Myelodysplastic syndrome (MDS) is a group of heterogeneous myeloid clonal diseases originating from hematopoietic stem cells, characterized by myeloid cell differentiation and dysplasia, manifesting as ineffective or failed hematopoiesis and refractory hemocytopenia and associated with a high risk of transformation to acute myeloid leukemia (AML). Peripheral blood cytopenia and bone marrow cell hyperplasia are the main features of MDS. According to the World Health Organization (WHO) classification criteria, at least one lineage of dysplasia can be isolated from the bone marrow (BM) of MDS patients. Abnormal proliferation of bone marrow cells is based on, for example, cell apoptosis and hemocytopenia in the peripheral blood. However, the cells leading to malignant transformation have not been directly elucidated, since research on the disease usually focuses on the cellular mechanisms of MDS development and prevention. MDS treatment includes blood component infusion, hematopoietic factor therapy, immunomodulator therapy and epigenetic drug therapy, and these different types of treatment for MDS patients are generally disappointing in their outcomes. As is well known, animal models are powerful tools for modelling and studying human diseases and are very useful preclinical platforms for studying problems that are difficult (or impossible) to solve clinically. A wide range of model organisms have been used in the biological study of myelodysplastic syndrome. Currently, established MDS animal models include mice, rats and zebrafish, among others. The models are classified into genetic modification models, chemical induction models, xenotransplantation models, etc. According to the modelling methods, their advantages and disadvantages are summarized in Table 1.
MOUSE MODELS OF MDS

Because of their small size, high fertility, good physiological characteristics and completely sequenced genome, experimental mice have become excellent model organisms for tumor research. The hemato-pathology subcommittee of the Mouse Models of Human Cancer Consortium has developed a set of guidelines in mice (Table 2), which can be used as a standard for the identification of a mouse MDS model.

2.1 | Xenograft mouse model

The xenotransplantation model is used to establish a human tumor in immunodeficient mice, and is an effective tool for studying malignant diseases. Establishing a xenograft model generally includes engrafting immortal human cell lines established from MDS patients (skm-1) or cells obtained directly from MDS patients. Some laboratories have constructed mouse xenotransplantation models by implanting immortal human cell lines established with primary cells from MDS patients. Nonobese diabetes (NOD)/SCID mice are the main strain used for xenograft models because these mice have defective complement immunity and NK cell activity, as well as B-cell and T-cell defects.

TABLE 1 | Animal models of myelodysplastic syndrome (MDS)

| Category          | Models                   | Advantages                                                                 | Disadvantages                                                                 | Ensample |
|-------------------|--------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------|
| Mouse             | Genetically engineered mouse model | Can transplant well; 1. Gene expression can be controlled; 2. Can progress to acute myeloid leukemia (AML); 3. Can be used to study mutations in specific genes; 1. Genetic engineering vector construction, embryo culture, microscope injection, etc; the operation is complex; 2. Its production cycle is long with great expense; 3. The corresponding model should be constructed according to the experimental requirements | Cannot be transformed into AML 1. 5q-mice models; 2. Tumor suppressor gene model; 3. RAS mouse model; 4. Tyrosine kinase mouse model; 5. Transcription factors and growth factors mouse model | MLL-PLD/RUNXI-291fs BMT Model |
| Bone marrow transduction/ transplantation model | 1. The operation is simple; 2. Whole procedure time consuming and short; 3. Can screen for targeted drugs | 1. It’s very different from the clinical patient; 2. Rate of tumorigenesis is low | 1. Subcutaneous transplantation model of human MDS cell line SKM-I; 2. The patient’s cells were inoculated directly to immunodeficient mice |
| Gene editing and modification | 1. The operation is simple; 2. It can better simulate the transformation of MDS to leukemia | 1. Biological property is unstable; 2. Chemical reagents do great harm to the environment | 1. Benzene induced model; 2. Alkylation reagent induction model; 3. Radiation induced model |
| Xenotransplantation | 1. Gene expression can be controlled; 2. Can be used to study mutations in specific genes; 3. It has the advantages of high-throughput and medicine analysis | 1. Its production cycle is long with great expense and the operation is complex; 2. Non mammalian vertebrate, it’s very different from the clinical patient | C-myb-gfp zebrafish model |
| Induced animal model | 1. The operation is simple; 2. It can better simulate the transformation of MDS to leukemia; 3. Biological property is easy to study | 1. Biological property is unstable; 2. Chemical reagents do great harm to the environment | Dimethylbenzanthracene (DMBA) induced model |
| Rat               | Chemical induced model | 1. The operation is simple; 2. It can better simulate the transformation of MDS to leukemia | 1. Biological property is unstable; 2. Chemical reagents do great harm to the environment | Dimethylbenzothiazole (DMBA) induced model |
| Zebrafish         | Genetically engineered models | 1. Gene expression can be controlled; 2. Can be used to study mutations in specific genes; 3. It has the advantages of high-throughput and medicine analysis | 1. Its production cycle is long with great expense and the operation is complex; 2. Non mammalian vertebrate, it’s very different from the clinical patient | C-myb-gfp zebrafish model |

TABLE 2 | Criteria for the diagnosis of myeloid dysplasias in mice

1. Neutropenia was found in peripheral blood but no leukocytosis or erythrocytosis.
2. Non-lymphoid hematopoietic cells showed dysgranulopoiesis, dyserythropoiesis, or dysplastic megakaryocytes, this may be accompanied by an increased non-lymphoid immature forms or blasts in the bone marrow or spleen.
3. Non-lymphoid leukemia was excluded.

Data from Blood 2002; 100:238-45. Hematol Oncol Clin North Am. 2010 Apr; 24(2): 361-375.
In one study, researchers implanted 5q− deficient hematopoietic cells taken from seven MDS patients into nonobese diabetes (NOD)/SCID mice. Mice implanted with cells from one of the seven patients showed a poor (12%) implantation, with CD45−CD15+ expression indicating 5q deficiency, but no clinical symptoms were found in these recipient mice.16 In another study, bone marrow isolated from MDS patients was injected into NOD/SCID mice that had been irradiated and subcomponents of human CD45+ cells were detected in the mouse bone marrow. However, no abnormal karyotypes similar to those of human MDS patients were found.17 These results indicated that most of the implanted human cells were derived from normal bone marrow cells, possibly due to decreased proliferation of human MDS cells in the mice and/or adverse cellular conditions and immune sensitivity. Therefore, to avoid immune rejection, human cytokines are given at the time of xenotransplantation.

Thanopoulou et al successfully transplanted MDS cells from 9 of 11 patients, with 4 of the 5 samples of MDS cloned cells showing human cytogenetic markers (trisomy 8 or 5q deletion).18 However, the level of implantation was particularly low, less than 1% of nucleated cells, and the mice did not develop clinical MDS. Similarly, the proportion of human MDS cell xenografts successfully established by Kerbauy et al using a NOD/scid−/−2 model was also small (0.14%-4%), and these mice did not develop clinical diseases. Moreover, recent research on patient-derived xenotransplantation models of human myeloid diseases found that engraftment of myelodysplastic syndrome samples is not robust.19

In summary, human MDS cells can be implanted in immunodeficient mice, but they do not cause clinical disease.20 Therefore, the challenge for future work is generating xenograft mice with clinical symptoms similar to those of MDS.

### 2.2 Genetically engineered mouse model

There are two known genetics methods of promoting the development of MDS in mice.6 One is the reverse-transcription bone marrow transduction/transplantation method, in which murine bone marrow nucleated cells (BMNCs) are harvested and infected in vitro with a retroviral construct that expresses the gene of interest. The infected BMNCs are then transplanted into homologous host mice undergoing lethal irradiation. Studies have shown that more than 20% of the observed chromosome translocation is associated with hematopoietic system malignant tumors involving the NUP98 gene.21 22 Researchers have also established an NUP98-HOXD13 mouse model in which primary murine bone marrow cells are transduced with a retrovirus carrying an NUP98-HOXD13 fusion gene.23 These cells are then transplanted into irradiated mice. The mice expressing NUP98-HOXD13 presented with leukopenia, and the fusion gene was found in bone marrow 4 weeks after transplantation. Unfortunately, this model failed to develop into acute myeloid leukemia.

The second method is to knock out genes related to MDS by gene targeting or transgenic technology and thereby obtain mouse embryonic stem cells featuring genes engineered via homologous recombination through intricate gene positioning and DNA fragment modification to generate hematopoietic mouse cells with characteristics of human MDS.5 24 Reverse transcription of the NUP98-HOXD13 fusion gene in a bone marrow mouse model did not simulate MDS or evolve into leukemia,25 but by utilizing Vav1 gene regulatory elements to guide transgenic NHD13 expression in hematopoietic tissue, NUP98-HOXD13(NHD13) transgenic mice developed anemia, neutropenia, and lymphopenia at 4-7 months. The progression observed in patients with MDS is similar, and at 10-14 months approximately one-half of the MDS NHD13 mice had developed acute leukemia.26

The application of new sequencing technology has helped us understand the genetic basis of MDS. In their summary review of MDS research progress, Rafael Bejar et al2 presented a pie chart of the distribution of mutations and karyotype abnormalities frequently seen in MDS patients, showing some MDS-related mutated genes (TP53, NRAS, RUNX1, TET2, ASXL1, etc) and some chromosome abnormalities (deletion of the 5q chromosome fragment, trisomy 8, etc).21 The discovery of these genes and chromosomal abnormalities provided the basis on which researchers have established genetically engineered MDS animal models. For example, 5q− mouse models (NPM1+/− mice and APC+/− mice) were constructed by screening for mouse candidate genes similar to the missing fragments in cases of human 5q− syndrome, and these mice can develop disease with the characteristics of human MDS. In addition, mouse models with gene mutations associated with MDS, such as NRAS, RUNX1, TET2, etc, have been reported to show characteristics of MDS that can develop into leukemia at a certain level. Some of these genetically engineered MDS mouse models have been systematically described in Sarah H. Beachy's review.6 It is not difficult to see that engineered models can simulate only a specific MDS characteristic; the development of the disease shows a highly complex progression and genetic basis, and some models with genetic perturbations found in humans with MDS do not develop MDS in mice.35

### 2.3 Induced mouse model

The induced MDS mouse model is artificially produced using physicochemical and biological agents. Mice exposed to carcinogenic chemicals (eg benzene and alklyation agents) or ionizing radiation (eg gamma rays) can be induced to develop MDS.36 37 These induced models are simple to maintain and simulate the basic processes in MDS, making them useful for establishing tumor models. Mahgoub et al12 found that cyclophosphamide, an alklyating agent, can induce MDS in mice exposed to toxic clinical chemotherapy drugs used to treat leukemia and myelodysplastic syndrome. In addition, people with frequent occupational exposure to benzene are susceptible to developing leukemia and MDS. To study the process of benzene-induced MDS, Das et al established a benzene-induced mouse model.11 However, because the biological characteristics of the induced model are unstable and the inducers are harmful to people, this induced mouse model is seldom used.
Compared with mice, rats are larger, and their physiological characteristics are easy to study. Rats are also the first choice in pharmacology research and are widely used in cardiovascular disease and sports disease research fields. Feng Baohang et al, from the Institute of Hematology and Chinese Academy of Medical Sciences, established an MDS rat model using chemical induction (TR1) in rats. The chemical mutagenesis agent used in this study was dimethylbenzantracene (DMBA). The changes in bone marrow and blood in the rats within 3 months of the DMBA injection in the tail vein were similar to those observed in human MDS, and different doses of DMBA caused different variations in severity. Approximately 30% of the rats with MDS developed leukemia, mostly erythroleukemia. Later studies showed that MDS rats that developed erythroblastic leukemia had the same C-erbb gene rearrangement and amplification as those in human erythroblastic leukemia, proving that the MDS rat model is useful for the study of human MDS. Currently, studies using the MDS rat model mainly focus on the therapeutic effect of traditional Chinese medicine (TCM) and TCM compounds such as Icariin, Yisui Lixue Decoction, and Rebound capsules on MDS.

### 4 | ZEBRAFISH MODEL OF MDS

Zebrafish, an internationally used biomedical research model organism, has a short reproductive cycle, is inexpensive to maintain and undergoes rapid development. Zebrafish are highly similar to mammals in blood content and gene regulation networks, which makes them good models for studying the pathogenesis of some blood diseases. The c-myb transcription factor is a key regulator of hematopoietic cell proliferation and differentiation, and c-myb disorders are usually associated with various blood diseases. One study found that high expression of c-myb-gfp in transgenic zebrafish can cause abnormal expansion of zebrafish granulocytes, which is similar to a human MDS symptoms. A few zebrafish with high levels of c-myb-gfp expression develop acute myeloid leukemia or acute lymphoblastic leukemia-like disease with age. A zebrafish model was established to study the development of leukemia related to c-myb and the cellular and molecular mechanisms of anti-leukemia drug screening.

The role of TET2 mutations in myeloid malignancies has been studied in a number of mouse models, and the importance of TET2 in maintaining the normal growth and development of myeloid lineage cells has been identified. A recent study has established a zebrafish MDS model by disrupting the Tet2 catalytic domain. In this model, the zebrafish can develop MDS at 24 months of age. Because the adult fish develop MDS, this zebrafish model can be used to identify suppressors of tet2 mutant hematopoietic cells.

### 5 | APPLICATION OF MDS MODELS

Of the three types of animal models of MDS described above, the mouse model is the most commonly used for preclinical research. For evaluating clinical drug efficacy, the SKM-1 cell line or MDS cells obtained directly from patients are usually used for establishing a xenograft mouse model, as exemplified by research on the anti-tumor effect of azacitidine, decitabine and deferasirox in combination with decitabine.

However, primary human MDS cells grow poorly in xenografted mice, and this makes genetically engineered mouse models a more attractive option. There are at least two mouse models that can replicate human MDS and progress to AML (NUP98/HOXD13 mice, and NPM1+/- mice). Because the NUP98/HOXD13 mice model exhibits a prolonged period of cytopenias prior to transformation to leukemia, it is more often chosen as the model for MDS research. For example, NUP98/HOXD13 mice were used to investigate the role of bone marrow microenvironment in the progression of MDS, and the impact of factors such as multi-kinase inhibitor (iogosertib), the BCL-2 family of proteins (BOK) and reactive oxygen species (ROS) on the bone marrow microenvironment in MDS pathogenesis. Similarly, NPM1+/- mice show disease progression similar to the progression of human 5q- syndrome, and are thus a powerful tool for studying dysplasia of myeloid lineage cells. Although it is difficult to reproduce all features of MDS in a single model, researchers can choose a model suitable to their experimental purposes.

### 6 | CONCLUSION

Animal models have been developed to study details of pathologies that cannot be resolved clinically. The models can be established to reflect accurately the genetic variations of different MDS patients and provide similar cellular conditions for the recovery of productive blood phenotypes (such as cells with impaired differentiation and bone marrow hematopoietic cell with increased rates of apoptosis). They are also useful for summarizing patient symptoms and assessing current treatment regimens, and for studying the progression of MDS into AML in cases established as being similar to those seen in the clinic. Although there may not be a model that satisfies every condition, at the same time, a comparison of several different models can be correlated to a corresponding clinical type to ensure that the best available animal models are selected for study. Once developed and validated, an MDS model can be used to improve the understanding of the molecular biology of this disease and as a platform for developing new treatments. Thus, the exploration and establishment of myelodysplastic syndrome (MDS) models is important for promoting the treatment of MDS and leukemia.

In this review, we described three types of MDS animal models - mouse, rat, and zebrafish - and analyzed the pros and cons of some existing MDS models based on these three model animals. Research on MDS has tended to focus on the development of genetically engineered models, but these remain imperfect as an experimental tool because they generally only recapitulate a subset of the phenotypes associated with human MDS. In xenotransplantation models, the dominant growth of residual normal hematopoietic cells and short survival time of MDS cells in the graft mean that current
MDS transplantation models can only partially recapitulate the genetic and epigenetic complexity of MDS patients; they also have low transplantation efficiency. Application of induced models is even more limited, because of their instability and safety concerns. Despite these limitations, modeling MDS in animals has recently met with some success, but new MDS models are also urgently needed. Developing a spontaneous animal model through breeding methods like those used for other tumor models may be the route to greater success in modeling human MDS. It is to be hoped that more animal models will appear in the near future to aid development of new therapeutic approaches for patients with MDS.

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