeloid disease based on clinical and experimental data

Gene name (location)	Cellular function	Cellular deletion phenotype	Hematopoietic murine deletion phenotype	CHIP gene?	Clinical Associations
SAMD9/SAMD9L (7q21.1)	Endosomal fusion protein, terminating surface receptor signaling [6]	Persistent cytokine receptor signaling and cytokine hypersensitivity [6]	Enhanced HSC colony-forming potential and *in vivo* reconstitution [6]	No	Germline activating mutations cause MIRAGE syndrome [8]
	Regulates protein synthesis rate [7■]	Gain of function mutations interfere with ribosome assembly in K562 cells [7■]	Late MDS in germline +/− and −/− mice [6]		Mutant allele lost through monosomy 7 via adaptation by aneuploidy [8–10]
ACHE (7q22.1) (CDR)	Hydrolyzes acetylcholine; associated with stress hematopoiesis [11]	Enhanced proliferation and decreased apoptosis in mouse bone marrow cultures [12]	Increased neutrophil cell number in +/− mice [14]	No	None reported
		Impaired erythroid differentiation in human CD34+ cells [13■]			
CUX1 (7q22.1) (CDR)	Homeobox transcription factor [15]	Enhanced proliferation, activation of PI3K-AKT signaling [17]	Mild monocytosis in shCux1^{mid} mice, increasing monocytosis and lethal anemia in shCux1^{low} mice [17]	Yes [19–21, 22■]	Significantly decreased expression in −7/del(7q) leukemias [5]
	Recruited to sites of DNA double strand breaks [16■]	Decreased apoptosis in hematopoietic progenitors [18■■]	Increased mean RBC volume in hematopoietic-specific +/− mice, monocytosis and anemia in −/− mice [18■■]		Inactivating mutations found in MDS, AML, and MDS/MPN overlap syndromes [23–25]
		Impaired DNA damage response [16■]	shCux1^{low} and −/− mice develop MDS/MPN-like disease [17,18■■]		Inactivating mutations associated with poor survival in MDS [24,25]
			shCux1^{low} mice treated with alkylating agents develop a rapid, fatal t-MN [16■]		
RASA4 (7q22.1) (CDR)	RAS GTPase-activating protein [26]	Elevated ERK phosphorylation in macrophages after FcγR stimulation [26]	No overt disease; germline −/− mice have impaired macrophage phagocytosis [26]	No	Promoter hypermethylation in JMML [27]
KMT2E (7q22.3)	Epigenetic regulator, capable of binding H3K4 methylation [28]	Cell cycle arrest in lung fibroblasts and HCT116 cells [29]	No overt disease; germline −/− mice have impaired neutrophil maturation, decreased RBC and hematocrit [31–33]	No	High expression associated with favorable outcome in cytogenetically normal AML [34]
	Reported catalytically inactive [28]	Increased ROS, impaired DNA damage response in +/− and −/− hematopoietic progenitors [30]	+/− mice have mild reduction in thymocytes and splenocyte, decreased RBC and hematocrit, increased RBC distribution width [14,32]		
DOCK4 (7q31.1)	GTPase activator [35,36]	RBC cytoskeletal defects, decreased erythroid colony formation in human CD34^{+} cells [35,36]	No reported hematopoietic phenotype in germline −/− mice [14,37]	No	Significantly decreased expression in MDS, associated with overall decreased survival in MDS [35,36]
MKLN1 (7q32.3)	Organization of F-actin networks [38,39]	Decreased retrograde intracellular transport in neurons [39]	No reported hematopoietic phenotype in germline +/− or −/− mice [39]	No	Associated with inherited predisposition for MPN [40]

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Table 1 (*Continued*)

Gene name (location)	Cellular function	Cellular deletion phenotype	Hematopoietic murine deletion phenotype	CHIP gene?	Clinical Associations
					Mutations observed in relapsed pediatric AML [41]
TRIM24 (7q33)	Nuclear receptor co-regulator; RING-domain E3 ubiquitin ligase [42,43]	Increased proliferation in human CD34+ cells [13▪]	Germline −/− mice develop hepatocellular carcinoma but have no hematopoietic phenotype [46]	No	High expression in AML reported, associated with poor survival [45]
	Targets p53 for degradation [44]	Decreased proliferation in AML-193 and Kasumi-1 cells [45]			*******Conflicting evidence for TRIM24 as hematopoietic oncogene or TSG*****
HIPK2 (7q34) (CDR)	Serine/threonine nuclear kinase [47–49]	Decreased p53 activation and apoptosis in MCF-7 cells [47]	No reported hematopoietic phenotype in germline −/− mice [14,51]	No	Low frequency missense mutations in MDS and AML [49]
	Phosphorylates p53 to activate apoptosis [47]	Decreased erythroid expansion and differentiation in human $CD34^+$ cells [50]			
		Increased cisplatin resistance in RKO colon cancer and H1299 lung cancer cell lines [48]			
LUC7L2 (7q34) (CDR)	Splicing factor, co-localizes with U1 snRNP [52,53▪,54▪]	Altered splicing in K562 and HeLa cells [53▪,54▪]	No overt disease; Increased platelet volume in germline +/− mice [14]	Yes [19,20, 22▪]	Heterozygous inactivating mutations observed in MDS and AML [52,56]
		Decreased expression of glycolysis genes; metabolic shift to OXPHOS in K562 and HeLa cells [53▪,54▪]	No reported hematopoietic phenotype in other germline −/− mice [55]		Decreased expression associated with reduced survival in MDS [52,56]
ATP6V0E2 (7q36.1) (CDR)	Intracellular proton pump [50]	Decrease erythroid expansion and differentiation in human $CD34^+$ cells [50]	None reported	No	None reported
CUL1 (7q36.1) (CDR)	E3 ubiquitin ligase; transcriptional repressor [57,58,59▪]	Increased transcription of c-MYC target genes in HeLa cells [59▪]	Germline −/− is embryonic lethal [57]	No	Rare mutations observed in myeloid neoplasms [52]
			Deletion in T-cell lineage yields T-cell lymphomas [58]		
EZH2 (7q36.1) (CDR)	Catalytic component of Polycomb Repressive Complex 2, places H3K27 methylation [60]	Decreased H3K27 methylation, partial compensation by EZH1 [61,62]	Conditional knockout mice observed up to 30 weeks do not develop myeloid disease [63]	Yes [19,20, 22▪,65▪, 66▪▪]	Mono-allelic and bi-allelic inactivating mutations observed in myeloid disease [3,67,68]
			Transplant recipients of $Ezh2^{-/-}$ cells develop mixed disease, including T-cell lymphoma and very late MDS [62,64]		Inactivating mutations associated with poor prognosis in MDS and drug resistance in AML [69,70]

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Table 1 (*Continued*)

Gene name (location)	Cellular function	Cellular deletion phenotype	Hematopoietic murine deletion phenotype	CHIP gene?	Clinical Associations
KMT2C [7q36.1] (CDR)	Core component of COMPASS complex, places H3K4 methylation [71]	Decreased H3K4me1 at some enhancer regions; compensation by KMT2D [73■■]	No overt disease; germline and hematopoietic-specific +/− and −/− mice have increased HSC number and self-renewal and splenomegaly [14,73■■]	No	Mutations observed in AML, possibly over-represented due to pseudogene [75–77]
	Recruited to sites of DNA double strand breaks [72■]	Decreased expression of DNA damage response genes after knockdown in HTB9 bladder cancer cells [74]	Mono-allelic knockout accelerates sh*Nf1*, *p53*$^{-/-}$ leukemogenesis [75]		Mutations observed in relapsed pediatric AML [41]
			Selective advantage in +/− and −/− HSCs after chemotherapy [73■■]		

+/−, heterozygous deletion; −/−, homozygous deletion; AML, acute myeloid leukemia; CHIP, clonal hematopoiesis of indeterminate potential; HSC, hematopoietic stem cell; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; OXPHOS, oxidative phosphorylation; RBC, red blood cell; t-MN, therapy-related myeloid neoplasm.
The cellular function, deletion phenotypes in cells and animal models, and clinical associations are provided with supporting references for 7q genes implicated in myeloid disease. Cell deletion phenotype is in hematopoietic cells unless otherwise specified.

[98]. Some studies have assessed -7 separately from del(7q) and report better prognosis for del(7q) in AML and MDS [99,100], though others have found no difference [101]. The concept that -7 is prognostically worse than del(7q) is perplexing as the majority of implicated chromosome 7 TSGs are located on 7q. Additionally, there is heterogeneity in the breakpoints for 7q deletions; whether different deletions spanning distinct genes carry unique prognostic implications remains unclear.

CUX1 MUTATIONS IN MYELOID DISEASE

CUX1, previously known as *CUTL1* and CCAAT displacement protein (*CDP*), is a ubiquitously expressed, nonclustered homeobox transcription factor that is both evolutionarily and functionally conserved from *Drosophila melanogaster* to humans. This review will focus on the role of *CUX1* mutations in myeloid disease; please see ref. [102] for the role of CUX1 in other models [102].

CUX1 is one of the few chromosome 7 genes that is recurrently mutated in cancer, with mutations identified in 2–4% of myeloid diseases including AML, MDS, and MDS/myeloproliferative neoplasms (MPN) [24,25]. *CUX1* is also mutated in 1–5% of various solid tumors [25]. *CUX1* mutation patterns fit a signature representative of TSGs, characterized by frameshift or nonsense alterations distributed throughout the coding frame [25,78,103] (Fig. 1). Further, bi-allelic *CUX1* mutations are rare, suggesting haploinsufficiency [24]. MDS and AML patients with inactivating *CUX1* mutations have decreased survival compared to those with wild type *CUX1*, with overall survival mirroring patients with -7/del(7q) [25]. Our lab has shown that *CUX1* knockdown in human CD34^{+} hematopoietic stem and progenitor cells results in a gene signature similar to patients with -7/del(7q) [17]. *CUX1* mutations have also been identified in CHIP, indicating *CUX1* inactivation can be an early event similar to -7/del(7q) [20,22■]. Collectively, the clinical data strongly implicate *CUX1* inactivation in myeloid disease development and support *CUX1* being a critical 7q TSG.

The cellular function of *CUX1* and the role of *CUX1* loss in myeloid malignancies is still under active exploration. Investigation of *CUX1* is complicated by the complexity of the locus. The *CUX1* gene is large, spanning 340 kilobases and 33 exons, with multiple RNA and protein isoforms [104]. Hematopoietic cells, however, only express the full-length p200 CUX1 protein [105■]. The p200 isoform contains four DNA-binding domains, consisting of three CUT-repeat domains and one homeodomain (Fig. 1) [106]. *CUX1* is further complicated by being

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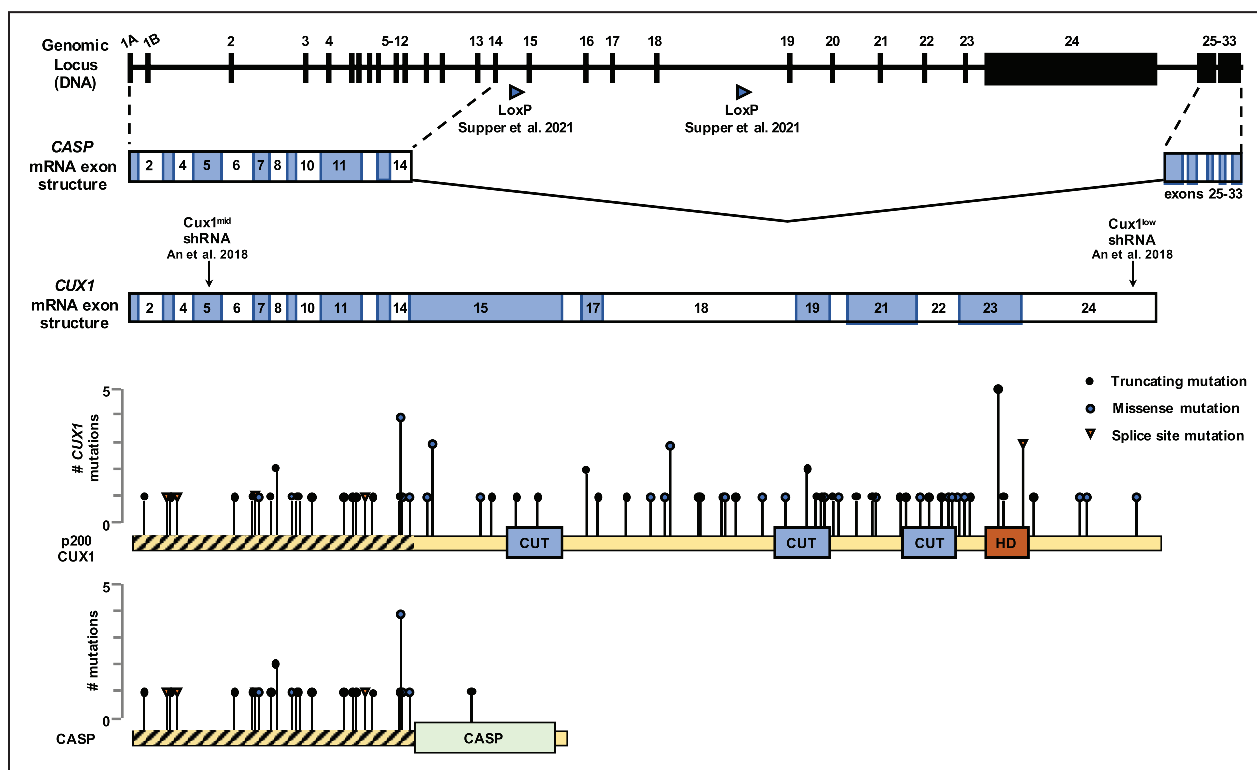

FIGURE 1. Structures of *CASP* and *CUX1*. The genomic locus of *CUX1* has two alternative start sites (exons 1A and 1B) and contains 33 exons which encode two gene products, *CUX1* and *CASP*. The locus organization is conserved between humans and mice. *CUX1* contains 24 exons; *CASP* is spliced from exons 1–14 and 25–33. The *CUX1* NM_181552 mRNA exon structure is shown with Cux1^{mid} and Cux1^{low} shRNA targeting locations from Ref. [17]; the LoxP Cre recombination sites from Ref. [18▪▪] are shown below the genomic locus. The p200 CUX1 protein is depicted below the exon structure with the 4 DNA binding domains depicted; exon length is drawn to scale to match the protein. Overlaid is a plot of *CUX1* mutations from AACR Project GENIE disease classes 'Leukemia', 'Myelodysplastic Syndromes', 'Myeloproliferative Neoplasms', and 'Myelodysplastic/Myeloproliferative Neoplasms' [Ref. [103]]. The distribution of mutations fits a pattern representative of tumor suppressor genes [Ref. [78]]. A plot of CASP is shown below CUX1; there is only a single mutation within the *CASP* exons not shared with *CUX1*. Regions shared by *CUX1* and *CASP* are hatched.

one of the few mammalian genes that shares exons with a second, independent gene, namely *CASP* (Cux1 Alternative Splice Product) [107]. Exons 15–24 are unique to *CUX1* and contain the four DNA-binding domains (Fig. 1). CASP does not have DNA-binding domains, nor is it located in the nucleus. Instead, CASP is a highly expressed Golgi-associated protein, thought to be involved in vesicle transport [108]. Unfortunately, *CASP* and *CUX1* isoforms are routinely aggregated in genomics datasets, such as RNA sequencing, making it a challenge to parse out independent roles of *CUX1* and *CASP*. Likewise, unless antibodies are carefully vetted for reactivity to either CUX1, CASP, or both, investigators can be misled by subsequent results [105▪].

Due in part to this complexity and the requirement for *Cux1* during development, the establishment of traditional *Cux1* knockout mice has been challenging [109]. To circumvent these issues, our lab developed inducible shRNA-based murine models for *Cux1* knockdown, reducing CUX1 protein levels to 54% (Cux1^{mid}) or 12% (Cux1^{low}) in thymocytes [17]. The Cux1^{mid} shRNA targets an exon shared by all *Cux1* and *Casp* transcripts and approximates CUX1 haploinsufficiency, whereas the Cux1^{low} model affects CUX1-encoding transcripts only (Fig. 1). Ubiquitous shRNA expression in Cux1^{mid} mice leads to a normocytic anemia and splenomegaly, whereas Cux1^{low} mice develop an MDS/MPN-like disease with fatal anemia, supporting the notion that *Cux1* is a dose-sensitive TSG [17]. These models further suggest the effects of mutations in shared exons can likely be attributed to CUX1 disruption and not CASP, as the disease caused by the Cux1^{low} shRNA (which does not target *Casp* mRNA) is more severe than that in the Cux1^{mid} mice (which does target *Casp* mRNA). Additionally, there are few reported mutations in exons unique to *CASP*, and there is currently no evidence *CASP* plays a role in human disease (Fig. 1) [103,108].

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Recently, Supper *et al.* reported a *Cux1* knockout model in which exons 15–18 were excised in the hematopoietic compartment driven by *Vav1-iCre* [18▪▪]. This approach, which avoids *Casp* isoforms, removes the first two DNA-binding domains and ablates protein expression in an allele-dependent manner in splenocytes. Similar to Cux1^{mid} mice, *Cux1*$^{+/-}$ mice develop mild anemia and bone marrow dysplasia [17,18▪▪]. This phenotype is exacerbated upon full *Cux1* loss, with *Cux1*$^{-/-}$ mice developing an MDS/MPN-like disease, akin to Cux1^{low} mice [17,18▪▪]. The authors further show *Cux1* loss cooperates with a *Flt3*$^{ITD/+}$ mutation to accelerate disease, though it is worth noting that *FLT3* mutations are not enriched in -7/del(7q) leukemias [18▪▪,89]. Still, this second model provides compelling evidence for the pathogenesis of *Cux1* loss in myeloid disease.

On a molecular level, CUX1 preferentially binds enhancer elements and acts as a transcriptional activator or repressor in a context-dependent manner [15,17,110]. Recently, our lab reported that *CUX1* loss also impacts the epigenetic landscape of cells, both basally and in the context of irradiation-induced DNA damage [16▪]. After irradiation, *CUX1*$^{-/-}$ cells show an impaired DNA damage response with decreased H3K27me2/3 and H3K9me2/3 at double-strand breaks, marks normally associated with DNA repair [16▪,111,112]. These changes indicate a novel epigenetic, nontranscriptional role for CUX1. Further, *Cux1*-deficient cells continue to proliferate after alkylating agent exposure, ultimately leading to alkylator-induced t-MN in *Cux1*-deficient mice [16▪]. Given the epidemiologic connection between -7/del(7q) t-MNs and alkylating agent chemotherapy, this study provides a missing mechanistic link between del(7q) and t-MN – ie. CUX1 is required for normal recognition and repair of chemotherapy-induced DNA damage [16▪,113▪]. Importantly, restoration of CUX1 levels postgenotoxic stress prevented transformation in this model, indicating that (i) sustained CUX1-deficiency is required for t-MN maintenance, and (ii) targeting putative negative regulators of *CUX1* may be a therapeutic avenue for myeloid disease with *CUX1* mutations or deletions [16▪]. The cellular functions of *CUX1* and consequences of *CUX1* loss are summarized in Fig. 2 [114].

7q AS A CONTIGUOUS GENE SYNDROME REGION

A CGS is a genetic disorder caused by large-scale chromosomal alterations affecting copy number, leading to dosage imbalance of multiple neighboring genes [115]. In addition to *CUX1*, multiple bona fide TSGs and myeloid regulators have been identified on 7q, many of which are also mutated in myeloid and solid tumors and yield hematopoietic phenotypes when deleted in mice (Table 1). We propose reframing chromosome 7 MDRs as CGS regions in cancer, similar to those observed on 5q and 8p [116,117]. Here we highlight the recent literature on the 7q-encoded genes *EZH2*, *LUC7L2*, and *KMT2C/MLL3*, and discuss potential interactions with combined *CUX1* deficiency.

Similar to *CUX1*, the 7q genes *EZH2* and, less commonly, *LUC7L2*, are also mutated in CHIP and are located in 7q MDRs [3,22▪]. Of note, *EZH2* is among the only 7q genes observed to have recurrent bi-allelic inactivation in myeloid disease, suggesting a canonical tumor-suppressive role for *EZH2* in these diseases [3,4]. In the recent CHIP study from Gao *et al.*, every event of chromosome 7 copy-neutral LOH co-localized with an *EZH2* mutation, implicating this alteration was selected to eliminate the remaining wild-type *EZH2* allele [65▪]. *EZH2* encodes the catalytic component of the Polycomb Repressive Complex 2, a major H3K27 methyltransferase complex, and loss of *Ezh2* in murine hematopoietic stem cells results in myelodysplasia with late development of myelodysplastic disorders [62]. As inactivating mutations in *EZH2* also carry a poor prognosis in MDS, there may be a compounding interaction upon combined loss of *EZH2* and *CUX1* in the context of del(7q), particularly as both proteins converge on the regulation of H3K27 methylation [16▪,70].

LUC7L2 encodes a splicing factor, and inactivating *LUC7L2* mutations have been identified in both MDS and AML [52,56]. Splicing factor mutations occur in over 50% of MDS cases but are challenging to characterize due to poor overlap of alternative splicing events [118]. Two new studies independently report an unexpected downregulation of glycolysis genes following *LUC7L2* loss, with the subsequent shifting of metabolism toward oxidative phosphorylation [53▪,54▪]. Both studies identify exon skipping as a mechanism of decreased gene expression, and link alternative splicing events to glucose metabolism, a novel mechanism not previously ascribed to splicing factor mutations [53▪,54▪,118]. Recent studies have also shed new light on the H3K4 methyltransferase KMT2C/MLL3. *KMT2C* mutations are not frequently detected in CHIP, though mutations are found in AML and *Kmt2c* haploinsufficiency enhances leukemogenesis [73▪▪,75]. Chen *et al.* characterized two novel knockout models of *Kmt2c* and report increased self-renewal in hematopoietic stem cells and a selective advantage of *Kmt2c* mutant cells in the presence of chemotherapy, though the mice do not develop any overt malignancies [73▪▪]. Chang *et al.* reported that, similar to CUX1, KMT2C is recruited to sites of DNA damage, and loss of *KMT2C*

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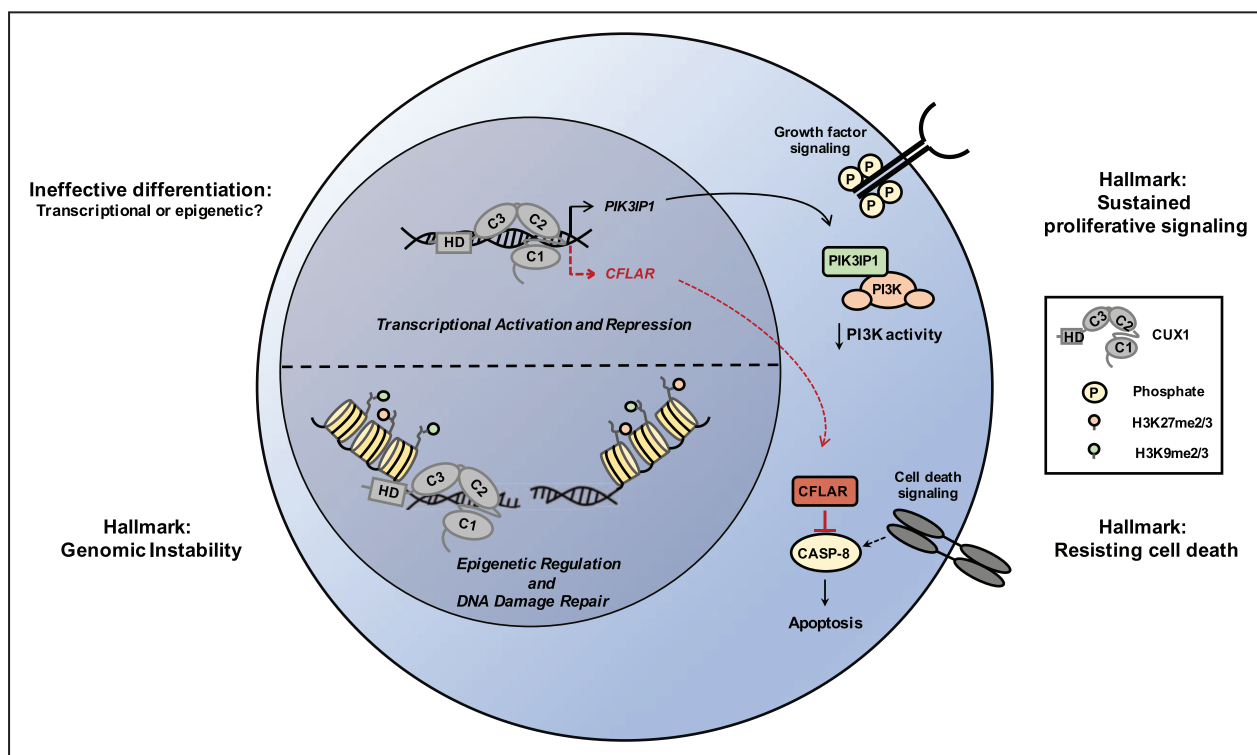

FIGURE 2. Cellular functions of CUX1 and consequences of CUX1 loss in hematopoietic cells. CUX1 is involved in transcription, DNA damage repair, proliferation, and differentiation. One target gene of CUX1 is *PIK3IP1*, which inhibits PI3K activity [Refs. [17,18▪▪]]. Loss of *CUX1* results in decreased *PIK3IP1* expression and increased PI3K-AKT signaling, promoting proliferation and resembling the 'Sustained proliferative signaling' Hallmark of Cancer [Ref. [114]]. CUX1 also downregulates expression of *CFLAR*, an antiapoptotic protein that inhibits caspase-8 [Ref. [18▪▪]]. Loss of *CUX1* results in alleviation of *CFLAR* repression and apoptosis resistance, promoting the hallmark 'Resisting cell death' [Ref. [114]]. CUX1 also regulates epigenetic histone marks and functions in epigenetic-driven DNA repair; *CUX1* loss results in sustained DNA damage, resembling the hallmark 'Genomic instability' [Ref. [114]]. *CUX1* loss also results in ineffective erythropoiesis and impaired differentiation, though the mechanism remains unknown [Refs. [17,18▪▪]]. CUX1 is depicted alone on the DNA strand for simplicity.

results in decreased expression of DNA damage response genes [72▪,74]. Given CUX1 involvement in the DNA damage response, combined loss of *CUX1* and *KMT2C* may synergize and further promote development of a t-MN [16▪,73▪▪]. Collectively, these findings indicate -7/del(7q) likely deregulates multiple cellular pathways involved in myeloid disease including cell signaling, energy metabolism, RNA splicing, DNA repair, and epigenetic regulation. Whether combinatorial loss of 7q genes acts in an additive or epistatic fashion remains an important, unanswered question.

MODELING del(7q)

Given the existence of multiple 7q TSGs, it is essential to innovate new models to interrogate combined gene deficiency. The lack of chromosomal synteny between humans and mice is a barrier to generating mouse models with large-scale deletions, and the variations in 7q deletion locations and length make determining boundaries challenging [119,120]. Alternative models include the use of induced pluripotent stem cells derived from del(7q) MDS patients, however, these cells are difficult to culture and can undergo spontaneous dosage correction, restoring the missing chromosome 7 segment to the diploid state [50]. Recently, CRISPR-Cas9 has been used to simultaneously target multiple loci on different chromosomes to model CHIP [121,122]; multiplex CRISPR-Cas9-based gene deletion may therefore be a novel means to model del(7q) that circumvents the challenges of other approaches.

CONCLUSION

As efforts to define the role of -7/del(7q) continue, clinical evidence is mounting that chromosome 7 deletions and *CUX1* mutations can be early, driving events. Emerging data indicate that certain pressures, such as genotoxic therapy, can select for

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CUX1-deficient clones, and this fitness advantage likely corresponds with the inherent drug resistance of malignancies arising from these clones. To understand the spectrum of environmental exposures that select for CUX1-deficient clones and to identify at-risk individuals, it is imperative that clinical and research CHIP sequencing panels probe for both *CUX1* and del(7q) going forward. Finally, several 7q TSGs have functions that converge on similar pathways. Although mechanistic studies of 7q genes have traditionally focused on individual genes, studies investigating combined gene deletions are warranted to refine our understanding of how -7/del(7q) drives malignancy.

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Conflicts of interest

There are no conflicts of interest.

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