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Engraftment of acute and chronic myeloid leukemia in NOD *scid* gamma mice

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SUMMARY

The immunodeficient mouse represents an established animal model for leukemic transplantation studies. It is used both as a self-contained research tool for the study of leukemia genesis and progression, as well as for confirmation of cell leukemogenic capability. The model as such has seen many modifications over the years, and while engraftment of primary acute and chronic myeloid leukemia samples is commonly feasible still not all samples can provide leukemic repopulation. This review specifically focuses on acute and chronic myeloid leukemia xenograft experiments using the current standard NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}*/SzJ* mouse model and aims to provide a basic insight into the topic. It also discusses the various specifics relevant for conducting such experiments.

KEY WORDS

xenograft, NSG mouse, AML, CML

SOUHRN

Čulen M., Dvořáková D., Semerád L., Šustková Z., Bouchnerová J., Palacková M., Mayer J., Ráčil Z.
Uchycení akutní a chronické myeloidní leukemie v NOD scid gamma myši

Imunodeficitní myši představují zavedený zvířecí model pro xeno-transplantační studie lidských leukemií, který se může použít jako samostatná in vivo metoda pro studium geneze a progrese leukemie, anebo může být použit pro potvrzení schopnosti transplantovaných buněk rozvinout leukemii. Tento myší model byl v průběhu času předmětem mnoha modifikací, a tak je v současné době přihojení transplantovaných buněk u akutní a chronické myeloidní leukemie zpravidla dosažitelné, i když ne u všech leukemických vzorků. Tato přehledová práce pojednává o xeno-trasplantačních experimentech u akutní a chronické myeloidní leukemie, ve kterých byl použit myší kmen NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}*/SzJ* představující v současnosti standardní animální model. Cílem práce je poskytnou základní náhled do problematiky myších modelů myeloidních leukemií člověka a představit hlavní kritické body při provádění těchto experimentů.

KLÍČOVÁ SLOVA

xenograft, NGS myš, AML, CML

INTRODUCTION

Myeloid leukemias are a group of hematological malignancies affecting the myeloid lineage of white blood cells. They can be simply divided into acute and chronic myeloid leukemia (AML, CML), where the former is characteristic by its rapid progression and high heterogeneity, with respect to both genetics and patient prognosis, and the latter represents a homogeneous disease, in 95% cases defined by the presence of the chromosomal translocation known as "Philadelphia chromosome" (Ph). A comprehensive description or understanding of AML is so far lacking, given its exten-

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sive heterogeneity. This provides very broad research options. On the other hand, in CML, tyrosine-kinase inhibitors represent a successful approach for disease suppression and research now mainly focuses on eliminating residual leukemic stem cells, which should eventually provide a definite cure for this disease.

The immunodeficient mice have played an important role in the study of leukemias as they allow *in vivo* modeling of patient disease. The importance of the first experiments involving severe combined immunodeficient (SCID) mice was that they allowed transplantation of primary patient leukemic samples without graft rejection [1]. Later, the residual immunity of this strain was suppressed in the NOD.CB17-*Prkdc*^{scid} (NOD/SCID, NS) mouse and a further deletion of the γ-common chain yielded the NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ (NSG) mouse, which currently represents a standard model for leukemic xenograft assays. The NSG mouse lacks mature T cells, B cells and functional natural killer (NK) cell. It has impaired cytokine signaling and does not spontaneously develop thymic lymphomas as the older NS model did. This fact has significantly extended the life span of the animals [2].

A direct comparison of the NSG model with NS and a related NOD.Cg-*Prkdc*^{scid}*B2m*^{tm1Unc}/J, (NOD/scid/b2 null, NSB) mouse strain was performed by Agliano et al., showing that the NSG mouse provided the highest number of successfully engrafted mice and also engrafted the highest number of primary acute myeloid leukemia (AML), acute lymphoid leukemia (ALL) and cell line samples [3]. In contrast, Risueno et al. showed engraftment of the same number of primary AML samples in all three NSG, NS and NSB strains, but still with the highest engraftment levels in the NSG mice, which was also confirmed in other studies [4–6].

Although the xenograft models are mainly used as an assay to confirm the presence of hematopoietic or leukemic stem cells, over the years, they have mediated several important discoveries involving leukemic stem cells (LSC). For example, it was shown that AML LSC are not only present in the CD34^{+}38^{-} population, which phenotypically defines healthy hematopoietic cells, but that even cells with progenitor phenotype and also patient samples without CD34 expression are capable of recapitulating leukemia in immunodeficient mice, thus underlining the complex nature of this disease [6, 7]. Similarly, in samples with mutated nucleophosmin (NPM), which represent around 60% of cytogenetically normal AML samples generally associated with low CD34 expression, it was shown that in some cases the CD34^{+} fraction gave rise only to multilineage engraftment, whereas only CD34^{-} cells initiated leukemia [18–10]. In CML, leukemic engraftment was then achieved with samples from patients with complete molecular response after long-term imatinib (IM) treatment, providing further confirmation that CML LSCs are not eradicated by therapy [11–13].

XENOGRAFTS OF AML

For AML, many factors and aspects influencing the engraftment of primary samples in mice have been studied. Despite the fact that the studies differed at some level in various technical details, as evidenced in Table 2 and discussed further in the text, some general points can be assembled. Regarding engraftment rates, Sanchez et al. documented 66% engrafting samples from a group of 35 patients [5]. Similarly, Risueno et al. reported a 61% engraftment rate [4]. But also higher success rates of 81.5 and 90.9% have been reported [14, 15]. It should be noted, however, that the engraftment rates depend on many factors. The most important is probably the selection of patient samples, which can be supported by the study of Mitchell et al. on 307 AML samples, using the NS strain [16]. The authors have shown that poor cytogenetic prognosis and worse patient outcome, as defined by achievement of complete remission, overall survival (OS) and event free survival (EFS), were strongly correlated with better engraftment characteristics, and this link between patient prognosis and engraftment was also proven by Woiterski et al. and Pearce et al. [15, 17]. Interestingly, the study by Mitchell et al. did not prove a positive effect of higher blast count on better engraftment, while many studies have considered this factor in their samples [5, 15, 16].

Also, pediatric AML samples were shown to engraft better than adult samples (100 vs. 76.3% engrafted samples) [14].

XENOGRAFTS OF CML

In general, the information on the xeno-graft assays of CML is scarce, as most of the studies used the model as an *in vivo* test method, while robust studies specifically investigating the engraftment of CML are lacking. One of the very few comprehensive studies of CML engraftment was performed by Dazzi et al. who also compared the engraftment kinetics of chronic phase (CP), accelerated phase (AP), blast crisis (BC) CML and the BV173 cell line in NS mice (see Table 1) [18]. The authors used rather high cell numbers of 5 million CD34^{+} cells per mouse obtained by leukapheresis, which however is not as commonly available as normal peripheral blood (PB) samples or bone marrow (BM) samples. Interesting data were then obtained

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Tab. 1 Engraftment kinetics of particular CML stages in NS mice [18]

% of hCD45+ cells in murine BM				
Time of analysis after cell injection (weeks)	**Chronic phase (n samples = 4)**	**Accelerated phase (n samples = 2)**	**Blast crisis (n samples = 2)**	**BV173 cell line**
4	0	18	18	-
8	2.5 (15–30% *Ph+)	-	-	54
10	3.5	6	59	-
18-20	21 (100% Ph+)	-	dead	-

Values show median percentages of human cells, as detected in mouse bone marrow using flow cytometry by human CD45 staining.
*Ph+ = Philadelphia chromosome positive.

by Chu et al. who tested engraftment of patients after imatinib treatment, showing that all six tested samples gave multilineage engraftment, with a predominant B-cell fraction and *BCR/ABL1* being detected for all engrafted samples. Interestingly, they reached engraftment levels from around 2.5% up to around 50%, while using low and commonly obtainable cell doses of 86–173 thousand $CD34^+$ cells per mouse [11]. Further comprehensive CML xenograft data were obtained by Herrmann et al. in an elegant study, where the authors injected a lineage depleted (Lin^-) stem cell fraction, further divided into LSC and hematopoietic stem cells (HSC) based on expression of the CD26 marker [19]. The injection of 0.1–0.8 million Lin^-CD26^+ cells, proposed as LSC provided myeloid engraftment with confirmed *BCR/ABL1* transcripts and engraftment levels ranging from 0.05 to 0.31% of $hCD45^+$ at 16 or 28 weeks after injection. The lin^-CD26- fraction, proposed as healthy stem cells, then provided myeloid engraftment or predominantly B-cell engraftment in 2/6 and 4/6 samples, respectively, where none of the samples were positive for *BCR/ABL1*. Rather low engraftment level (5% $hCD45^+$) was also achieved in a study with as much as 6 million $CD34^+$ cells per one mouse, which provides yet another indication that low engraftment levels are generally more common for CML xeno-graft assays [20].

EFFECT OF PARTICULAR PARAMETERS ON ENGRAFTMENT

Cell dose

The effect of the number of injected cells was investigated, for example, by Pearce et al. who have shown on NS mice that non-engrafting samples do not engraft irrespective of the cell dose [17]. Nevertheless, in samples capable of engraftment, the injected sample has to carry LSC/s to provide engraftment – and thus successful engraftment depends on the LSC frequency and the cell dose of the sample. This was nicely documented by Sarry et al. in a comprehensive study where only 3/6 patients engrafted with 0.1 million mononuclear cells (MNC) injected, but 6/7 of the same patient samples engrafted with 0.5 million cells and engraftment of all samples in all mice was achieved with 10 million cells [6].

Injection route

The effect of the injection route has so far not been directly assessed for myeloid leukemia xenograft assays, although it has been shown that intra femoral injection leads to better engraftment of HSC [21, 22]. However, the high technical demands of the intra bone injection are a limiting factor and intravenous (i. v.) injection through the tail vein remains the standard route. Intraperitoneal injection was also documented, but with a high cell load (10 million MNC/mouse), and its efficacy has not been directly compared with other routes [3].

Pre-treatment

Irradiation of mice recipients prior to cell injection to enhance the engraftment is a common practice, although it was challenged for AML in the NSG mice in some works. For example, Watanabe et al. showed a stable HSC mediated engraftment in non-irradiated mice; Agliano and colleagues then showed equal engraftment of the HL-60 cell line in irradiated and non-irradiated mice [3, 23]. Moreover, there were further studies completely omitting irradiation [14, 15]. According to the authors' knowledge, the effect of irradiation was not tested for CML xenografts and all reported CML studies employed myeloablation through irradiation (see Table 3).

In previous models, such as the NS mouse, CD-122 antibody was commonly used for depletion of NK cells and had a significant effect on engraftment improvement. Nevertheless, due to the innate deletion of γ-common chain in the NSG mice, this pre-treatment is no longer needed in this model [21, 24].

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Tab. 2 Summary of technical approaches in AML NSG xenografts

AML	Woiterski et al., 2013 [15]	Herrmann et al., 2012 [27]	Agliano et al., 2008 [3]	Sanchez et al., 2009 [5]	Malaise et al., 2011 [14]	Risueno et al., 2011 [4]	Sarry et al., 2011 [6]
Patients	n = 11	n = 3	n = 3	n = 35	n = 49	n = 23	n = 7
+ 5 cell lines							
Patient status	diagnosis/ relapse	diagnosis/ relapse	diagnosis	-	diagnosis	diagnosis	-
Cell origin	BM	PB/BM	PB/BM	leukapheresis	PB/BM	PB/BM	leukapheresis
Cell processing	– erythrolysis – T cell depletion if > 10% T-cells present –fresh cells	separation of MNC	– separation of MNC – frozen cells	– separation of MNC – frozen cells	frozen and fresh cells	separation of MNC	– separation of MNC – frozen cells
n cells per mouse	0.1–3 million	2.5 million	10 million	5–10 million	2 million	10 million	0.005–10 million
Inj. medium	–	150 μl of *PBS + 2% **FCS	–	200 μl of PBS	50 μλ FCS	–	–
Inj. route	i.v. – tail vein	i.v. – tail vein	#i.p.	i.v. – tail vein	intrafemorally	i.v. – tail vein	i.v. – tail vein
Mice irradiation	none	240 cGy	none	250 cGy	none	315 cGy	250 cGy
Sacrifice at	> 60% engraftment in PB or moribund appearance	8–10 weeks	demonstration of symptoms	12 weeks	variable	8 weeks	12–18 weeks
Successful engraftment criteria	> 0.3% hCD45+ cells in PB	> 0.1% hCD45+ cells in BM	–	> 0.1% hCD45+33+ cells in BM	based on hCD45+ cells	based on hCD45+ cells	> 0.1% hCD45+CD33+ cells in BM
Successful engraftment	– 90% samples engrafted – 27/29 mice engrafted – average engraftment level = 34.6% human leukocytes	–	–	66% samples engrafted	81.5% samples engrafted	61% samples providing myeloid engraftment	–

The table shows technical details of engraftment experiments for each selected study and states the origin of the injected leukemic cells, preparation of the cells prior to engraftment, information on the engraftment assays and engraftment results.
Engraftment was assessed by flow cytometry, based on the frequency of either human leukocytes (stained for human CD45) or human myeloid cells (stained for human CD45 and CD33) present in the given mouse tissue (if specified).
*PBS = phosphate buffered saline
**FCS = fetal calf serum
#i.p. = intraperitoneal

Cell handling

One of the options for achieving higher engraftment rates is the injection of fresh cells. It was demonstrated that fresh samples showed better engrafting rates (96.3% for fresh vs. 63.6% for thawed samples) with shorter time to engraftment (8 and 19 weeks for fresh and frozen samples respectively) [14]. These results are striking, although the use of fresh cells is often not feasible.

Sex of recipient mice

It was demonstrated that NSG females engraft HSC better than males, where the difference was most pronounced with the use of limiting cell numbers [21, 25]. With cell doses above 10 million of cord blood MNC, the effect of sex was not observed [26]. In contrast, Woiterski et al. reported higher engraftment in males for both non-limiting numbers of HSC and

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Tab. 3 Summary of technical approaches in CML xenografts

CML	Herrman et al., 2014 [19]	Chu et al., 2011 [11]	Eisterer et al., 2005 [28]	Dazzi et al., 1998 [18]	Tanizaki et al., 2010 [29
Patients	n = 8	n = 6	n = 9	n = varies	n = 3
Patient status	CP	CP - min. 4 years on IM	CP all patients had 100% Ph+ cells	CP, AP, BC, BV173 cell line	BC
Study description	Lin- cells were sorted according to CD26 expression into: CD26+ fraction carrying LSC and CD26- fraction carrying HSC	Samples from long-term treated patients were transplanted into mice, in various cell counts. The engraftment and BCR/ABL1 levels in mice were studied.	Engraftment of patient cells was observed.	Engraftment of patient cells from chronic phase, accelerated phase and blast crisis was compared along with a BV173 cell line.	Study of engraftment of sorted patient cells.
Cell origin	PB or BM	BM	PB or BM or leukapheresis	PB-MNC	BM
n of cells per mouse	– 0.1-0.8 million Lin-CD26+ cells – 0.5-1.5 million Lin-CD26- cells	8-20 thousand CD34+ cells	variable	– 5 million CD34+ patient cells (> 95% purity) – 3 million BV173 cells	1.5-10 million MNC containing > 80% leukemic cells
Mouse type	NSG	NSG	NS, NSB	NS	NOG
Inj. route	i.v. – tail vein	i.v. – tail vein	-	i.v. – tail vein	i.v. – tail vein
Mice irradiation	240 cGy	300 cGy	350 cGy	325 cGy	none
Sacrifice at	16 or 28 weeks	11–12 weeks	3–20 weeks	4–20 weeks	
Engraftment criteria			presence of human CD45 and/or CD71 or CD34	> 1% hCD45 cells	> 1% hCD45+ in PB at 8 weeks
Level of engrafted hCD45+ cells in mouse samples	0.01–5.09%	25–50%	- NS mice: ~1% - NSB: ~5%	- various - 85% with patient cells	

The table shows technical details of engraftment experiments for each selected study and states the origin of the injected leukemic cells, preparation of the cells prior to engraftment, information on the engraftment assays and engraftment results.
Engraftment was assessed by flow cytometry, based on the frequency of either human leukocytes (stained for human CD45) or human myeloid cells (stained for human CD45 and CD33) present in the given mouse tissue (if specified).

samples of acute leukemias, where in the latter case this may have been caused by the higher frequency of high-risk patient samples injected into male than female recipients [15]. Based on the findings with the high-enough cell doses, the selection of a specific sex of the mouse recipients for AML may be questioned. But for CML, where often only limiting cell doses are available, the use of female mice would be highly recommended.

CONCLUSIONS

The xenograft models represent thus far the ultimate assays for demonstrating the repopulating ability of leukemic cells or their specific subpopulations. For AML and CML, the NSG mouse represents a standard model although it does not offer successful engraftment of all samples. This is primarily dependent on the sample itself, while certain technical details also play role. There is no doubt that new modifications and improvements of the recipient animals will bring a new standard in this field and already a modification of the NSG mouse has been presented, denoted NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}Tg(CMV-IL3,CSF2,KITLG)1Eav/MloySzJ (NSGS, NSG-SGM3). This relatively new model should eliminate the "lymphoid bias" i.e. the preferential growth advantage of lymphoid cells in the NSG mouse through stable production of human interleukin-3 (IL-3), human granulocyte/macrophage-stimulating factor (GM-CSF) and human Steel factor (SF). These three soluble factors have already been shown to improve engraftment in previous SCID based mouse models either after administration or transgenic introduction

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[30, 31]. The new NSGS strain has so far shown to provide more pronounced engraftment of AML samples as well as engraftment of samples not repopulated in the NSG mouse. However, more works would be required to prove or specify its benefits [32, 33]. Another modification expected to significantly improve the engraftment options has been described and involves implantation of a humanized niche into immunodeficient mice [34, 35]. Although the model is technically more challenging, it offers vast research potential through modification of the implanted niche and such studies, involving engraftment of primary patient samples, may radically broaden our options for simulation of patient leukemia in the future.

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