建立人急性粒细胞白血病M_2裸鼠模型****★

刘 媛，董瑞红，李玉华，汪涯雅，毋 静，黄 睿，邓 兰，宋朝阳，陆志刚，胡海燕

Establishment of human acute myeloblastic Leukemia M_2 type nude mouse model

Liu Yuan, Dong Rui-hong, Li Yu-hua, Wang Ya-ya, Wu Jing, Huang Rui, Deng Lan, Song Zhao-yang, Lu Zhi-gang, Hu Hai-yan

Abstract

BACKGROUND: It is easy to established human solid tumor nude mouse model, but for leukemia which is difficult. We inhibited immune system further by radioactive ray or CTX, to decrease cost and increase the stability.

OBJECTIVE: To establish a human acute myeloblastic leukemia M_2 Kasumi-1 models containing AML/ETO positive genes in BALB/c nude mouse.

METHODS: Nude mice were randomly divided into three groups: CTX group was injected CTX 2 mg/day in abdominal cavity for two days, and injected 8×10^5/mouse Kasumi-1 cells in caudal vein next day; irradiation group was exposed to total body irradiation, and injected 8×10^5/mouse Kasumi-1 cells in caudal vein that day; untreated group was inoculated with 8×10^5/mouse Kasumi-1 cells by caudal vein injection. Three additional mice were considered as the normal control group. The blood smearing and bone morrow slides were detected, immunity type of BMC was detected using flow cytometry, loading of leukemic cellular tumor was detected using RT-PCR, and positive ratio of AML/ETO fusion gene was detected using FISH method.

RESULTS AND CONCLUSION: After inoculated into untreated nude mice by caudal vein injection for 14 days, the ratio of leukemia cell in blood smearing was 3.5%, and over 40% in bone marrow slides, which was equal to the results of FISH and FCM. The increasing of tumor loading was time-dependent. For irradiation group and CTX treated group, the tumor loading was higher that untreated group, and the cells also survived more than 60 days. AML/ETO band was observed by RT-PCR in all experimental groups, for normal mice it was negative. The results indicated that the systemic disseminated leukemia model was established successfully by caudal vein injection 8×10^5/mouse Kasumi-1 cells in the three experimental groups.

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摘要

背景：人实体瘤细胞容易在小鼠体内成瘤，但人荷瘤白血病模型很难构建。通过放射线或环磷酰胺抑制裸鼠免疫系统预处理，可构建低成本、高稳定性的裸鼠模型。

目的：探讨融合基因 AML/ETO 阳性的人急性粒细胞白血病 M_2 白血病细胞 Kasumi-1 在 BALB/c 裸鼠体内建立白血病模型的方法。

方法：将 BALB/c 裸鼠以抽签法随机分 3 组：环磷酰胺组腹腔注射环磷酰胺连续 2 d 后，尾静脉注射 Kasumi-1 细胞 8×10^5/只；照射组给予 X 射线全身照射，照射当天尾静脉注射 Kasumi-1 细胞；无预处理组未作任何处理，尾静脉注射 Kasumi-1 白血病细胞。另取 3 只正常 BALB/c 裸鼠作为正常对照。检测外周血涂片、骨髓涂片，流式细胞仪检测骨髓细胞免疫分型，RT- PCR 检测白血病细胞瘤负荷，FISH 检测骨髓细胞 AML/ETO 融合基因阳性细胞百分比。

结果与结论：未经任何预处理裸鼠建模 14 d 血涂片中白血病细胞达 3.5%，骨髓中肿瘤细胞百分比可达 40%以上，与 FISH 和流式细胞仪检测白血病细胞比例一致，且随着接种时间延长，瘤负荷不断增加。全身照射和环磷酰胺注射后的裸鼠瘤负荷高于无预处理组，但仍可带瘤生存 60 d。正常裸鼠外周血单个核细胞 RT-PCR 未发现有融和基因 AML/ETO，其他 3 组均可见融和基因 AML/ETO 的 mRNA 表达。提示给予环磷酰胺组和 X 线照射预处理或单纯尾静脉接种 Kasimi-1 细胞均可建立急性粒细胞白血病 M_2 裸鼠模型。

关键词：急性粒细胞白血病模型；AML/ETO 融合基因；裸鼠；环磷酰胺；放射线
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Department of Hematology, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, Guangdong Province, China

Liu Yuan★, Studying for master's degree, Department of Hematology, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, Guangdong Province, China
xuri1104@163.com

Correspondence to: Hu Hai-yan, Associate investigator, Department of Hematology, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, Guangdong Province, China
xuri1104@163.com

Correspondence to: Lu Zhi-gang, Professor, Master's supervisor, Department of Hematology, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, Guangdong Province, China

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0 引言

NOD/SCID免疫缺陷小鼠补体途径和巨噬细胞功能缺陷[1]，体内缺乏T、B、NK细胞，近年来已有大量人白血病细胞株在NOD/SCID小鼠体内移植成功建立荷瘤小鼠模型的报道[2-6]。但部分NOD/SCID小鼠8周时会发生胸腺淋巴瘤而死亡，而且NOD/SCID小鼠价格昂贵，饲养条件高，荷瘤小鼠带瘤生存期短。BALB/c裸鼠先天无胸腺，细胞免疫缺陷，保留B细胞、补体及NK细胞功能，人源实体瘤细胞在裸鼠极易成瘤，但人源造血系统肿瘤在裸鼠体内生长却较为困难。本课题欲研究口服特异性融合基因疫苗抗白血病效应，为研究口服疫苗服用后抗原如何刺激小鼠肠道M细胞和淋巴结细胞激活体液免疫，选择B细胞功能完整的裸鼠欲构建低成本的能长期带瘤生存的白血病模型，以研究白血病

南方医科大学珠江医院血液科，广东省广州市510282

刘　媛★，女，1986年生，江西省高安市人，汉族，南方医科大学在读硕士，主要从事肿瘤免疫研究。xuri1104@163.com

通讯作者，胡海燕，副研究员，南方医科大学珠江医院血液科，广东省广州市510282 xuri1104@163.com。

通讯作者：陆志刚，教授，硕士生导师，南方医科大学珠江医院血液科，广东省广州市510282

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发生、发展的病理过程，以及药物的筛选。

1　材料和方法

设计：对比观察，动物体内实验。

时间及地点：于2008-09/2009-02在南方医科大学珠江医院血液科实验室和中心实验室完成。

材料：人急性粒细胞白血病M_2型Kasumi-1细胞由浙江大学第一附属医院金洁教授惠赠，常规传代培养取对数生长期的细胞用于实验。4周龄雌性BALB/c裸鼠24只购自南方医科大学动物中心，在SPF级动物合格环境下饲养。人急性粒细胞白血病M_2型Kasumi-1细胞由浙江大学第一附属医院金洁教授惠赠。实验过程中对动物处置符合动物伦理学标准。

主要试剂：

试剂	来源
AML/ETO融合基因探针	VYSIS公司
兔抗人CD45-FITC单抗	BD公司
注射用环磷酰胺0.2g/支	江苏恒瑞医药公司
RT-PCR试剂盒	大连宝生物公司
Trizol、胎牛血清和RPMI1640培养基	Gibico公司
苯酚、氯仿、异丙醇，瑞-吉和苏木精-伊红染液	广州市第一化玻厂

实验方法：

裸小鼠白血病移植瘤模型的建立：将BALB/c裸小鼠以抽签法随机分成3组：环磷酰胺组腹腔注射环磷酰胺 2 mg/只，连续2 d，第3天尾静脉接种白血病Kasumi-1细胞接种4×10^9 L^{-1} /只；照射组给予X射线照射3 Gy，于照射当日所有小鼠尾静脉接种白血病Kasumi-1细胞接种$4\times10^9L^{-1}$ /只；无预处理组直接尾静脉接种白血病Kasumi-1细胞接种$4\times10^9L^{-1}$ /只，分别于接种后14，21，28，42，60 d处死小鼠，60 d处死所有存活小鼠，未到处死时间死亡的小鼠记录死亡日期，归入死亡日期最接近的处死时间组。另取3只同鼠龄的雌性裸鼠，同等条件饲养，作为正常对照。

瘤细胞形态学分析和计数：于接种瘤细胞14，21，28，42，60 d，每只小鼠尾静脉取血20 μL，加入0.38 mL白细胞稀释液内，分别取10 μL连续计数3次，计算平均值。并制备血涂片，经瑞氏染色，油镜下分类、计数。处死小鼠取上肢骨，刀片沿骨纵轴线切开后涂片，经瑞氏染色，油镜下分类、计数。

FISH检测模型鼠骨髓AML/ETO和XY基因阳性细胞百分比：收集各时间点处死小鼠的骨髓细胞，每份标本在荧光原位杂交仪59 ℃烤片2 h，各加DNA 探针1.0 μL 和4 μL 杂交稀释液，盖上18 mm ×18 mm 盖玻片，Rubber Cement封固后，75 ℃变性2 min，37 ℃杂交过夜。小心揭去盖玻片后，将玻片置于预热至72 ℃ 00.4×SSC/0.3NP40 中洗2 min，再将玻片移入常温浓度为2×SSC/0.1NP40 中洗1 min，室温下自然干燥。每张玻片加6 μL DAPI/Antifade，避光复染20 min后，Leica CW400荧光显微镜系统观察和采集图像。

RT-PCR 检测白血病细胞瘤负荷：经外周血细胞涂片、流式细胞仪等检测发现白血病细胞明确小鼠于接种后14 d成瘤，于接种瘤细胞28 d，取裸鼠眼眶静脉血0.5 mL，用DEPC 处理过的冰冷PBS 洗涤2 次，淋巴细胞分离液分离单个核细胞，加入1 mL Trizol，酚氯仿法提取RNA，28S、18S 两条带清晰，紫外分光光度计测A_{260}/A_{280}在1.8~1.9。引物：AML1-A：CTA CCG CAG CCA TGA AGA ACC；ETO-B：AGA GGA AGG CCC ATT GCT GAA，产物大小395 bp。起始变性：95℃ 30 s，PCR循环：94 ℃ 30 s(变性)，65 ℃ 1 min(退火)，72 ℃ 1 min (延伸)，共35个循环。凝胶成像分析系统进行成像分析。

流式细胞术检测骨髓CD45 阳性细胞率：于接种瘤细胞14，21，28，42，60 d后，取裸鼠双下肢骨的骨髓单个核细胞，PBS 洗涤2次，加入抗人CD45-FITC单抗，4 ℃孵育40 min, PBS洗涤2次，流式细胞仪检测。

主要观察指标：外周血涂片、骨髓涂片骨髓细胞免疫分型，白血病细胞瘤负荷，骨髓细胞AML/ETO融合基因阳性细胞百分比。

设计、实施、评估者：实验设计为第九作者，实施者为第一作者，评估者为第八作者。

统计学分析：应用SPSS 10.0分析，采用多因素方差分析，统计学处理由第一、九作者共同完成。

2　结果

2.1　实验动物数量分析　24只裸鼠均进入结果分析。

2.2　发病情况　裸鼠在接种Kasumi-1细胞14 d后均发生白血病，裸鼠萎糜少动，腹部膨隆，

皮下可触及大小不等的结节，随肿块增大体质量减轻，42 d后部分小鼠出现步态不稳，侧偏或转圈。

2.3 不同时间点模型鼠外周血象及骨髓细胞改变 接种Kasumi-1细胞的环磷酰胺组裸鼠外周血象在接种后第14天起白细胞数略有升高，且血细胞分类可检测到4%左右的白血病细胞，骨髓涂片可见30%以上的白血病细胞，白细胞计数及白血病细胞百分比随病程延长而增高。其余两组接种后14 d白细胞计数无名显改变，无预处理组外周血涂片未见白血病细胞，全身照射组亦可在见1%~3%白血病细胞。接种后21 d各组均可见白细胞计数升高，血片及骨髓片可见白血病细胞，无预处理组细胞瘤负荷较另两组低，但无统计学意义，见表1。

表1 各组裸鼠接种白血病细胞后血象及骨髓象变化
Table 1 Change of blood cells and bone marrow cells after transferring leukemia cells

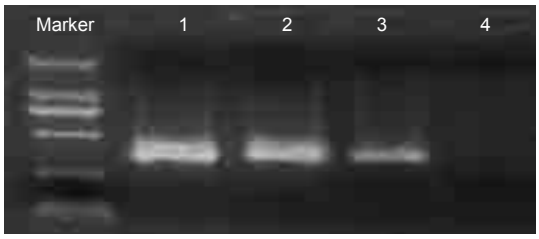
Time	PBC					
	Cell count of WBC (1×10^9)			Ratio of leukemia cell (%)		
	1	2	3	1	2	3
14 d	2.3	2.3	2.1	4.5	2.5	0
21 d	3.1	3.3	3.2	6.0	7.5	4.5
28 d	3.9	3.9	3.4	14.0	15.5	11.0
42 d	5.2	5.4	5.1	21.0	20.0	17.5
60 d	8.7	8.7	8.2	37.0	39.5	34.0

Time	Bone marrow								
	Ratio of leukemia cell (%)			Ratio of CD45 positive cell (%)			Ratio of AML/ETO positive cell (%)		
	1	2	3	1	2	3	1	2	3
14 d	32.0	36.5	28.5	34.6	30.6	29.2	32.0	36.0	28.0
21 d	47.5	46.0	45.5	43.9	45.4	44.3	47.5	46.5	45.5
28 d	63.5	65.5	61.5	60.4	66.8	60.7	63.5	66.0	63.0
42 d	80.0	81.5	77.5	82.4	80.7	78.2	80.0	82.0	80.5
60 d	92.5	93.5	88.5	94.6	96.2	90.2	92.5	93.0	89.0

1: CTX group; 2: irradiation group; 3: untreated group

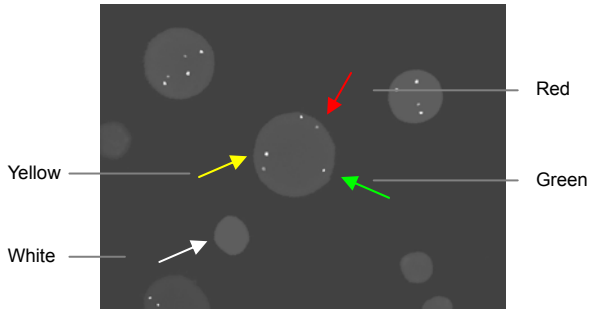
2.4 白血病裸鼠各脏器AML/ETO基因mRNA水平 正常对照组裸鼠外周血单个核细胞未发现有Kasumi-1细胞特有融和基因AML/ETO。环磷酰胺组、照射组、无预处理组均可见融和基因AML/ETO的mRNA表达，但无预处理组条代弱于环磷酰胺组、照射组，见图1。

2.5 模型鼠骨髓AML/ETO基因阳性细胞比例改变 小鼠细胞明显小于人源肿瘤细胞，同时仅有DAPI核染色。正常对照组裸鼠骨髓细胞未发现有Kasumi-1细胞特有融合基因AML/ETO。实验的3个组在接种Kasumi-1细胞4周后,在骨髓单个核细胞中发现融和基因AML/ETO的杂交信号(见图2)，其表达率见表1。



1: CTX group; 2: Irradiation group; 3: Untreated group; 4: Normal control group

Figure 1 mRNA level of AML/ETO fusion gene expressed on all groups
图 1 各组模型鼠 AML/ETO 融合基因表达



White arrow: any hybridization probe are not observed in mice cells; AML (red), ETO (green), and AML/ETO (yellow) gene recombination signals are observed in tumor cells

Figure 2 Detection of AML/ETO fusion gene by FISH method
图 2 AML/ETO 融合基因表达

3 讨论

AML/ETO融合基因是21号染色体的AML-1基因(RUNXI)的第5，6外显子基因断裂融合和8号染色体的ETO基因(MTG8)融和而成，是急性髓系白血病最常见的染色体畸变之一，在急性髓系白血病检出率为20%左右，在AML-M_2中检出率约40%，在AML-M_{2b}检出率高达80%以上，AML-M_{2b}白血病细胞形态学容易与M_3型细胞混淆，胞浆内分别由Ⅰ、Ⅱ、Ⅲ型原粒细胞组成，易见奥氏小体，部分可见粗大的嗜天青颗粒，过氧化物酶和AS-D奈酚酯酶染色可见条索或团块状阳性分布[7-11]。AML/ETO融合蛋白由752个氨基酸构成，N端包含AML的RHD结构域，C端几乎包含全长的ETO蛋白。AML-1是调控造血和细胞周期相关基因表达的转录因子，生理情况下，在造血各系中均有表达[12-18]。AML/ETO融合蛋白以定位于独特的不同于AML-1的细胞核核体，基因

通过runt同源结构域和CBFβ结合形成异源二聚体结合，runt识别增强子核心区域的TGT/cGGT序列，实现显性负模式阻滞AML-1的转录激活作用。AML/ETO保留全长的ETO结构[19-26]，募集与相关的转录抑制蛋白如N-COR、SMRT、mSin3A、HDAC等转录共抑制物一起聚集于亚核水平，抑制转录干扰正常造血细胞的增殖、分化与凋亡，AML/ETO高表达则细胞多阻抑于G_1期。

本科题受国家自然基金资助，选择AML/ETO为靶标，制备基因和肽疫苗研究其抗白血病效应，其第一步是构建AML/ETO基因阳性的白血病模型。由于裸鼠B细胞活性和非特异性免疫活性比较高，为减轻种属间非特异性免疫排斥反应，本实验据参考文献[27]在接种细胞前给予小鼠腹腔连续两天注射环磷酰胺2mg/支或给予全身照射处理。本实验在接种Kasumi-1细胞前给予小鼠腹腔连续2 d注射环磷酰胺2 mg，腹腔接种Kasumi-1细胞后2周左右出现白血病症状，外周血片光镜下即可见白血病细胞。由于小鼠骨髓细胞有限，鉴于选用人与小鼠间白细胞抗原表达种属差异较为明显，本实验仅选用髓系抗原CD45 作为检测指标之一。同时由于荧光原位杂交技术所需细胞量低，敏感性特异性高，已常规应用于白血病诊断，本文以此为监测指标之一[28-31]。本实验室在应用FISH对该白血病细胞检测时发现，细胞培养传代过久将出现融合基因变异，如3红3绿而无黄色信号的细胞，此意味着细胞存在基因断裂，但未出现融合，此变异株细胞表型及增殖等生物学性状尚待进一步研究。临床检测 也发现部分患者融合基因突变现象，在格列卫治疗后的慢性粒细胞白血病最为显著。本次实验发现，人鼠虽然基因高度同源，但小鼠细胞内未见AML/ETO基因的杂交信号；其次由于体内细胞分裂增殖周期不同步，瘤细胞出现杂交时出现3红3绿1黄，以及2红2绿2黄等异常信号，可能与细胞亚二倍体，超二倍体等变异出现相关，也可能是融和位点的突变，这都说明肿瘤细胞突变具有多样性，突变的差异是否会引起对疫苗敏感性的差异呢？尚有待进一步深入研究。

4 参考文献

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