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EDITORIAL

Myelodysplastic syndromes: lost between two states?

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Myelodysplastic syndromes (MDSs) are a heterogeneous group of clonal hematological diseases characterized by bone marrow hypercellularity, dysplasia, various degrees of cytopenia and a risk of progression to acute myeloid leukemia (AML). There has been little progress toward the molecular classification of MDSs and the identification of new markers and therapeutic targets. Using the International Prgonostic Scoring System, MDSs are classified as being at low, intermediate and high risk of developing AML.[1,2] New developments in the understanding of the molecular alterations and mechanisms leading to MDS could result in a better understanding of the physiology of the hematopoietic system, an accurate classification of the syndromes, a reliable evaluation of the prognosis for the patients and the design of efficient therapies. Here, we propose a speculative interpretation of the latest molecular results in the field.

Molecular alterations of MDSs

In MDSs, chromosomal abnormalities are recurrent but not specific. Epigenetic deregulations such as hypermethylations are frequent, and represent the rationale for current treatments.[3–5] MDSs are also characterized by a high degree of apoptosis, which explains the contrast between bone marrow hypercellularity and cytopenias.[6] Thus, to understand MDSs, it is necessary to explain two prominent features, hypermethylations and apoptosis. As it happens, some recent discoveries shed light on both.

Single nucleotide polymorphism array or array comparative genomic hybridization have confirmed the frequency of genomic abnormalities and shown the importance of uniparental disomy.[7–13] They have also revealed heterozygous deletions of regions and genes that are potentially involved in MDS genesis, such as *ASXL1*, *TET2* and *UTX*.[11,14] *UTX*, which encodes a histone 3 (H3) demethylase,[15] has been found to be mutated in many cancers, including myeloid diseases and multiple myeloma, in which it is inactivated.[16] Nonsense and frameshift mutations in *TET2* at 4q24 and in *ASXL1* at 20q11 were recently identified in 15–25% of MDS cases.[14,17–21] Mutations/deletions are often heterozygous, leading to haploinsufficiency, but the two alleles of the gene may be affected. TET2 and ASXL1 function is not completely understood, but could be linked to regulation of transcription. ASXL1 helps recruit polycomb and trithorax complexes to specific chromatin domains.[22,23] It can also enhance histone acetylation and stimulate retinoic acid target's expression, such as *JMJD3*.[24] TET2 could have a role similar to TET1 in the generation of hydroxymethylcytosines and contribute to epigenetic regulations.[25] We found one MDS case with a heterozygous loss of *ASXL2* and another case with a heterozygous loss of *TET3*.[14] The sequencing of these genes in a series of chronic myelomonocytic leukemia (CMML) revealed one nonsense mutation of *ASXL2* but none of *TET3*. A similar absence of mutation has been reported by Abdel-Wahab *et al*.[26] for *TET1* and *TET3*. Deletions of *ASXL3* have been found in MDS.[21] *TET2*[26] (Kosmider *et al*., submitted) and *ASXL1*[14] are mutated at a high frequency (40–50%) in CMML, a related disease classified as a MDS/myeloproliferative neoplasm (MPN). The same high frequency of mutations in CMML has also been reported for other genes such as *RUNX1*.[27,28]

Heterozygous deletions of the long arm of chromosome 5 affect two regions.[29] One at q33.1 is associated with the 5q− syndrome, and the *RPS14* gene has been identified as the gene responsible for this class of MDS.[29] *RPS14* is required for the maturation of 40S ribosomal subunits, and ribosome production is impaired in 5q− cases. The second region is q31.2, and it is involved in all other classes of MDS and in AML. No single gene has been identified as being responsible. The haploinsufficiency of several genes in that region, including that of *CXXC5*[30,31] or *JMJD1B*,[32] could be involved.[33] The 5q31.2 region is paralogous to 4q24 where *TET2* is located, but no *TET* family member has been identified. Deletions of 20q are also frequent in MDSs. No *bona fide* tumor suppressor gene has been identified yet that could account for those alterations. *ASXL1* could be involved, especially in some centromeric alterations.[34] Another good candidate is *L3MBTL1* at 20q12, which encodes a protein involved in chromatin function.[35] Inactivation of micro-RNA loci could also explain the loss of large regions.[36,37]

Thus, several recent studies have identified new genes whose alterations are involved in leukemogenesis. In more than half the cases, the mechanism involved seems to be haploinsufficiency caused by a mutation or a deletion.[38] However, uniparental disomy is frequent and may reduce a number of mutations to homozygosity.[9,10,12,13]

Molecular processes involved in MDS

Self-renewal of the hematopoietic stem cell is ensured by a complex regulation of transcription programs involving specific stem cell genes and chromatin modeling. The major players are polycomb and trithorax complexes, whose subtle interplay keeps the stem cell in an undifferentiated and pluripotent state by repressing developmental and differentiation transcriptional programs.[39–43] Activation and repression of transcription programs is mediated by specific modifications of DNA and chromatin, such as methylation marks. Normally, progenitors of stem cells lose their self-renewal potential when entering a differentiation pathway (Figure 1). In AML, some oncogenic alterations lead to *de novo* acquisition of self-renewal potential in these progenitors by inducing modifications of histone marks and chromatin modeling.[44,45] This re-programming leads to cells blocked early at the blast phase, which is characteristic of AML.

What happens in MDS? The potential role of TET2, ASXL1 and UTX in chromatin modeling and transcription programming is an interesting area of investigation.[46] Conversion of methylcytosine in hydroxymethylcytosine may facilitate DNA demethylation;[25] thus, loss of TET2 would lead to an increase in methylations. ASXL1 has a PHD (plant homeodomain) finger,

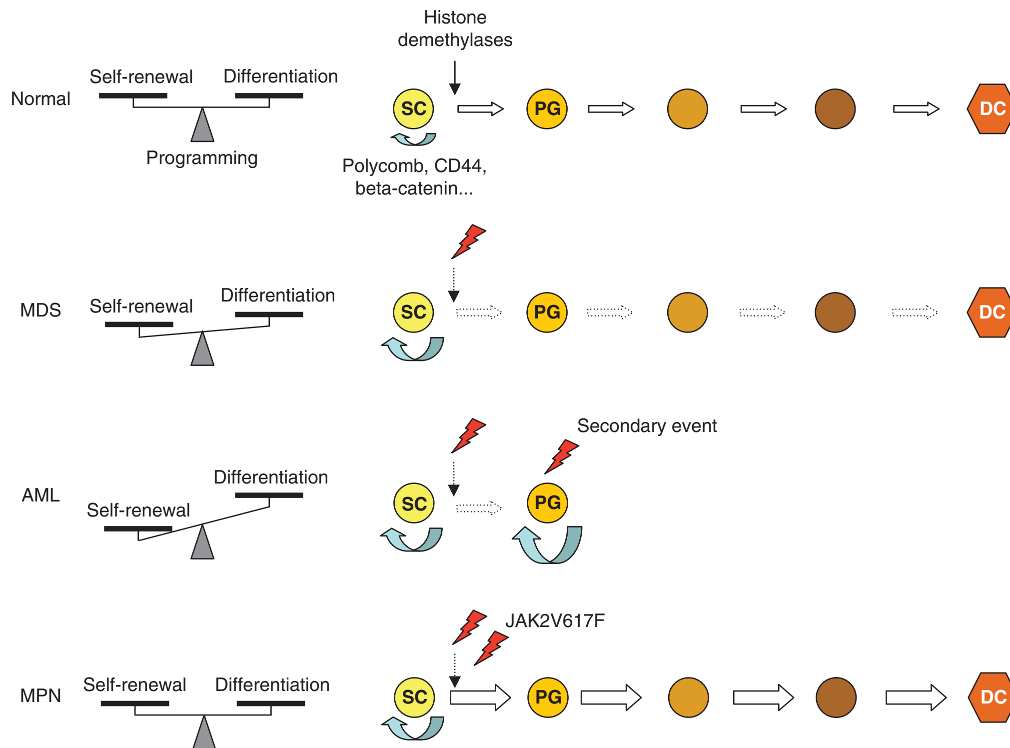

Figure 1 Hypothetical mechanism of Myelodysplastic syndrome (MDS) genesis. The normal hematopoietic cell differentiation pathway from a stem cell (SC) to a differentiated cell (DC) is represented by a cell lineage; it is regulated by a balance between self-renewal and differentiation schematized on the left by the drawing of a scale. Differentiation is triggered (among other mechanisms) by chromatin remodeling, which can be modified by histone demethylases that remove repressive marks. Abnormal hematopoiesis in MDS is represented on the second lane; the balance is slightly in favor of self-renewal, possibly after inactivation of histone demethylases or TET2. The cell targeted by this alteration could be either the hematopoietic stem cell or the progenitor cell (PG). In AML, the balance is even further tilted and a strong block of differentiation occurs. This can happen, for example, when a dominant fusion gene is generated by chromosome translocation, or by the accumulation of several events leading to the induction of self-renewal. In MPN, displayed on the lower panel, mutations favoring self-renewal are equilibrated by mutations favoring proliferation and differentiation and protecting from apoptosis.

which is found in nuclear proteins, and whose substrate tends to be chromatin.[47,48] UTX is a histone demethylase.[49] UTX and its paralog, JMJD3, demethylate trimethylated (me3) lysine 27 (K27) on H3 (H3K27me3).[50] In stem cells, which do not express UTX,[51] H3K27me3 blocks the transcription of genes necessary for differentiation. A rapid decrease of H3K27me3 marks occurs during stem cell differentiation.[52] Thus, inactivation of histone demethylase in stem cells should lead to the maintenance of H3K27me3 marks on target genes, and should prevent differentiation. Inactivation of histone demethylases could not only be due to mutations and deletions of the corresponding gene[16] but also due to protein complex alterations such as the SMRT complex that regulate histone modifiers.[53]

The molecular alterations identified in MDS suggest that gene expression programs can be altered in MDSs, and this is in favor of an increased activity of polycomb complexes[54] and a corresponding prominence of the self-renewal activity of stem or progenitor cells over the differentiation pathway (Figure 1). However, in MDSs, modifications do not induce a complete block of differentiation as they do in AML, allowing some differentiation to take place. This increase in self-renewal activity is likely to be proportional to the number of alterations and likely to depend on the cell that is targeted by those alterations. The early oncogenic hit may occur in a stem cell and result in a slight increase of self-renewal and pluripotency. It may also affect progenitors, which will partially acquire some capacity to self-renew without completely losing the possibility to differentiate. The two scenarios, incomplete block and abnormal, incomplete differentiation struggle for prominence, result in neither one being optimal. Differentiation hindrance would lead to a high level of apoptosis, and AML would occur when a secondary alteration induces a complete block of differentiation and resistance to apoptosis.

Haploinsufficiencies of regulatory genes, such as *TET2*, *ASXL1* or *UTX*, unless they accumulate, could have a moderate effect on epigenetic marks. In contrast, in AML, chimeric proteins produced by fusion genes, such as MLL H3K4 methyltransferase or MYST3 histone acetyltransferase, can encode strong epigenetic modifiers acting on important switches.[55–57] Deregulation of a PHD finger through a fusion with NUP98 can trigger leukemogenesis.[58] These fusions operate through HOX-linked pathways. However, not all AML gene fusions or mutations are able to trigger AML in mice when acting alone.[59–61] Thus, another possibility is that some AML alterations cooperate with tumor suppressor inactivation, such as *TET2* mutation, to enhance self-renewal programming, block differentiation and stimulate proliferation (Figure 1). Indeed, mutations of *TET2*[18,26] and *ASXL1* (unpublished observations) are found in AML. It will be interesting to survey *de novo* AMLs and AMLs secondary to a chronic hematological disease, to determine whether they display at least one mutation in a tumor suppressor, such as *TET2* and *ASXL1*, and their associations with gene fusions and *FLT3* and *NPM1* mutations. Combinations of mutations in several tumor suppressors are certainly possible. The gravity of the disease could parallel the intensity of the differentiation block and, thus, depend on the power of gene alterations to modify stem cell programming. In MDSs, only combinations of alterations, and not single ones,

should have a strong effect, and are expected to be found in high-risk MDSs. To establish the prognosis of a myeloid disease, it would then be important to determine the total burden of mutated alleles. Therefore, it will be necessary to identify all potential tumor suppressors and to search for their mutations in each sample.

Self-renewal is also balanced by senescence and apoptosis. The latter programs are induced by the CDKN2 tumor suppressors (P16, P19/ARF) in response to various stress signals and oncogenes, such as an activated RAS/MAP pathway.[62,63] One key requirement for self-renewal activity is the repression of the *CDKN2* genes. DNA and histone methylations control the transcription of these genes. Abnormal inactivation of *CDKN2* after the loss of a histone demethylase, for example, may shut off RB/P53-induced senescence and enhance self-renewal (Figure 2). The same mechanism may be controlled by NPM1.[64]

One important issue remains. Although MPNs and MDSs are different chronic diseases, *TET2*, *ASXL1* and *UTX* mutations are found in both.[16,17,65–67] As in CMML, *TET2* and *ASXL1* mutations do not seem to be mutually exclusive in MPNs.[67] In MPNs, hematopoietic cell differentiation is preserved. If our hypothesis of gene alteration increasing self-renewal is true, then a simultaneous increase in proliferation and differentiation in the MPN stem cells should take place. This could be ensured by JAK2 or CBL mutation,[68] for example. RAS pathway mutations may have this role in the myeloproliferative form of CMML.[27]

The study of the physiopathology of chronic myeloid diseases may teach us a lot about how cell fate is regulated and how cancer arises. It is probable that other, yet unknown genes will be involved in leukemogenesis. Upcoming studies will have to determine the number of genes needed to trigger a chronic or acute disease, whether the alterations of these genes need to occur in specific combinations or in a particular order, and whether they affect the phenotype and prognosis of the disease. It is possible that every MDS (and MPN) has at least an equivalent of a *TET2* and/or *ASXL1* mutation, perhaps many more, which affects stem cell behavior and provokes clonal expansion. In clinics, the distinction of the earliest lesions from the cooperative ones will be important to select the therapeutical strategy and surveillance.

It is not yet known how specific to myeloid diseases (or of hematopoietic diseases altogether) *ASXL1* and *TET2* mutations are, but *UTX* mutations have been found in several types of solid tumors.[16] Anyhow, even if the altered proteins are different in various cancers, they may belong to similar families and function in similar modules, and the cellular processes altered may be the same. The balance between self-renewal and differentiation/senescence programs is a likely universal target of oncogenic events and histone demethylases are possible central

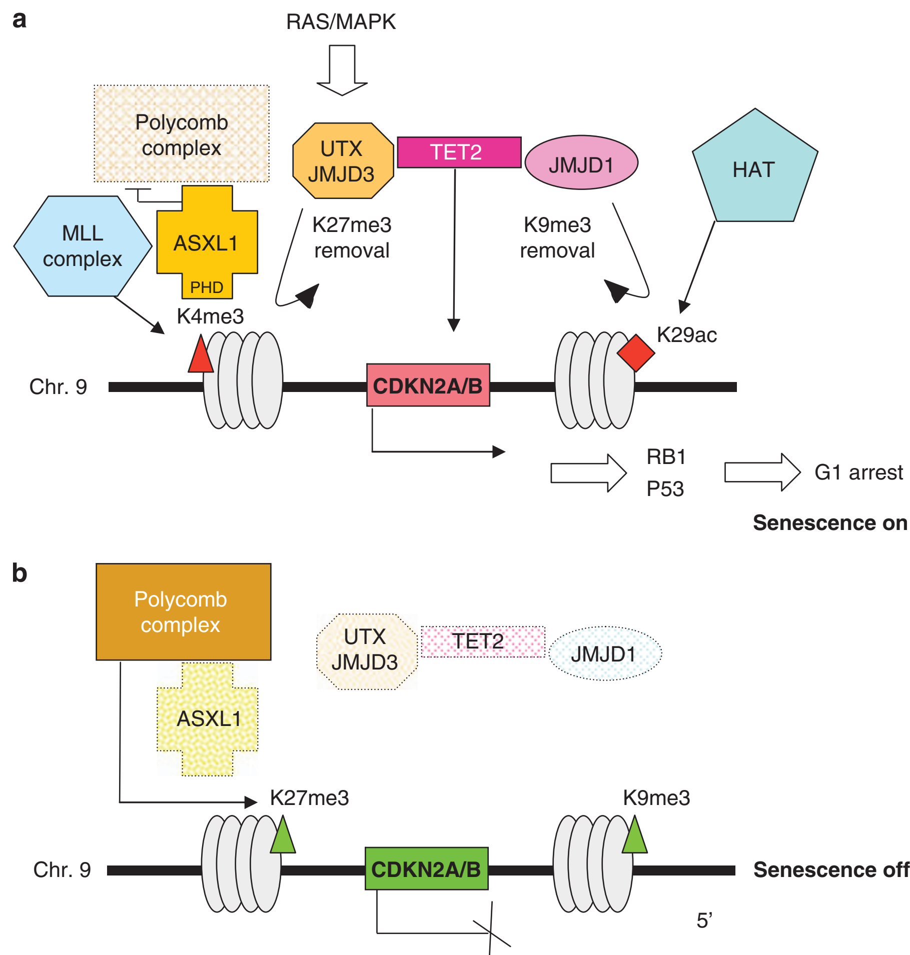

Figure 2 Speculative view of a self-renewal/senescence gene switch in a hematopoietic myeloid progenitor cell. (**a**) Expression of the *CDKN2A/B* loci on chromosome arm 9p induces G1 arrest and senescence through the RB/P53 pathway. (**b**) Repression of *CDKN2A/B* and shut off of senescence failsafe program is essential for self-renewal and is ensured by repressive marks and polycomb action. Inactivation of DNA and histone regulators, such as JMJD3,[63] leads to repression of the *CDKN2A/B* loci. Color code: Histone marks: repressive, green; activating, red.

players. Fortunately, we could now firmly handle the loose end of the wool ball.

Conflict of interest

The authors declare no conflict of interest.

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