Moving low-risk myelodysplastic syndromes from humans to mice: is it truly that simple?

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Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal bone marrow diseases featuring ineffective hematopoiesis, morphological dysplasia and persistent peripheral cytopenia that can affect one or more cell lines. The spectrum of genetic abnormalities is in ceaseless expansion and includes chromosomal abnormalities, such as del(5q) and del(7q) and recurrent mutations affecting transcription factors (*RUNX1*, *ETV6*), splicing factors (*SF3B1*, *SRSF2*), and epigenetic modifiers (*TET2*, *ASXL1*, *DNMT3A*).[1,2]

The therapeutic strategies for and survival of patients with MDS are decided according to the most common predictor, the Revised International Prognostic Scoring System (IPSS-R), defined by number and severity of cytopenia, percentage of blasts in the bone marrow, as well as the type and number of chromosome changes.[3] However, with all the data on molecular diagnostics now available, the topography of MDS patients is more precise. This is why new recommendations are in favor of the use of the Molecular-IPSS (IPSS-M), which incorporates data on 31 driver genes and helps to classify people with MDS into six groups with different rates of survival.[4] As far as concerns therapy, the approach consists of disease and patient monitoring, supportive care (blood transfusions, antibiotics), luspatercept, lenalidomide and erythropoietin for low-risk MDS, whereas the hypomethylating agents, azacitidine and decitabine, are used for high-risk MDS, which are known to be aggressive diseases with an increased risk of progression to acute myeloid leukemia.

The first patient-derived xenograft (PDX) model was described back in 1969 and in 1981 a genetically engineered mouse model was introduced.[5] Since then the use of PDX models has improved the predictability of clinical therapeutic response to greater than 80%.[6] However, primary MDS cells are difficult to manipulate, which leads to a paucity of cell lines and PDX models. This lack of PDX models hinders the development of novel therapies, particularly in the case of low-risk MDS. Getting to know the biology of low-risk MDS better is the key to a greater understanding of disease evolution, and perhaps the development of new, targeted drugs.

A major breakthrough came through the research of Song *et al.*, who found that low-risk MDS cells could reliably engraft MISTRG mice (highly humanized complex immunodeficient mice).[7] This model promised to recapitulate the morphological features, immunophenotype and clonal complexity of MDS via transplantation of $CD34^+$ cells from patients with low-risk MDS. Nevertheless, and somewhat surprisingly, this model has not led to the predicted increased in scientific output regarding novel drug testing in low-risk MDS. Although engraftment in MISTRG mice was shown to be superior to that in NSG mice, perhaps the requirement for intrahepatic injections in newborn animals or intrafemoral injections in adults or maybe the lack of unrestricted access to MITRG mice has limited the use of this exciting PDX.

In this issue of *Haematologica*, Teodorescu *et al.* describe a new xenograft model of low-risk MDS that makes use of readily available reagents (NSG-S mice and clodronate) and involves simple laboratory techniques (intravenous injection)[8] (Figure 1). The authors hypothesize that the barrier to xenotransplantation in these heavily immunocompromised animals is represented by residual mouse macrophages that cannot recognize the CD47 present on malignant human cells. Moreover, they show that macrophages are not eliminated by conditioning with radiation and are, therefore, still present during transplantation. So perhaps the use of intrafemoral or intrahepatic routes is less suitable for overcoming this xeno-barrier. Nevertheless, by giving one injection of liposomal clodronate, the authors could completely, albeit transiently, eliminate spleen macrophages.[9] The approach is disarmingly simple and amenable to upscaling for complex, clinical trial-like investigations of multiple concomitant treatments. The authors provide proof-of-concept for therapeutic interventions by using azacitidine treatment of a small number of mice; but upscaling this model may need further optimization. Nevertheless, this PDX recapitulates the clonal

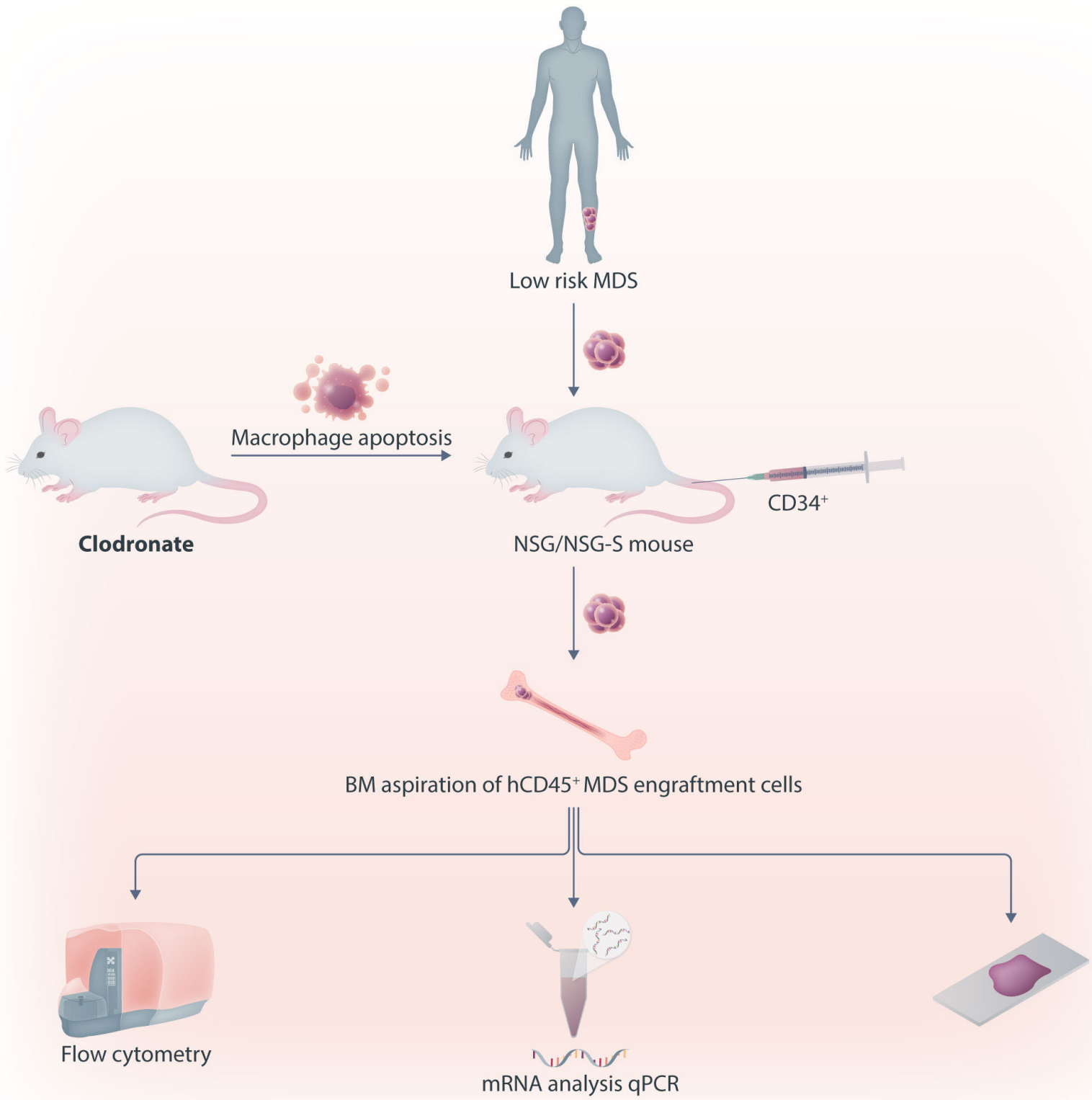

Figure 1. A simplified diagram of an improved patient-derived xenograft model using CD34 cells from patients with low-risk myelodysplastic syndrome. MDS: myelodysplastic syndromes; BM: bone marrow; hCD45$^+$: human CD45$^+$; qPCR: quantitative polymerase chain reaction.

molecular architecture of the original disease and even maintains some of the splicing events characteristic of the respective mutations in spliceosome genes. Although the authors specifically used samples from patients with low-risk MDS with spliceosome mutations, one may hypothesize that patients with MDS with other molecular features could also be used to create PDX models employing a similar approach.

As expected with PDX models of MDS, human engraftment was vastly represented by myeloid cells but, interestingly, some erythroid and megakaryocytic lineage cells were found in the bone marrow at 3 months after transplantation. This is particularly noteworthy as human erythrocytes are rapidly eliminated by murine macrophages and the clodronate-mediated depletion of murine macrophages was performed only once in the current study, during conditioning. It is tempting to hypothesize that subsequent injections of clodronate could improve the persistence of human erythropoiesis in these PDX mice. Clarifying the extent to which MDS dyserythopoiesis is recapitulated is of the utmost importance prior to testing therapeutic interventions aimed at improving anemia in patients with low-risk MDS, particularly MDS with ring sideroblasts.

Lastly, while the study by Teodorescu *et al.* models low-risk MDS, it would be useful to test whether premalignant

clonal hematopoietic conditions, such as clonal hematopoiesis of indetermined potential or clonal cytopenias of unknown significance, could also be modeled in mice using this approach. PDX models of these conditions would provide the tools to study clonal competition and uncover the mechanisms responsible for clonal dominance resulting in MDS.

We hope that the model described in the current issue of *Haematologica* will catalyze preclinical research in MDS and hematopoietic aging and result in an outburst of novel therapeutic approaches in these conditions. Time will tell!

Disclosures

No conflicts of interests to disclose.

Contributions

Both CMS and DC contributed to the final version of the manuscript. DC supervised the project.

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