Animal Models of Acute lymphoblastic leukemia: recapitulating the human disease to evaluate drug efficacy and discover therapeutic targets

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Abstract

Acute lymphoblastic leukemia (ALL) is a malignant hematologic tumor with highly aggressive characteristics, which has few clinically effective drugs. It is meaningful to gain a better understanding of its pathogenesis in order to discover and evaluate potential therapeutic drugs and new treatment targets. However, the process of new drugs from research and development to clinical application is long and difficult. Many promising drugs were rejected by the US Food and Drug Administration (FDA) due to serious adverse drug reactions (ADR) in clinical phase I trials. Animal models provide us with an excellent tool to understand the complex pathological mechanisms of human diseases, to evaluate the potential of new targeted drugs and to assess the potential ADR they may have on healthy organs. In this article we briefly introduce the clinical status of ALL, review ALL animal models' progression, their roles in revealing the pathogenesis of ALL and drug development.

1.Introduction

ALL is a serious hematological system disease with highly aggressive characteristics(Terwilliger & Abdul-Hay, 2017). The lymphocytes proliferate and accumulate abnormally in the bone marrow, and transfer to other tissues and organs, causing systemic organs and tissue infiltrations and infections, seriously affecting normal hematopoietic function(Tan, Bertulfo & Sanda, 2017). ALL includes T-cell acute lymphoblastic leukemia (T-ALL) and B-cell acute lymphoblastic leukemia (B-ALL). Among them, T-ALL accounts for about 12% to 15% in pediatric ALL cases (You, Medeiros & Hsi, 2015). ALL is prone to occur in adolescents and children, and patients under 20 years old account for 60% of the total cases. The five-year event-free survival (EFS) of ALL is 60%-75%(den Hoed et al., 2015), significantly lower than other types of leukemia. With the development of new drugs and the application of new technologies, the survival rate of ALL patients has improved. In pediatric ALL, overall cure rates are approaching 90%,but in adult ALL, long-term survival rates are ~ 35 - 50%(Wei & Cleary, 2014), EFS and overall survival (OS) are still less than 70%, and the prognosis of relapsed and refractory ALL is poor(Sánchez-Martínez et al., 2019). Due to ethical reasons, clinically common refractory diseases are obviously impossible to replicate in human body to study the pathological and genetic mechanisms of disease occurrence(Adams et al., 1985). The remarkable functions of animal models are to: (1) simulate human genetic conditions and tumor growth microenvironment, (2) evaluate drug treatment effects, targets and ADR, (3) assess biomarkers related to tumor malignant transformation, (4) study the exogenous predisposing factors and pathogenesis of leukemia. At present, the animals commonly used to study ALL are mainly including mice, rats, zebrafish and*Drosophila melanogaster* (Milne, 2017). Among them, mice are very similar to humans in terms of genetics and hematopoietic system, and this unique advantage makes it important to establish mouse leukemia models to study the cellular molecular biology, biochemical and immunological characteristics, pathophysiological changes, pathogenesis, and drug treatment of human leukemia(Fortier & Graubert, 2010). Moreover, mice have the advantages of low price and good

reproducibility, and the mouse xenotransplantation model and transgenic mouse model have been paid more and more attention and application. This article reviews the latest research progress of animal models of ALL.

2.The Development of Drugs and Treatments of ALL in Recent Years

ALL is prone to occur in children around 5 years old and adults around 50 years old, it is mainly considered to be a kind of pediatric leukemia, accounting for 80% of cases in children and 20% in adults(Jabbour, O'Brien, Konopleva & Kantarjian, 2015). The 5-year OS rate for children is about 90%, compared to only 30% to 40% for adults and elderly patients(Inaba & Mullighan, 2020). The chemotherapeutics used in clinical to treat ALL include glucocorticoids, microtubule inhibitors, anthracyclines, purine and folate antimetabolites, asparaginase and DNA alkylating agents. In recent years, great progress has been made in therapeutic target discovery and drug development, such as antibody-drug conjugate (ADC) inotuzumab ozogamicin. Inotuzumab ozogamicin is used to treat relapsed or refractory CD22-positive precursor B-cell ALL (pre-B ALL), and calaspargase pegol-mknl (Cal-PEG), the asparagine-specific enzyme, is used to treat children and adolescents ALL. It is worth mentioning that blinatumomab, which was approved by the FDA in 2014, is the world's first approved CD19 drug by the FDA for the treatment of Ph- relapsed/refractory pre-BALL. At present, the main clinical methods to treat ALL include early intensive therapy, hematopoietic stem cell transplantation (HSCT), cranial radiation therapy (CRT), Central Nervous System (CNS)-directed chemotherapy, and chimeric antigen receptor T-cells (CAR-T). Intensive therapy has significantly improved the prognosis of pediatric patients, but has the disadvantage of long-term sequelae. In addition, only 30-40% of adult ALL patients achieve long-term remission(Jabbour, O'Brien, Konopleva & Kantarjian, 2015), elderly patients and patients with high-risk subtypes of leukemia, such as early T-cell precursor ALL(ETP-ALL), often cannot tolerate such treatment regimens and have a poorer prognosis(Ballesteros-Arias, Silva, Paiva, Carbonetto, Faísca & Martins, 2019). Although multi-drug chemotherapy has certain therapeutic advantages, many patients still relapse and develop refractory leukemia(Gianfelici et al., 2016), and only 20% of relapsed pediatric patients can be cured(Richter-Pechańska et al., 2017). In addition, the use of genotoxic drugs in the treatment process may lead to secondary malignancies(Teepen et al., 2017). Thus, we need more effective and less toxic treatments to improve the prognosis of ALL patients. One report replaced chemotherapy with targeted therapy, dasatinib combined with dexamethasone to treat ALL, and then performed two cycles of bispecific anti-CD3 and anti-CD19 antibody blinatumomab, proving that targeted therapy can avoid the induction of combined chemotherapy, with an OS of 95% and a disease-free survival of 88%(Foà et al., 2020). Targeted drugs can pinpoint and identify cunning tumor cells, delivering precise and thorough strikes with few ADR cases, without damaging their own tissues. However, targeted drugs are expensive and mostly are not suitable for all cancer patients. Animal models can replicate human diseases in a short period of time, which makes it more convenient and effective to understand the occurrence and development of human diseases and offers the measures to prevent and overcome diseases, therefore laying the foundation to develop potential targeted drugs, individualized treatment and new therapeutic tools.

3. Spontaneous ALL Animal Models

Some strains of mice will spontaneously develop leukemia during growth, and only need to screen them to obtain the desired animal model. AKR mice are the strain with the highest incidence of leukemia, and C57BL mice can also be used for screening. AKR strains have a high incidence of lymphocytic leukemia, with a prevalence of 70%-90%, and were commonly used for lymphocytic leukemia research before the development of transgenic technology and xenograft models. As early as 1975, researchers studied whether the genetic factors of AKR mouse strain played a role in the occurrence of leukemia. Later, researchers studied the sequence characteristics of AKR mouse leukemia virus substrain and the structure of the integrated recombinant genome in tumor tissues and found that AKR, as a spontaneous leukemia mouse, was born with a carcinogenic RNA virus(Quint, Quax, van der Putten & Berns, 1981). Compared with tumors induced by experimental methods, the clinical symptoms of spontaneous models and human tumors are more similar, and the conditions for tumor occurrence are more natural. However, the etiology of spontaneous models is quite different from the pathogenesis of human diseases, which are mainly caused by genetic factors. Moreover, such

model is easily affected by environmental factors, and the model takes a long time to establish and has poor stability, so it is rarely used in practice. In order to establish an animal model with a short incubation period and the tumor that is more similar to human cancer in pathogenesis, researchers have explored induced animal models.

4.Induced ALL Animal Models

4.1 Chemical-Induced ALL Animal Models

Early work in murine models was based on the chemical-induced models to test possible therapeutic agents. In 1954, Dr. Law exposed DBA/2 mice to the carcinogen 3-methylcholantrene and isolated the L1210 leukemia cell line(Law, Taormina & Boyle, 1954). The cells can be propagated *in vitro* , and then injected into a large number of recipients, these recipients will then develop leukemia. In addition to the important L1210 cell line, there are several other chemically induced leukemia cell lines, including P388, P1534 and L5178Y(McCormack, Bruserud & Gjertsen, 2005). The use of antimetabolites was first tested in these models. The animal models established by the transplantation of L1210 and P388 cell lines provide a platform for the test, kinetic study and evaluation of the anti-leukemia efficacy of chemotherapy drugs(Skipper & Perry, 1970), mainly for screening anthracyclines(Casazza, Pratesi, Giuliani & Di Marco, 1980), antimetabolites including cytarabine(Kline, Venditti, Tyrer, Mantel & Goldin, 1966), and evaluating the efficacy of topoisomerase II inhibitors(Jensen et al., 1990). In addition to the transplantation of leukemia cell lines, in the early years, scientists induced leukemia models by directly administering chemical carcinogens to laboratory animals. In 1973, researchers repeatedly injected 7,12-dimethylbenzanthracene (DMBA) intravenously on the Wistar/H-Onc rat strain. After 5-9 months, 10% of the rats developed leukemia(Gál, Somfai & Szentirmay, 1973). In order to explore the genetic damage caused by benzene-induced acute leukemia, chronically exposed CBA/Ca mice to 300 ppm benzene by inhalation, and successfully established an acute leukemia mouse model(Rithidech, Dunn, Bond, Gordon & Cronkite, 1999). However, these models have some disadvantages which limit their application. The etiology of chemically induced leukemia is different from the pathogenesis of most human ALL, because only a minority number of patients develop leukemia after prolonged exposure to chemical agents. In addition, this type of model is not stable enough, often induces multi-site tumors, and has a high fatality rate, so it is rarely used as a screening model for drugs.

4.2 Radiation-InducedALL Animal Models

Leukemia is one of the first malignant tumors to be identified as radiation-induced. Many X-ray workers who work near particle accelerators and ionizing radiation(IR) have developed leukemia(Committee on the Analysis of Cancer Risks in Populations near Nuclear Facilities-Phase, Nuclear, Radiation Studies, Division on, Life & National Research, 2012). In a systematic study of Japanese atomic bomb survivors, researchers discovered many patients suffering from hematological malignancies, especially ALL and AML(Rivina, Davoren & Schiestl, 2014). Patients receiving high doses of therapeutic radiation also often develop leukemia, proving the correlation between radiation exposure and leukemia. Later, researchers found that IR-induced leukemia has age differences, with children between the ages of 5 and 9 appearing to be more likely to develop ALL, while older children and adults are more likely to develop AML(Little, Weiss, Boice, Darby, Day & Muirhead, 1999; Preston et al., 1994; Weiss, Darby, Fearn & Doll, 1995).

Stage I and II lymphoid tumors are mainly treated with radiotherapy, which uses radiation to kill tumor cells, but often has greater ADR incidence, damaging its own normal cells and tissues, producing bone marrow suppression and CNS toxicity. There is a lack of "perfect" drugs on the market to reduce radiation-induced toxicity and avoid other cancerous risks caused by radiation. Animal models are needed to simulate the molecular and pathophysiological characteristics of human radiation-induced malignant tumors. The radiation-induced mouse models are widely used to study the development of radiation-induced leukemia and gain insights into the biology of human leukemia/lymphoma. For example, in order to identify the key carcinogenic drivers of radiation-induced leukemia, researchers administered 1.8 Gy total-body irradiation(TBI) to mice for four consecutive weeks and performed whole-exome sequencing on normal mouse tissues for four weeks, and found that Notch1 signaling activation played a key role in the multi-step carcinogenesis of mou-

se thymic lymphoma, which laid the foundation for a better understanding of the multi-step carcinogenesis mechanism of hematologic malignancies after TBI(Lee et al., 2021). Irradiated mice with different intensities of X-ray and analyzed the samples to study the mechanism of radioactive leukemogenesis, revealing that abnormal regulation of Sfpi1/PU.1 is an important step in the development of induced AML(O'Brien et al., 2020). Multiple murine strains develop leukemia on exposure to high and low-grade radiation, including the C57BL, BALB/c and NFS mouse.

C57BL mouse has become widely used in the laboratory since 1921. In the early years, C57BL mice were irradiated with different radiation doses, and the optimal dose for inducing thymic lymphoma was determined(Kaplan, 1952), the incidence of leukemia/lymphoma was 15% to 19%(Lieberman & Kaplan, 1959). In recent years, radiation-induced C57/BL mouse models have been used to study the mechanism of radiation carcinogenesis(Takabatake et al., 2008) and the relationship between changes in the thymic microenvironment and radiation-induced leukemia/lymphoma development(Tsuji et al., 2013). Since 1932, BALB/c mice have been widely used in animal experiments in immunology and physiology(Potter, 1985), and have played a pivotal role in studying the mechanism of radiation-induced tumors. In the radiation-induced BALB/c mouse model, it was discovered that the tumor suppressor gene miR-21 was involved in radiation-induced carcinogenesis(Liu et al., 2011). The inbred NFS mouse is an inbred strain of the NIH Swiss mouse. The unique advantage of the NFS mouse strain is that the genetic information of the virus is not expressed under normal conditions and the expression of the virus genes induced by radiation is easier to be detected. Similar to the induction method of BALB/c and C57BL mice, NFS mice received 1.7Gy irradiation 4 times a week to induce leukemia/lymphoma from 1 month-old. Leukemia first appeared in NFS mice approximately 3 months after irradiation, and most mice developed leukemia 4 to 6 months after irradiation. The incidence of leukemia is 90% in females and 89% in males. In addition, approximately 10% of this strain develop spontaneous thymic lymphoma(Ihle, 1978).

4.3 Virus -Induced ALL Animal Models

AKR mice are susceptible to leukemia and murine leukemia viruses(Mulv) have been widely used to simulate human leukemia in susceptible mouse strains(Rein, 2011). In the 1950s, Dr. Charlotte Friend injected the MuLV supernatant from the spleen suspension of leukemia-affected AKR mice into newborn mice to induce leukemia in adult Swiss mice or DBA/2 mice and cause serial transmission(Friend, 1957). Lymphoblastic leukemia and lymphoma caused by retroviral insertion mutations can be used to characterize new genes related to the occurrence of lymphoid leukemia by describing the virus insertion sequence, and confirming misregulation of several Notch signaling genes (Weiser et al., 2007).

Leukemia caused by C-type RNA tumor viruses or retroviruses is mostly T-cell type. If the body's control system is out of control, this tumor virus can turn hematopoietic cells into leukemic cells under the action of reverse transcriptase, resulting in adult T-cell leukemia. Bovine leukemia virus (BLV) and human T-cell leukemia virus type 1 (HTLV-1) make up a unique retrovirus family. Both viruses cause lymphoproliferative disease, with BLV affecting the B-cell lineage and HTLV-1 affecting the T-cell lineage(Aida, Murakami, Takahashi & Takeshima, 2013). BLV can infect a variety of cell lines(Graves & Ferrer, 1976) and spread to rats(Altanerova, Portetelle, Kettmann & Altaner, 1989), pigs, goats and sheep(Mammerickx, Portetelle & Burny, 1981)artificially. It is estimated that HTLV-1 has infected 5 to 10 million people worldwide and is a causative agent in adult T-cell leukemia/lymphoma (ATLL), as well as other inflammatory diseases(Gallo, Willems & Hasegawa, 2016; Martin, Tagaya & Gallo, 2018; Sodré Barmpas et al., 2019). Researchers injected HTLV-1-infected cell lines into NOG mice intraperitoneally, and other groups were given IR-treated HTLV-1 donor cells. Studies have found that the expression of Tax oncoproteins was up-regulated, and its relationship with Extracellular Vesicles (EVs) had a potential role in continuation of Tax-mediated pathogenesis, and ultimately promoted the development of ALL(Pinto et al., 2019). Tax oncoprotein enhanced uncontrolled replication of T cells and cellular genes (such as IL-2/IL-2R), disrupted DNA repair mechanisms, causes genetic instability, inhibits apoptosis of infected cells, and interferes with cell cycle checkpoints(Ahmadi Ghezeldasht et al., 2013; Currer et al., 2012). In addition, the levels of $CD4^+$and $CD8^+$ T cells in peripheral blood were significantly increased, indicating that HTLV-I infection in peripheral blood may cause the virus to

invade $CD4^+$ and $CD8^+$ T cell populations, as well as cells of the monocyte/macrophage cell line(Anderson et al., 2018; Knight, Macatonia, Cruickshank, Rudge & Patterson, 1993). These models are helpful for the identification and function of ALL-associated proto-oncogenes, facilitating us to better understand the mechanisms of virus-induced leukemia, helping to develop new strategies aimed at limiting virus transmission, and playing a huge role in promoting the development of virus-induced leukemia treatment strategies.

5.

Xenotransplantation ALL Animal Models

Since the culture system cannot replicate the complex interaction between leukemia cells and the bone marrow microenvironment, it is very difficult to culture and expand clinically aggressive patient-derived leukemia cells *in vitro* . The rate of cancer metastasis and cell characteristics may change depending on the culture environment. To overcome these limitations, researchers transplanted primary ALL cells and cell lines into immunodeficient mice and developed mouse xenograft models. The establishment of xenograft models is essential to study the molecular mechanisms of human leukemia and to improve treatment options by simulating human disease in animals for a more extensive evaluation of human ALL.

5.1 Experimental animal pretreatment

Before ALL cell transplantation, the experimental animals should be pretreated to produce bone marrow suppression and immunosuppression, thereby reducing or eliminating the immune rejection reaction of immune cells to human cell implantation and improving the success rate of transplantation. The common pretreatment modalities nowadays mainly include γ-ray total body irradiation (TBI), injection of cytotoxic drugs and administration of natural killer cell monoclonal antibodies to experimental animals. TBI can significantly improve the success rate of transplantation, the success rate of transplantation with TBI was 91.7%, while without TBI it was only 15.4%(Patel et al., 2014). However, mice treated with high-dose TBI have high mortality, while low-dose TBI resulted in low cell implantation rate. Therefore, injection of cytotoxic drugs is more common. The study found that when NSG mice were given a TBI dose of 2.4Gy, the survival rate at week 24 was only 33%, while the survival rate of NSG mice that received a large dose of busulfan was 100% at week 24(Choi et al., 2011).Anti-CD122 antibody pretreatment is also commonly used, which can inhibit the activity of natural killer(NK) cells and target NK cells and macrophages, thereby exerting an immunosuppressive effect(Yuan, Dong, Tsurushita, Tso & Fu, 2018).

Transplantation donors generally choose immune-deficient mice aged 4-5 weeks and the main methods of transplantation are subcutaneous injection, tail vein injection and intraperitoneal injection. The number of cell inoculation is generally 10^6-10^7 per mouse. Mice generally show symptoms of slowness, paralysis, and curvature of the spine in about three weeks, and leukemic cell infiltration can be detected in peripheral blood, bone marrow, liver, spleen, lung and meninges.

5.2 Humanized Mouse Models

5.2.1 Nude Mouse

Since the 1970s, athymic nude mice have been widely used for xenotransplantation of human solid tumors(Fogh, Fogh & Orfeo, 1977). Athymic nude mice are mutant mice with congenital thymus defects and lack functional T cells. In 1982, researchers tried for the first time to transplant primary AML cells into nude mice whose Foxn1gene (encoding for a forkhead box transcription factor) mutations caused immune damage. Since the functions of B cells and NK cells were basically normal(Panoutsakopoulou, Little, Sieck, Blankenhorn & Blank, 1998), the transplantation effect of leukemia cells was very poor, only granulocytic sarcoma is produced, and bone marrow and other organs are not affected(Nara & Miyamoto, 1982). In 1992, Federica Cavallo established a leukemia animal model that selectively invaded the CNS. This model reproduces some aspects of human meningeal leukemia, if human leukemia cells diffuse directly into the CNS mainly through the bone marrow, then cranial radiotherapy may be a more effective method to prevent leukemia cell infiltration than systemic blood therapy(Cavallo, Forni, Riccardi, Soleti, Di Pierro & Forni, 1992).

Xenograft nude mouse models all along have played a pivotal role in studying the clinical features, pathogenesis and medication of ALL, which are closer to the clinic because they retain the tumor biological characteristics. A human leukemia xenograft model established by transplanting highly tumorigenic leukemia cell line HL-60 cells subcutaneously in nude mice to investigate the growth inhibition and apoptosis-inducing effects of deferoxamine (DFO) combined with arsenic trioxide (ATO) on human HL-60 nude mice transplanted tumors and its mechanism. The results showed that the drug combination inhibited tumor growth more significantly than the drugs alone, this finding provides solid evidence for adjuvant therapy of leukemia(Yu, Wang, Ren, Zeng & Liu, 2014). Signal transducer and activator of transcription 5(STAT5) is frequently overexpressed or aberrantly activated in leukemia and plays an important role in cell survival, proliferation and differentiation(Verhoeven et al., 2020). On this basis, researchers have discovered that STAT5 can be used as a therapeutic target with the aid of nude mouse transplantation model. STAT5 constitutively activated cell line HL-60CS5 cells were injected into female BALB/c nude mice to establish a xenograft model, and a new AURKA inhibitor AKI604 was found to overcome STAT5-induced leukemic proliferation by inducing mitochondrial damage in AML treatment, suggesting that targeted therapeutic strategies overcome the disadvantages of intolerance and drug resistance of chemotherapy regimens for the treatment of acute leukemia(Wang et al., 2020).

5.2.2 The Severe Combine Immunodeficient (SCID) Mouse

In 1983, Dr. Bosma discovered SCID mice while raising a colony of C.B-17 mice, and the genetic background of SCID is basically the same as that of BALB/c mice. SCID mice are mutant mice caused by mutations in a single recessive gene on autosome 16 of C.B-17 inbred mice. Inactivation and mutation of the protein kinase DNA-activated catalytic polypeptide (Prkdc) gene leads to incorrect recombination of the immunoglobulin V-D-J gene and ultimately leading to the inability of T and B lymphocytes to develop properly(Bosma, Custer & Bosma, 1983).

The development of SCID mice was an important progress for the development of humanized ALL mouse models. SCID mice have less immune rejection to human tumor cells, and the implantation rate of primary ALL cells by intraperitoneal injection or implanted under the kidney capsules is significantly increased(Sawyers, Gishizky, Quan, Golde & Witte, 1992). Later, researchers treated SCID mice with human stem cell factor (SCF) and granulocyte-macrophage colony stimulating factor (GM-CSF). This was the first evidence of a hierarchy of leukemia cells. This model replicates many aspects of human leukemia and defines a new type of leukemia-initiating cell that is less mature than colony-forming cells(Lapidot et al., 1994). In1995, the first adult ALL SCID mouse leukemia model was established successfully, describing for the first time the relationship between the phenotypic-genotypic characteristics of adult ALL cells and their implantation and propagation in SCID animals, providing an *in vivo* adult ALL model to study the biology and pathophysiology of adult ALL and therapeutic methods(Jeha et al., 1995). In addition, the SCID mouse model is also used to evaluate the advantages and prospects of targeted therapy.CD19-targeted therapy is a novel cell therapy with significant efficacy and is considered one of the most promising oncology treatments for acute leukemia and non-Hodgkin's lymphoma. Researchers established the first SCID mouse model which using monoclonal antibodies targeted therapy to treat ALL. They demonstrated that when the radioactive metal binds to the anti-CD19 antibody, it can specifically target the spleen, liver and bone marrow infiltrated by leukemia cells, prolonging the survival time of SCID mice(Mitchell et al., 2003). This model can be used to evaluate treatment methods and lay the foundation for subsequent targeted drug research.

Notably, approximately 10% of SCID mice show "leakiness" of the SCID mutation in youth(Forsberg et al., 2019; Nonoyama, Smith, Bernstein & Ochs, 1993), that is, a certain degree of immune function recovery, which is manifested in the recovery of functional B and T cell activity, the enhancement of NK cell activity, and the activation of complement which reduces the implantation efficiency(Carroll, Hardy & Bosma, 1989).

5.2.3 The Non-obese Diabetic/Severe Combine Immunodeficient (NOD/SCID) Mouse

To overcome the problem of low transplant success rate in SCID mice, researchers combined the SCID background mice with a non-obese diabetic (NOD) strain to create a mice strain with more severe immun-

odeficiency(Prochazka, Gaskins, Shultz & Leiter, 1992) that provided a supportive microenvironment for normal and malignant human hematopoietic cells. NOD/SCID mice lack of functional T or B cells, and the activities of NK cells and macrophages are reduced(Nagamoto et al., 2015), a variety of tumor cells can be implanted, immune rejection and graft-versus-host disease are less likely to occur. Therefore, NOD/SCID mice have gradually become a useful tool for hematological experimental research.

Researchers have made a breakthrough through the NOD/SCID ALL model and found that a shorter "time to leukemia (TTL)", that is, the time from transplantation to the appearance of leukemia is closely related to the high risk of early relapse. The proliferation of neonatal ALL cells transplanted into NOD/SCID mice has predictive value for patient prognosis, thus determining an independent prognostic factor(Meyer et al., 2011). TTL^{short} means TTL is less than 10 weeks, and longer time periods are classified as TTL^{long}. TTL^{short} identifies patients with early relapse, while TTL^{long} relapse-free survival is as high as 100%. The NOD/SCID ALL model provides a powerful tool for identifying prognostic factors in acute leukemia at the cellular and molecular levels, thus providing a rational target for therapeutic strategies. The intact apoptotic body function reflected by a positive Cytochrome c-related activation of caspase-3 (CRAC positive) is closely associated with long-term implantation of NOD/SCID (TTL^{Long}) in primary leukemia cells and a good prognosis. The complete formation and function of apoptotic bodies means that the time of NOD/SCID implantation is prolonged, the treatment response is good, the prognosis is good, and the patient survives without recurrence(Queudeville et al., 2012). To determine disease prognostic factors, the NOD/SCID mouse model has also played an important role in exploring novel drug targets. ATLL is an aggressive disease that is highly resistant to chemotherapy. Due to the high expression of KU70 in Jurkat cells, the researchers injected Jurkat cells which knocked out of the KU70 gene into NOD/SCID mice, discovered that KU70 may be a new target for ATLL treatment and help to overcome chemo-resistance(Yu, Li, Wang, Zhang, Xu & Liang, 2018). Another xenotransplantation method is to extract hematopoietic progenitor and stem cells (HP/HSCs) from patients or mice, transduce the cells through reverse transcription or lentivirus, and then transplant them into the recipient. Researchers transplanted $CD34^+$ hematopoietic progenitor cells and stem cells ($CD34^+$HP/HSCs) from patients infected with HTLV-1 into NOD/SCID mice, which specifically developed $CD4^+$T-cell lymphomas similar to ATLL, and increased proliferation of virus-infected human stem cells ($CD34^+CD38^-$) in mouse bone marrow was observed. This model provides an important tool for identifying the molecular mechanism of the occurrence and development of leukemia/lymphoma, exploring potential therapeutic targets for inhibiting tumor development and evaluating the role of HTLV-1 helper genes in the pathogenesis of the virus(Banerjee et al., 2010).

NOD/SCID mice are host that are more receptive to the proliferation of human leukemia, however, the high transplantation rate of T-ALL cells suggests that this model fails to identify risk groups, and the researchers found that human-derived T-ALL cells appear to be more readily transplanted in NOD/SCID mice, suggesting that this model may be more useful than SCID mice in studying the biology and treatment of T-ALL(Steele et al., 1997). NOD/SCID mice have lower immune function and higher tumor formation rate. More importantly, this model retains the morphological, phenotypic and genotypic characteristics of ALL donors(Bonnet & Dick, 1997). However, this mice strain will also have "leakiness". Due to the development of thymic lymphoma and the recovery of NK cell activity, it cannot be implanted for a long time, and usually the implantation time cannot exceed 8.5 months(Shultz et al., 1995).

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NSG mouse strain is an immunodeficient mouse that knocks out the interleukin 2 receptor gamma chain (IL2Rγ) gene on the basis of NOD/SCID(Ito et al., 2002). This mice strain lacks mature T and B lymphocytes and completely loses NK cell activity(Koller & Smithies, 1989). Compared with NOD/SCID mice, the transplantation survival rate of human cell and tissue in NSG mice is significantly improved, and at the same time, a higher proportion of normal or cancerous human cells and tissues can be implanted.

The NSG mouse xenograft model is considered the gold standard for evaluating human hematologic malignancy grafts(Sontakke et al., 2016) and is widely used to assess disease pathogenesis and explore potential therapeutic strategies. Researchers have used the NSG mouse xenotransplantation method to elucidate the

leukemia-initiating cell (LIC) biology of pre-B ALL in order to optimize the disease model. Different *in vivo* growth requirements were determined between adult and child ALL subtypes, and the importance of age/leukemia subtype specific research was discovered. This animal model improves our understanding of the biology of ALL disease(Patel et al., 2014). In addition, the NSG model is also used to evaluate the effect of cytokines on leukemia. Studies have shown that IL-27 can promote the proliferation and differentiation of $CD34^+$ cells in non-leukemia patients(Seita et al., 2008), suggests that the cytokine may have an effect on normal hematopoietic stem cells. Based on this, researchers injected pediatric leukemia cell samples intravenously into NSG mice for*in vivo* studies to evaluate the anti-tumor activity of human IL-27. IL-27 reduces the angiogenesis potential of tumor cells, regulates tumor spread-related genes, and exerts an anti-tumor effect(Zorzoli et al., 2012). In recent years, cellular immunotherapy has proven to be an effective treatment for B-cell malignant hematologic diseases. T cells modified with CD19-specific chimeric antigen receptors (CARs) have significant clinical advantages for the treatment of leukemia. NSG mice model is also an excellent tool for evaluating the superiority of CAR-T therapy, and it has been demonstrated that a lentiviral vector targeting CD8 (CD8-LV) could generate CD19-CAR T cells in NSG mice(Pfeiffer et al., 2018). Recently, researchers have made further progress by using CD4-targeted lentiviral vector (CD4-LV) to selectively produce CD19-CAR T cells in $CD4^+$ cells successfully. Transplanted Nalm-6 cells which encoded by $CD19^+$ luciferase into NSG mice and injected activated PBMCs cells. According to the luciferase intensity measured by the*in vivo* imaging system (IVIS) to evaluate the growth, spread and regression of leukemia in the body, it was found that the mice given CD4-LV showed faster and better tumor cell killing ability, indicating that $CD4^+$CAR-T cells have a stronger ability to eliminate tumor cells(Agarwal, Hanauer, Frank, Riechert, Thalheimer & Buchholz, 2020).

Xenograft models provide powerful tools for studying normal and malignant human hematopoietic systems. However, current models cannot simulate the human bone marrow (BM) microenvironment, and many human leukemia cells cannot be xenotransplanted. In order to overcome these limitations, scientists have used new advances in the field of bioengineering and synthetic material development to manufacture biological inserts or scaffolds that support the growth and differentiation of implanted cells effectively(Abarrategi, Mian, Passaro, Rouault-Pierre, Grey & Bonnet, 2018). Implanted ceramic scaffolds containing mesenchymal stromal cells (MSCs) into NSG mice to generate a human bone marrow (huBM-sc)-like niche and observed that AML MLL-$AF9^+$ and ALL BCR-ABL^+ patient cells were efficiently implanted, maintaining an immature primitive cell-like phenotype in the huBM-sc ecotype compared to the murine bone marrow (mBM) niche(Sontakke et al., 2016). Later, based on the discovery that human bone marrow mesenchymal stromal cells (BM-MSC) transplanted into heterotopic NSG mice can rebuild the functional hematopoietic microenvironment(Reinisch et al., 2015), the researchers mixed human bone marrow BM-MSC with extracellular matrix and transplanted subcutaneously to form a humanized bone marrow microenvironment in the ossicle after 8-10 weeks. The implantation level of normal human HSCs and leukemia cells containing subcutaneous humanized ossicles model is much higher than that of untreated mice, and direct intraosseous transplantation accelerates cell implantation and leads to an increase in the frequency of leukemia initiating cells(Reinisch et al., 2016). The scaffold implantation approach can evaluate the multicellular interactions between human MSCs and HSCs, and generate patient-specific human microenvironment in mice, which can be used to unravel the human tumor microenvironment, disease pathology and the role of drug physiological response(Abarrategi, Mian, Passaro, Rouault-Pierre, Grey & Bonnet, 2018).

6. Transgenic ALL Animal Models

Traditional transgenic(Tg) animal model is to inject the DNA fragments into the pronucleus of the fertilized egg directly, and then into the pseudopregnant female mice(Würtele, Little & Chartrand, 2003),or injected DNA into embryonic stem (ES) cells through electroporation(Thomas & Capecchi, 1987). In order to more accurately simulate the occurrence of leukemia, homologous recombination is used to generate vectors targeting specific sites in the genome. These vectors conditionally express genes in response to doxycycline (Tet ON/OFF system) or Cre recombinase (using Lox/Cre system) to produce tissue-specific expression of transgenes, and chromosomal translocations can be produced in mice through Cre-loxP-mediated recombination(Drynan et al., 2005; Forster et al., 2003), thereby mimicking the chromosomal translocations that

often lead to the formation of tumor-specific fusion oncogenes in human malignancies(Corral et al., 1996). In addition to the expression of oncogenes, oncogenic alleles can also be "knocked in" to the corresponding normal loci, or "knocked out" of tumor suppressor genes to establish transgenic animal models. In recent years, transgenic animal models have played a huge role in the general study of ALL subtypes, including B-ALL, T-ALL, and Burkitt's leukemia/lymphoblastic lymphoma, facilitating the discovery of drug targets and improving the treatment of leukemia, which will be described in detail in the following.

6.1 BCR-ABL

transgenic models

The BCR-ABL fusion protein is the result of t(9;22)(q34;q11) translocation, which is common in CML, but can also be found in B cell ALL. There are several isoforms of this fusion protein, including the P210 form and the P190 form, with the P120 form progressing to B and T lymphoma or myeloid leukemia after a longer latency period and the P190 form progressing to B-ALL(Voncken, Kaartinen, Pattengale, Germeraad, Groffen & Heisterkamp, 1995).

Researchers injected patients' BM cells which transfected with MSCV BCR-ABL1 lentivirus into C57BL/6 mice, and used this mouse model to determine the important role of tumor suppressor γ-catenin in the initiation and maintenance of BCR-ABL1$^+$B-ALL, determining the potential therapeutic target for the treatment of BCR-ABL1$^+$B-ALL(Luong-Gardiol et al., 2019). Cyclin-dependent kinase (CDK) is a promising drug target in cancer treatment, the loss of CDK8 significantly prolonged disease latency and inhibited disease progression(Menzl et al., 2019). Through the BCR-ABL transgenic mouse model, researchers found that CDK8 played a key role in B-ALL, and degradation of CDK8 might be a potential therapeutic strategy for the treatment of ALL. InLong non-coding RNAs(lncRNA)-Iur knockout transgenic mice, researchers explored the functional relevance between aberrantly expressed lncRNAs and BCR-ABL-mediated leukemia(Wang et al., 2019).

This model has explored the effect of obesity on the progression of ALL. For the first time, it was found that obesity could accelerate the development of ALL, in a controlled experiment between BCR/ABL transgenic mice and high-fat diet AKR/J mice(Yun et al., 2010). In addition, this model was also used to test the activity of tyrosine kinase inhibitors. The 8093ALL cell line was established in the background of P190 BCR-ABL transgenic mice and transplanted into C57BL/6J mice. It was found that nilotinib was significantly more effective than imatinib and was able to eliminate a significant number of ALL cells *in vivo* (Kaur et al., 2007). Later, researchers induced BCR-ABL expression in mice by the Tet-OFF system, and treatment with nilotinib reduced the number of leukemic cells and prolonged survival in mice. This suggests that combined inhibition of BCL-2 and BCL-ABL tyrosine kinases has the potential to significantly improve the cure rate of CML, while tyrosine kinase inhibitors targeting BCL-2 and BCL-ABL can overcome this limitation of disease relapse(Carter et al., 2016). These findings are of great significance for adjusting clinical treatment plans and improving patient prognosis.

6.2 MLL-AF4 transgenic models

The MLL-AF4 fusion protein is seen in patients with t(4;11) and it is strongly associated with B-ALL. As early as 1996, J Corral et al. fused the AF9 sequence into the mouse MLL gene, and used the method of embryonic stem cell homologous recombination to create an MLL-AF9 gene knock-in model, and the chimeric mice carrying the fusion gene produced tumors(Corral et al., 1996). Based on the success of this model, researchers established an MLL-AF4 "knock-in" transgenic model in which the majority of Mll-AF4 mice developed B-cell lymphoma after a long latency period(Chen, Li, Hudson, Kumar, Kirchhof & Kersey, 2006). In order to establish a mouse model more similar to human MLL-AF4, the researchers microinjected MLL-AF4 MSCV into the pronuclei of eggs from C57BL/6N Crj mice and established an MLL-AF4 transgenic mouse model by high expression of the human MLL-AF4 fusion gene. This is the first transgenic mouse to test the potential of human MLL-AF4 fusion protein to induce B-cell lymphoma/leukemia(Tamai et al., 2011). The above-mentioned MLL-AF4 Tg mouse models have also proved the effectiveness and feasibility of gene therapy for MLL-AF4$^+$ALL and the specific mechanism, gene therapy is a promising strategy for

the treatment of MLL-AF4$^+$ALL(Tamai et al., 2012). Later, the researchers evaluated the potential of the anti-allergic drug amlexanox to improve the clinical efficacy of MLL-AF4$^+$ALL and found that amlexanox reduced the resistance of MLL-AF4$^+$ALL to TNFα by down-regulating the expression of S100A6(Tamai et al., 2017).

Another model was generated using an inverted AF4 allele targeted to an intronin the MLL gene. An AF4 cDNA flanked with loxP sites inserted in reverse orientation into the endogenous MLL locus,and then,cell-specific Cre expression was used to generate Mll-AF4 expression. Regardless of whether the Cre gene is controlled by a B-cell or T-cell promoter, mice develop B-cell lineage tumors only, but their phenotype is more mature than that normally observed in childhood leukemia(Metzler et al., 2006).

6.3 Eμ-Mψς τρανσγενις μοδελς

Burkitt lymphoma/leukemia is a subtype of ALL, which is characterized by chromosomal translocation leading to Myc gene expression under the control of immunoglobulin heavy chain or light chain promoters. Myc oncogenes are usually highly expressed in human T-ALL(Erikson et al., 1986). Under the control of the IgG heavy chain promoter, the mouse Myc gene produces transgenic mice that mimic the clinically seen t(8;14),most of the mice suffer from B-cell lymphoma/leukemia(Harris, Pinkert, Crawford, Langdon, Brinster & Adams, 1988).

Researchers established three Myc transgenic mouse models. According to the level of Myc, the tumor phenotypes of Myc mice are different, with high expression leading to rapid-onset T-cell lymphoma, low expression leading to late-onset myeloid tumors, and moderate expression levels producing both tumor types(Campbell, Vandenberg, Anstee, Hurlin & Cory, 2017). Later, analyzed the gene expression and function of senescent and non-senescent B-cell lymphomas in Eμ-Myc transgenic mice, researchers found that previously senescent cells *in vivo* presented a higher tumor initiation potential. It is worth noting that in p53-regulated ALL and AML models, temporary strengthening of senescence can reprogram non-stem bulk leukemia cells into self-renewing, leukemia-initiated stem cells. These findings have far-reaching implications for cancer treatment(Milanovic et al., 2018). Recently, in order to analyze the important role of the microenvironment in regulating human AML population dynamics, researchers investigated the effects of oncogene (c-Myc) and exposure to cytokines such as IL3, GM-CSF and SCF on human AML cells in immunodeficient mice. This finding emphasized the key role these cytokines play in activating normally differentiated human hematopoietic cells(Bulaeva et al., 2020). The leukemia induced by these methods have rapid and powerful reproducibility, which provides a useful and powerful platform for testing and evaluating new treatment medication in human acute leukemia.

6.4 NOTCH1 transgenic models

NOTCH1 was first identified in the human T cell ALL-bearing translocation, t(7;9)(q34;q34.3). Activation of the NOTCH1 signaling pathway is the most important tumorigenic event in the pathogenesis of T-ALL(Weng et al., 2004), and this gene is related to the pathogenesis of most T-cell ALL types.

Researchers established a mouse bone marrow transplant (BMT) model in which Cre recombinase induces HSCs Notch activation, thereby inducing T-ALL in mice. The activation of Notch in HSCs leads to the expansion of hematopoietic progenitor cells and T cell precursor cells, and then the production of HSCs and T cells is gradually lost. The over-activated Notch signal in HSCs promoted the leukemia stem cell (LSC) activity of T cell precursor cells and inhibited the self-renewal of HSCs. This conditional transgenic model provides further evidence for T-ALL targeting, and also emphasizes the necessity of strictly regulate Notch signaling to expand the normal HSC population for clinical applications(Chiang, Shestova, Xu, Aster & Pear, 2013). Later, the CD4 promoter was used to express NOTCH1 mutants in Tg mice, including Notch1$^{\mathrm{IC}}$ and Notch1$^{\mathrm{EC}}$ produced by type I mutations, and Notch1$^{\Delta^{\sim}\mathrm{T}}$ produced by type II mutations, double (Notch1$^{\mathrm{IC}}\times$ myc) or (Notch1$^{\Delta^{\sim}\mathrm{T}}\times$myc) Tg mice developed thymoma with a much shorter latency than single Tg mice, providing genetic evidence of a collaboration betweenthese two oncogenes. These Notch1 mutations are very similar to some forms of human T-cell leukemia, and these Tg mice may represent relevant models of these human leukemias(Priceputu et al., 2006). The NOTCH Tg model also plays an important role in the

evaluation of drug efficacy. Researchers investigated the drug sensitivity of T-ALL cells in Notch1-induced $CD8^+CD4^+$ and $CD8^+CD4^-$ cell subsets in T-ALL mice and examined the sensitivity of $CD8^+CD4^+$ and $CD8^+CD4^-$ to cyclophosphamide and the mTORC1 inhibitor rapamycin. They found that the combined use of cyclophosphamide and rapamycin reduced the number of leukemia cells and prolonged the lifespan of T-ALL mice compared with the use of drugs alone. This indicates that the combination of cyclophosphamide and rapamycin is expected to improve the clinical treatment of NOTCH-induced T-ALL(Zhang et al., 2013).

7. Non-mouse Models

Insights into the pathophysiology of leukemia have been obtained in non-mouse models. These different animal models help us to understand the underlying mechanisms of leukemia treatment resistance and disease relapse, and are expected to improve treatment strategies.

Zebrafish's conservative hematopoietic system and unique experimental advantages, combined with the development of transgenic, genome editing and xenotransplantation technologies, reveal the details of leukemogenesis, progression and regression(Harrison, Laroche, Gutierrez & Feng, 2016). Zebrafish has become an attractive model for research on drug screening for hematological malignancies(Idilli, Precazzini, Mione & Anelli, 2017). The first zebrafish T-ALL model was created in 2003 by fusing the mouse c-Myc gene with the Enhanced Green Fluorescence Protein (EGFP) gene, and the lymphocyte-specific promoter rag2 drove the expression of the EGFP-mMyc fusion gene, resulting in T-ALL in zebrafish(Langenau et al., 2003). Later, the researchers modified the model and induced it with 4-hydroxy tamoxifen, and the Myc gene was activated, causing T-ALL in zebrafish(Gutierrez et al., 2011; Langenau, Feng, Berghmans, Kanki, Kutok & Look, 2005). In addition to the T-ALL model induced by Myc gene, researchers also successfully established a zebrafish T-ALL model by overexpressing the human NOTCH1 gene under the rag2 promoter(Sabaawy, Azuma, Embree, Tsai, Starost & Hickstein, 2006). Zebrafish are rapidly expanding our understanding of disease mechanisms and helping to develop treatment strategies to improve the prognosis of patients with leukemia. Based on the progress of zebrafish in high-throughput drug screening, it is expected to accelerate the development of novel leukemia therapeutic medications.

Rats are sometimes used when establishing carcinogens and radiation induced leukemia models(Huggins, Grand & Ueda, 1982; Svejda, Kossey, Hlavayova & Svec, 1958). It is reported that repeated injection of DMBA into Wistar rats, which induced 10% of rat leukemia in 5-9 months(Huggins & Sugiyama, 1966). A subline of inbred Sprague-Dawley rats has a high incidence of T cell malignancies and has been used for preclinical evaluation of treatment(Bua et al., 2018; Otová, Sladká, Panczak & Marinov, 1997). Drosophila has a strong hematopoietic capacity, and its genetic simplicity and ease of manipulation make it an attractive model for studying leukemia caused by complex chromosomal translocations. In order to study the detailed molecular mechanism of leukemia caused by the AML1-ETO chimeric protein, two AML1-ETO drosophila models were established using genetic engineering technology(Lebestky, Chang, Hartenstein & Banerjee, 2000). Later, researchers found in Notch-induced drosophila tumor models that Notch signaling and PI3K-AKT pathway have a synergistic effect in tumorigenesis. The transcriptional control of PTEN and the regulation of the PI3K-AKT pathway are key elements of the leukemia progress activated by NOTCH1. These findings provide the basis for the design of new T-ALL treatment strategies(Palomero et al., 2007).

8. Summary and Prospect

It is undeniable that animal models have played a huge role in revealing the mechanism of tumorigenesis and evaluating new drugs. It not only avoids the huge risks that may be caused by human trials, but also provides a safe and reliable method for leukemia research. More importantly, animal models provide an experimental platform for testing the efficacy of novel therapeutic compounds on human ALL and for studying drug resistance mechanisms. To sum up, these models provide a basis for drug development, screening and testing. And ultimately, they provide a basis for individualized treatment.

The advantage of the spontaneous model is that the clinical symptoms are more similar to those of human tumors, and the conditions for tumor occurrence are more natural. However, the etiology of the spontaneous model is different from that of humans, and is mainly caused by genetic factors. Moreover, this type of

model is easily affected by environmental factors, may cause disease complications, and has poor stability. In the past, chemistry, irradiation and viral models have played a significant role in ALL research and have been used to discover and evaluate ALL drugs. The tumorigenesis mechanisms of the induced animal model are clear, and the tumorigenesis rate is relatively high. However, this type of model is unstable and has a high fatality rate. Due to species differences, the pharmacodynamic results of these animal models are not conducive to derivation of human medications. In order to better simulate human diseases, researchers implanted humanized tumor cells into immunodeficient mice and established xenograft models, which have now become the main tool for studying ALL, providing us with the opportunity to observe the entire process of the development and regression of lymphocytic leukemia and may play a crucial role in clinical. The advantages of xenotransplantation are that the model is easy to establish, the speed of tumor formation is fast, and the clinical manifestations are similar to those of human leukemias, especially in terms of histopathology, immunohistochemical phenotype and karyotype. The transgenic model has obvious practicality in preclinical drug efficacy testing and exploring the interaction of matrix-immune cells. The advantages of transgenic models are that, these models overcome the problem that xenograft models cannot better simulate the microenvironment of tumor cell growth, and can accurately simulate human leukemia. These have made transgenic models have been successfully used to screen for and test novel targets and inhibitors. The major disadvantage is that there is a certain difference in interstitial components between mice and humans. In addition, transgenic animals are expensive, and the tumor formation process is complicated. We list the advantages and limitations of the various animal models in Table 1.

Evaluating therapeutic targets in transgenic and xenograft models is expected to enter clinical trials to improve the lives of leukemia patients. In future, advances in genome editing technology and cooperation in multidisciplinary fields will promote the production of more humanized mouse strains, which will help researchers to simulate the complex biology of ALL in mice more accurately. Ultimately, the use of many bioengineering models and continuous efforts to improve their effectiveness and physiological relevance will push preclinical research into a new era of targeted treatment development.

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Competing interests

The authors declare that they have no competing interests.

Author contribution

Qianling Xin wrote the manuscript and created the figures, all authors developed the outline, discussed, edited, and approved the manuscript.

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