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REVIEW ARTICLE

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Revertant somatic mosaicism as a cause of cancer

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Abstract

Revertant (somatic) mosaicism is a spontaneous correction of a causative mutation in patients with congenital diseases. A relatively frequent event, revertant mosaicism may bring favorable outcomes that ameliorate disorders, and is therefore called "natural gene therapy." However, it has been revealed recently that "overcorrection" of inherited bone marrow failure in patients with sterile alpha motif domain containing 9 (SAMD9)/9L syndromes by revertant mosaicism induces myelodysplastic syndrome (MDS) with monosomy 7 that occasionally proceeds to acute myelogenous leukemia (AML). In this review, we interpret very complex mechanisms underlying MDS/AML in patients with SAMD9/9L syndromes. This includes multiple myeloid tumor suppressors on the long arm of chromosome 7, all of which act in a haploinsufficient fashion, and a difference in sensitivity to interferon between cells carrying a mutation and revertants. Overcorrection of mutants by somatic mosaicism is likely a novel mechanism in carcinogenesis.

KEYWORDS

haploinsufficiency, revertant mosaicism, SAMD9/9L syndromes, somatic mutation, tumor suppressors

1 | INTRODUCTION

Somatic mutations, ranging from a single nucleotide mutation to the loss of chromosomes, will inevitably occur in mammals. The earlier a mutation occurs in postzygotic development, the larger the percentage of cells that will carry the mutation, resulting in "somatic mosaicism."[1] However, once development is complete, only mutations that occurred in long-lived cells, such as tissue stem cells, are retained indefinitely in a very low percentage of cells. The percentage increases when a cell gains an autonomous growth potential. This type of somatic mosaicism is called cancer. In addition, somatic mutations contribute to aging.[2]

Somatic mutations, however, do not always lead to unfavorable outcomes. For example, such mutations are indispensable for mammals in achieving diversity. More specifically, the cornerstones of acquired immunity are T and B lymphocytes that specifically target each of hundreds and thousands of harmful microorganisms. Needless to say, the mechanism of generating the variations in T/B lymphocytes depends heavily on somatic mutations, which also play critical roles in organs other than the immune system. For instance, the very high frequencies (up to 50%) of aneuploid hepatocytes are observed probably to adapt the exposure of countless xenobiotics.[3] Even in the brain, where a vast majority of neurons cannot be renewed, mutations that occurred early in the development would remain present until old age, generating individual physiological diversity in brain function.[4]

Revertant (somatic) mosaicism, a term popularized by Jonkman et al,[5] is one more favorable outcome of mutation, which is observed in patients carrying an inherited or de novo mutation that causes congenital disease. Since the first report of spontaneous reversion of Lesch-Nyhan mutations by *HPRT* gene rearrangement in 1988,[6] hundreds of such cases have been reported. It has been revealed that in patients with congenital immunodeficiency, for example 30/272 (11%) cases of Wiskott–Aldrich syndrome,[7] are ameliorated by a

spontaneous additional somatic mutation that repairs or compensates the causal inherited mutation. Cases of revertant mosaicism have also been reported in various congenital diseases, including epidermolysis bullosa[8] and Fanconi's anemia.[9] Since this brings benefits to patients, revertant mosaicism is called "natural gene therapy." However, taking into consideration that mutations have both favorable and unfavorable aspects, revertant mosaicism might cause additional diseases, although these have not been reported until recently.

An unfavorable outcome by revertant mosaicism was eventually reported in patients with SAMD9/9L syndromes, a recently established category of inherited bone marrow failure (IBMF) syndromes.[10] SAMD9/9L syndromes are caused by gain of function (g/f) mutations of either the *Samd9* or related *Samd9L* gene, which locates on the long arm of chromosome 7 (7q) in tandem. SAMD9/9L syndromes are characterized by the development of myelodysplastic syndromes (MDS) at extremely high frequency that sometimes progress to overt acute myeloid leukemia (AML). In the process of developing MDS, the region of 7q that contains the mutated *SAMD9/9L* gene is always lost, converting the genotype of bone marrow cells from *SAMD9/9L*$^{+/mut}$ to *SAMD9/9L*$^{+/-}$. Thus, the elimination of the mutated *SAMD9/9L* gene by an "adaptation by aneuploidy" mechanism results in revertant mosaicism, which, however, brings on MDS/AML, not an improvement in bone marrow failure.

In this review, we interpret the very complex mechanisms of how revertant mosaicism causes MDS/AML in patients with SAMD9/9L syndromes. This involves multiple myeloid tumor suppressors on 7q, all of which act in a haploinsufficient (h/i) fashion. Another important factor to promote myeloid malignancies is interferon (IFN). Finally, we will discuss whether this is a rare story of carcinogenesis or just the tip of the iceberg.

2 | TUMOR SUPPRESSORS ACTING IN A HAPLOINSUFFICIENT MANNER: ANOTHER PARADIGM OF ANTIONCOGENES

Monosomy 7 and the interstitial deletion of 7q [-7/del(7q)] are one of the most frequent (~15%) chromosomal abnormalities in adult patients with MDS and AML. -7/del(7q) is also frequently found in children with MDS and juvenile myelomonocytic leukemia (JMML). Intriguingly, as we discuss later, familial monosomy 7 syndrome, defined as bone marrow monosomy 7 occurring as the sole anomaly affecting more than two siblings, has been reported in 14 families (references in ref.[11]), in which most patients are children or adolescents.

Investigating del(7q) cases provided researchers with an opportunity to identify the responsible myeloid tumor-suppressor gene(s). In the 1970s and 1980s, recessive tumor suppressors, such as *retinoblastoma* (*Rb*) and *tumor protein P53* (*TP53*) genes, were the focus of intensive research. These genes typically lose their function completely after the loss of one allele together with a loss of function (l/f) mutation on the remaining gene. Thus, a commonly deleted region (CDR) is an ideal guide to lead researchers to where the tumor suppressor gene is located. Once a CDR is identified, candidate genes within the CDR can be sequenced to find mutations. In spite of the enormous effort of laboratories worldwide using then-current techniques such as restriction fragment length polymorphism assessments, fluorescence in situ hybridization, and microsatellite surveys, the CDRs of MDS/AML patients with del(7q) identified by each laboratory did not overlap (reviewed in refs.[12,13]). As a result, instead of narrowing down the location of the relevant CDRs, these were reported to be spread over the whole 7q region. The wide distribution of CDRs among del(7q)-myeloid malignancies was later confirmed by comparative genomic hybridization (CGH) microarray.[14]

The lack of CDRs in 7q suggests that myeloid tumor suppressor genes on 7q are totally different from the recessive-type classical tumor suppressors. Indeed, a relevant precedent exists: -5/del(5q). The deletion of -5/del(5q) is just a carbon copy of -7/del(7q) in that it is frequently detected in myeloid malignancies with broad and irregular borders of deletion, and has been explained by multiple genes that lose their myeloid tumor suppressor function by a one-allele loss of 5q.[15] This suggests that multiple tumor suppressors that act in a haploinsufficient manner (h/i suppressors) are also involved in myeloid malignancies with -7/del(7q).

Although just the loss of one allele or l/f mutation of one gene encoding an h/i suppressor (= one hit) promotes cancer progression, little doubt exists that the effect is much smaller than the complete loss of the antitumor function of classical recessive tumor suppressors by two hits (eg, loss of one allele together with an l/f mutation in the remaining gene; Figure 1). If a one-allele loss of an h/i suppressor promotes carcinogenesis a great deal, the incidence of cancers will increase to levels that threaten the persistence of a species (eg, the very high incidence of cancers in patients with 13q- or Li-Fraumeni syndromes, who have a congenital one-allele loss of *Rb* or *TP53* genes, respectively). Nevertheless, if h/i suppressor genes are located in a specific region of a chromosome, a deletion of this region (= one hit) causes the loss of multiple tumor suppressors, greatly promoting carcinogenesis. Localization of multiple h/i myeloid tumor suppressors to the specific region of chromosomes, such as 5q or 7q, can also explain why del(5q) or del(7q) is generally wide with no clear CDRs.

3 | H/I MYELOID TUMOR SUPPRESSORS IN 7q

The broad deletion regions with ambiguous borders of MDS/AML patients with del(7q) made it very difficult to identify tumor suppressor genes. Thus, it is not surprising that promising candidates have been identified only recently (Figure 2). Different strategies other than narrowing CDRs were necessary. One approach is to use microarray CGH to search for microdeletions in patients with myeloid malignancies that might be present on an apparently normal chromosome 7. By selecting JMML and JMML-like diseases, a common microdeletion spanning approximately 100 kb was identified in the

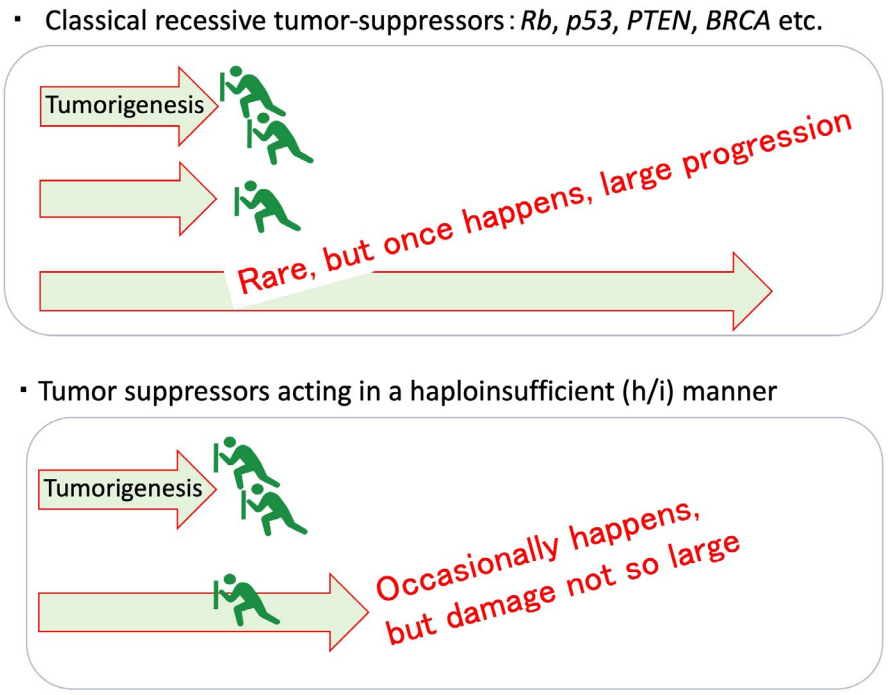

FIGURE 1 Two types of tumor suppressors. Classical recessive tumor-suppressor genes (upper panel), such as *RB*, *TP53*, *PTEN*, and *BRCA*. Cancer progression occurs only when all alleles on each gene lose their function by deletion, mutation or methylation. This is a rare event, but once it happens this would have a substantial effect on carcinogenesis. By contrast, tumor suppressor genes acting in a haploinsufficient (h/i) manner lose their function by lacking just one gene (lower panel). This will occasionally happen and damage is expected to be small

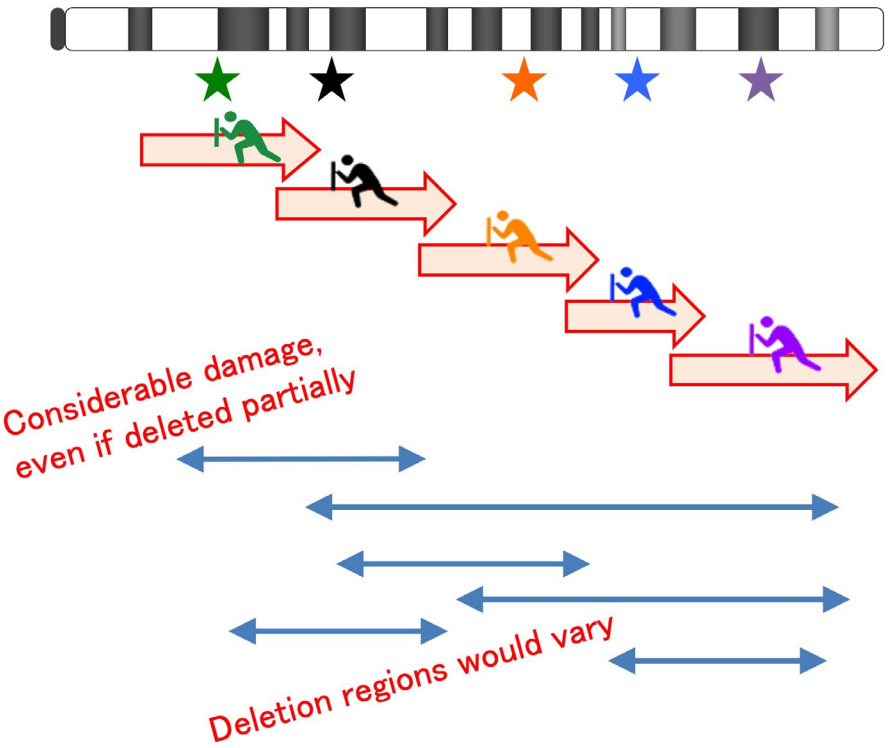

FIGURE 2 Deletion of a chromosome region that contains many haploinsufficient (h/i) tumor suppressor genes would greatly increase cancer progression. Because considerable damage would be caused by even a partial deletion of the region, the deleted area in each patient would vary

7q21.3 sub-band that contains *SAMD9/9L*,[16] details of which are described in the following sections. Similarly, from *EVI1*-dysregulated AML cell lines, two small microdeletions (0.39 and 1.33 Mb) in sub-band 7q36.1 were detected, the latter of which included the *EZH2* gene[17,18] that encodes a methyltransferase for lysine 27 of histone H3 (H3K27).[19-21] It is well known that l/f mutations of *EZH2* are frequently found (ca. 10%) in patients with MDS and related myeloproliferative neoplasms (MDS/MPN), as well as in patients with secondary AML.[18,22,23] In addition, a focal deletion (8.8 Mb) at 7q35-36 encompassing the mixed-lineage leukemia protein (*MLL3*) gene (7q36.1) was isolated from a patient with relapsed AML showing a normal karyotype.[24] MLL3 possesses histone methyltransferase activity for lysine 4 of histone 3 (H3K4),[25,26] and l/f mutations of *MLL3* have been identified in MDS and AML.[27,28] The contribution of these four genes to the development of myeloid diseases has now been validated by gene targeting in mouse models.

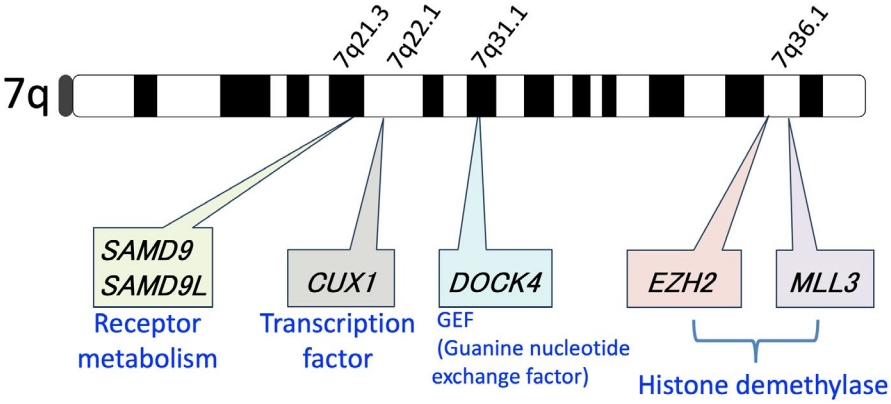

FIGURE 3 Haploinsufficient (h/i) myeloid tumor suppressor genes on 7q

In addition, two more genes, cut like homeobox 1 (*CUX1*, 7q22.1) and Dedicator of cytokinesis 4 (*DOCK4*) were considered to be h/i myeloid tumor suppressors. *CUX1* encodes a homeobox transcription factor.[29,30] Loss of one allele of this gene is frequently detected not only in myeloid tumors but also in uterine leiomyomas and breast cancers. Inactivating point mutations in one allele are also frequently found in cancers of the endometrium, large intestine, and lung.[31] *DOCK4* (7q31.1) encoding a guanine exchange factor is disrupted in murine osteosarcoma cells,[32] and its low expression has been linked to erythroid dysplasia.[33]

4 | *SAMD9/9L* AS H/I MYELOID TUMOR SUPPRESSOR GENES

Human *SAMD9/9L* encode related cytosolic/endosomal proteins (60% amino acid identity). Interestingly, the distribution of these two genes in mammals is very odd. For example, (a) humans (and other higher primates), horses, and rats have both *SAMD9* and *SAMD9L*, (b) cows, sheep, and primitive primates (such as galagos) possess only *SAMD9*, and (c) cats, dogs, and mice have only *SAMD9L*.[34] This implies that the two gene products have common functions and can compensate for the biological functions of each other.

Using fibroblasts established from homo- and heterozygous *Samd9*L-deficient mice, it was revealed that Samd9L induce the homotypic fusion of primary/early endosomes to form sorting endosomes, which regulate endosomal trafficking including virus invasion and cytokine receptor metabolism.[35] Indeed, SAMD9/9L is a crucial factor for the defense against viruses. *Samd9L* gene was identified as IFN-inducible genes,[36] since the mouse *Samd9L* gene has IFN-responsive *cis* elements in the promoter, to which IFN regulatory factor 1 binds.[37] In addition, SAMD9/9L suppresses the replication of viruses, including Japanese encephalitis virus,[38] and serves as a barrier against cross-species poxvirus transmission.[39-41]

Heterozygous (*Samd9L*$^{+/-}$) as well as homozygous (*Samd9L*$^{-/-}$) mice were found to develop MDS and die after 1.5 years.[35] Most *Samd9L*$^{+/-}$ as well as *Samd9L*$^{-/-}$ mice exhibited leukocytopenia and anemia with dysplasia in multiple hematopoietic lineages in their normal-to-hypercellular bone marrow. Competitive repopulation assays revealed that *SAMD9L*-deficiency confers a proliferative advantage on hematopoietic stem/progenitor cells (HSPCs). Indeed, *SAMD9L*-deficient HSPCs possessed an enhanced sensitivity to cytokines, most likely due to disturbed metabolism of ligand-bound cytokine receptors.

5 | G/F MUTATIONS OF *SAMD9/9L* AS A CAUSE OF IBMF

In contrast to the involvement of *SAMD9/9L*-deficiencies in MDS/myeloid leukemia in both the human and mouse, the g/f mutations of *SAMD9/9L* were identified in young IBMF patients, with or without additional nonhematopoietic symptoms (mainly degeneration of multiple organs), and were collectively defined as "SAMD9/9L syndromes."[10] The entities initially reported were myelodysplasia, infection, growth restriction, adrenal hypoplasia, genital phenotypes, and enteropathy (MIRAGE) syndrome carrying *SAMD9* mutations,[42,43] and ataxia pancytopenia (AP) syndrome with *SAMD9L* mutations.[44-46] The common symptom of these two syndromes is pancytopenia with hypocellular bone marrow in infancy that often requires transfusion but gradually improves over time. Degeneration of nonhematopoietic organs, such as the adrenal gland, testis/ovary, and cerebellum occurs. More recently, germline g/f mutations of the *SAMD9/9L* genes were identified at high frequencies in the cohorts of children and adolescents with IBMF[47] and isolated MDS at high frequencies.[48,49] The latter cohorts include familial cases.

Mechanisms of how SAMD9/9L g/f mutations cause anemia or the degeneration of nonhematopoietic organs were analyzed by generating mice carrying a Samd9L mutation equivalent to the human *SAMD9* mutation causative of MIRAGE syndrome.[50] These mice mimic the MIRAGE syndrome presenting with growth retardation, a short life, bone marrow failure, and multiorgan degeneration. In the erythroblasts of such mice, the endocytosis of transferrin and transferrin receptors is markedly slower than in normal erythroblasts, resulting in a decrease of iron uptake. Additionally, the internalization of c-Kit (the receptor for stem cell factor) in HSPCs is also delayed. In nonhematopoietic cells, in comparison, enhanced endocytosis of cytokine receptors, such as epidermal growth factor with activated lysosomes, degrades ligand-bound cytokine receptors, resulting in the downregulation of cytokine signals. In both

hematopoietic and nonhematopoietic cells, SAMD9/9L g/f mutants suppress cell growth and function through abnormal metabolism of surface receptors.

6 | REVERTANT MOSAICISM AS A CAUSE OF MDS IN SAMD9/9L SYNDROME

Children with SAMD9/9L syndromes develop MDS with -7/del(7q) at extremely high frequencies that sometimes progresses to AML. The age of onset is mostly less than 5 years and, intriguingly, the mutated allele is always lost. This means the genotype of bone marrow cells changing from *SAMD9/9L*$^{+/mut}$ to *SAMD9/9L*$^{+/-}$ can "successfully" eliminate an IBMF-causative mutated *SAMD9/9L* gene (Figure 3). However, instead of an improvement in BMF by "revertant mosaicism" through a mechanism called "adaption by aneuploidy," patients developed new diseases, MDS/AML. Obviously, a loss of multiple h/i myeloid tumor suppressors on 7q, as mentioned above, was strongly involved in the development of myeloid malignancies, but it is most likely that two additional factors that are unique for patients with SAMD9/9L syndromes are also critical to promoting leukemogenesis.

One is the impaired proliferation potential of the surrounding bone marrow cells of patients with SAMD9/9L syndrome (namely, *SAMD9/9L*$^{+/mut}$; Figure 4). It has been reported that MDS cells from SAMD9/9L syndromes have few additional gene/chromosome alterations other than -7/del(7q),[49] in contrast to sporadic childhood MDS with -7/del(7q), which generally carries relevant gene mutations such as *GATA2* or those involved in the Ras pathway.[51] Accordingly, it is assumed that HSPCs with -7/del(7q) (HSPC/-7) are susceptible to the development of MDS per se, but surrounding HSPCs suppress the expansion of HSPC/-7. When neighboring HSPCs are "weak" and unable to suppress HSPCs/-7, as is the case for the HSPCs of patients with SAMD9/9L syndrome, then HSPCs/-7 can develop into MDS without a long latency that allows additional mutation(s) to HSPCs/-7.

The other factor is IFN. Patients with SAMD9/9L syndromes experience recurrent severe viral infections. The resulting elevation in IFN disturbs a balance between HSC self-renewal and differentiation, which is the fundamental regulatory mechanism of hematopoiesis.[52,53] IFNγ signaling induces myeloid-biased HSC differentiation at the expense of self-renewal and differentiation to lymphoid and erythroid lineages. Because SAMD9/9L are IFN-responsive genes, the self-renewal of HSCs carrying a mutated SAMD9/9L will be further repressed by IFNγ. Indeed, anemia and lymphocytopenia of patients with SAMD9/9L syndromes are worsened after episodes of viral infection. In addition, intraperitoneal injections of poly(I:C), an IFN inducer, into *Samd9L*$^{+/mut}$ mice resulted in more profound anemia than *Samd9L*$^{+/+}$ mice, while no significant hemoglobin reduction occurred in *Samd9L*$^{-/-}$ mice.[50] These data suggest that IFNγ induced by recurrent viral infection facilitates clonal expansion of HSCs with -7/del(7q) in the bone marrow of patients with SAMD9/9L.

This logic may extend to the pathogenesis of sporadic adult MDS. It is generally accepted that the accumulation of additional genetic and/or epigenetic alterations is required for HSPCs/-7 to develop MDS. This is assumed to be a reason why the great majority of MDS patients are >40 years of age. However, if the expansion potential of HSPCs/-7 is determined by the *relative* strength of the surrounding HSPCs, aging may also contribute to the development of MDS by "weakening" surrounding HSPCs to allow the expansion of HSPCs/-7. In addition, the elevation of IFNγ by viral infection or aberrant expression from bone marrow stroma cells could lead to a difference between HSPCs/-7 (SAMD9/9L$^{+/-}$) and surrounding cells (SAMD9/9L$^{+/+}$). Indeed, several lines of evidence revealed aberrant expression of IFN-inducible genes in MDS cells,[54] suggesting cross-talk of cytokines and IFN signaling contributes to the development of MDS.

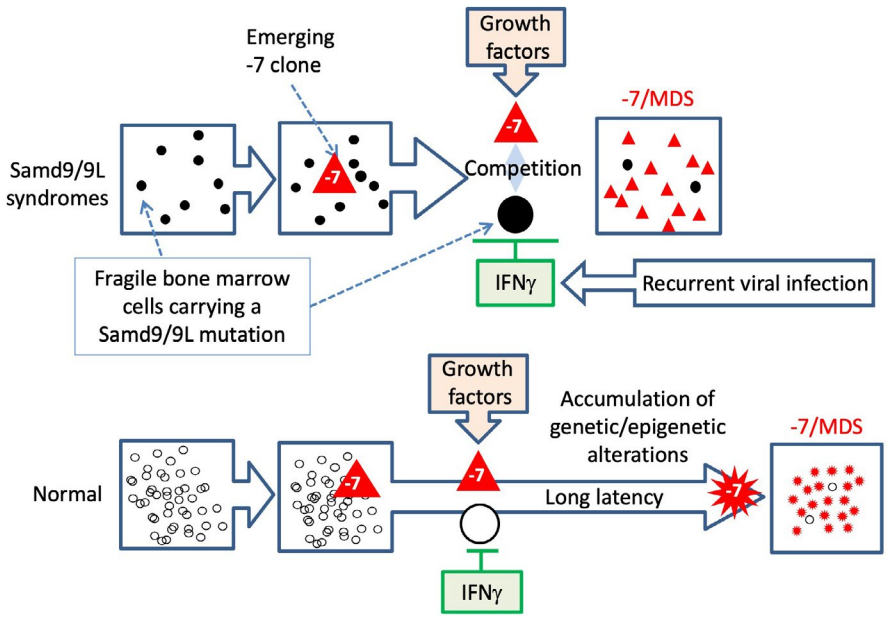

FIGURE 4 A scheme of myelodysplastic syndrome (MDS) carrying -7/del(7q). In patients with SAMD9/9L syndromes, bone marrow cells with SAMD9/9L$^{+/-}$ (revertants) show a high sensitivity to growth factors and a low sensitivity to (the suppressive effects of) interferon (IFN)γ. In addition, surrounding bone marrow cells (SAMD9/9L$^{+/mut}$) have a high sensitivity to IFNγ. As a result, the rapid expansion of a -7/del(7q) clone causes an "overcorrection," leading to MDS. This mechanism would be partially applied to sporadic MDS patients with -7/del(7q) in old age

7 | DOES REVERTANT MOSAICISM CAUSE CANCER OTHER THAN MDS/AML IN SAMD9/9L SYNDROME?

In the case of SAMD9/9L syndrome, the accumulation of h/i myeloid tumor-suppressor genes on 7q "overcorrects" BMF, resulting in MDS/AML. Thus the answer to the question "Does revertant mosaicism cause cancers other than MDS/AML in SAMD9/9L syndromes?" most likely depends on whether h/i tumor-suppressor genes accumulate on a specific chromosome or not. Since nonrandom loss and/or large deletions of chromosomes are frequently observed in a wide variety of cancers, we consider that SAMD9/9L syndromes are not alone in this regard.

DISCLOSURE

The authors have no conflict of interest.

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