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MLL GENE ALTERATIONS IN RADIATION-ASSOCIATED ACUTE MYELOID LEUKEMIA

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Aim: **Although acute myelogenous leukemia (AML) arising after radiation exposure is considered to be secondary, little is known about the molecular mechanisms by which the radiation induces the leukemogenic phenotype. The aim of the study was to analyze whether the *MLL* translocations are as frequent in radiation-associated AML as in spontaneous AML cases.** ***Methods*****: Sixty one AML samples obtained at diagnosis were analyzed for the presence of *MLL* abnormalities using fluorescent *in situ* hybridization and/or reverse transcription polymerase chain reaction. Of these patients, 27 had experienced radiation exposure due to the Chernobyl accident, 32 were non-irradiated (spontaneous AML), and 2 developed therapy-related AML after chemotherapy with topoisomerase II inhibitors.** ***Results*****: *MLL* gene translocations were detected in both groups of spontaneous and therapy-related AML (1/32 and 1/2 cases respectively). The sole *MLL* rearrangement found in the group of radiation-associated AML patients was a duplication of the gene.** ***Conclusion*****: Our data preclude the involvement of *MLL* gene translocations in radiation-induced leukemogenesis, but support the assumption that loss and gain of chromosomal material could be crucial in the leukemogenesis of AML patients with the history of radiation exposure due to the Chernobyl accident.**

Key Words: **acute myelogenous leukemia, ionizing radiation, Chernobyl accident, *MLL*, translocation, duplication.**

The *MLL* gene, also called *HRX* or *ALL-1*, was originally identified by its involvement in recurrent chromosomal translocations in acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML) in 1991. It represents the human homolog of the *Drosophila trithorax gene* whose function is required for proper homeotic gene expression and regulation of chromatin structure. MLL acts as a transcription factor and can regulate target genes that are involved in cell growth and proliferation. The *MLL* gene, located at cytogenetic band 11q23, has been reported to fuse with more than 50 different translocation partner genes, many of which have been cloned [1]. In all cases studied thus far, the chromosome 11 breakpoints have been clustered within a 9-kb region spanning exons 5–11 of *MLL*. The translocations result in an in-frame 5′*MLL*/3′ partner-gene transcript resulting from the joining of the amino-terminal part of MLL to the carboxyl end of the partner product, creating fusion proteins that are critical for leukemogenesis [2, 3]. A high partner diversity favors the hypothesis that the *MLL* disturbance by itself is sufficient for disruption of normal hematopoietic differentiation. AML with 11q23/*MLL* rearrangement involving different partner genes seems to comprise a biologically and clinically homogeneous entity despite the large variety of different fusion partner genes. Overall survival is short and is comparable to AML with an unfavorable karyotype [4].

The detection and characterization of chromosomal rearrangements in AML has provided the means to identify distinct biologic and prognostic subgroups and to establish a WHO pathogenesis-oriented classification of the disease [5]. *MLL* abnormalities are being observed both in *de novo* and secondary AML cases. AML patients with *MLL* abnormalities but without a documented exposure to therapeutic, occupational or environmental genotoxins prior to the onset of the disease are considered as *de novo* or spontaneous cases, although these terms are not completely appropriate. The other category of AML patients with *MLL* abnormalities represents secondary cases related to therapy with agents that bind to and inhibit DNA-topoisomerase II. Secondary AML after treatment with topoisomerase II inhibitors are well characterized and usually present with overt leukemia without a myelodysplastic phase, have a short latency period (6–36 months), and a relatively favorable response to chemotherapy [6–14].

Although AML developing after radiation exposure are also considered to be secondary, little is known about the molecular mechanisms by which the radiation induces the acute leukemogenic phenotype. There

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Abbreviations used: ALL — acute lymphocytic leukemia; AML — acute myelogenous leukemia; FISH — fluorescence *in situ* hybridization; RT-PCR — reverse transcription polymerase chain reaction.

is no convincing evidence for the involvement of any distinct chromosomal aberrations in the process of radiation leukemogenesis. The fact, however, that secondary AML share some clinical features irrespective of the causative agent makes it likely that leukemias developing after exogenous genotoxic agents have some common molecular alterations. Therefore, in our search for specific molecular genetic alterations in radiation-associated disease, we have examined samples of radiation-associated AML for the presence of *MLL* gene alterations. Two different methods, fluorescence *in situ* hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR) were applied. The cohort of patients was recruited at the Research Centre for Radiation Medicine from former clean-up workers at the Chernobyl NPP and from the exposed population from the surrounding settlements. All patients were exposed to various degrees of external radiation during or after the 1986 accident at the Chernobyl power plant. As a control cohort, tumor samples from AML patients without any history of preceding radiation exposure were analyzed. The main aim of the study was to analyze whether the *MLL* translocations are as frequent in radiation-associated AML as in spontaneous AML cases.

MATERIALS AND METHODS

Patients. Bone marrow or peripheral blood samples were preserved from 61 unselected adult AML patients, initially diagnosed between 1997 and 2004. Of these patients, 27 had experienced radiation exposure due to the Chernobyl accident, 32 developed spontaneous AML and served as the main controls, and 2 developed secondary (therapy-related) AML after treatment with topoisomerase II inhibitors for Hodgkin's lymphoma. In the group of patients with radiation-associated AML there were 13 clean-up workers and 14 patients either evacuated from the Chernobyl exclusion zone or domicited in Ukrainian territories with high contamination from radionuclide fallout. Individual dosimetry was not available for the patients, except of one clean-up worker who survived 2nd degree acute radiation syndrome (dose 2.5 Sv). For this reason an approximate dose range estimation could be assumed according to the published data for the respective cohorts [15–18]. These data served as a framework to classify a tumor in those cases as radiation-associated. Details of patients' age, sex, French-American-British (FAB) type are given in Table.

FISH. Mononuclear cells were isolated by Ficoll-Hypaque density gradient centrifugation and shock-frozen at –70 °C or immediately fixed on slides and stored at –20 °C. Interphase FISH was performed using the two-color *MLL* "break-apart" and the centromere specific CEP 11 SpectrumGreen probes (Vysis, Downers Grove, USA) according to the manufacturer's instructions. Archival specimens were thawed and resuspended in physiological saline solution. After hypotonic treatment in 0.07 M KCl, cells were fixed in methanol/acetic acid (3 : 1), dropped on slides, air dried, and held at 37 °C. Slides were treated with 0.1 mg/ml pepsin in 0.01 M HCl for 2–3 min at 37 °C, then washed in PBS

Table. Clinical and molecular genetic data from AML patients

Pts No.	Sex/age* (yr)	Group	FAB type	MLL translocation detection		
				FISH results	RT-PCR results	
					MLL/AF9	MLL/AF4
1	M/60	CW	M0	–	ND	ND
2	M/59	CW	M1	–	–	–
3	M/54	CW	M1	–	ND	ND
4	M/76	CW	M2	–	ND	ND
5	M/73	CW	M2	ND	–	–
6	M/55	CW	M2	–	ND	ND
7	M/66	CW	M2	–	ND	–
8	M/59	CW	M4	–	ND	ND
9	M/29	CW	M4	–	ND	ND
10	M/62	CW	M5a	–	–	ND
11	M/35	CW	M5a	–	ND	ND
12	M/43	CW	M5a	–	ND	ND
13	M/42	CW	M6	ND	ND	–
14	M/71	Victim	M0	–	ND	ND
15	M/49	Victim	M1	–	ND	ND
16	F/26	Victim	M1	–	ND	ND
17	F/69	Victim	M2	–	ND	ND
18	M/74	Victim	M2	ND	–	–
19	M/50	Victim	M3	–	ND	ND
20	M/31	Victim	M4	–	ND	ND
21	M/45	Victim	M4	–	ND	–
22	F/67	Victim	M4	ND	ND	–
23	F/68	Victim	M4	–	ND	ND
24	F/50	Victim	M4eo	–	ND	ND
25	F/35	Victim	M5a	–†	ND	ND
26	M/57	Victim	M5a	–	ND	ND
27	M/42	Victim	M5b	–	ND	ND
Total in group of radiation-associated AML						0/27
28	M/60	Control	M0	–	–	ND
29	M/24	Control	M1	ND	–	–
30	F/27	Control	M1	ND	–	ND
31	F/87	Control	M2	ND	ND	–
32	M/25	Control	M2	–	ND	ND
33	F/36	Control	M2	–	ND	–
34	M/27	Control	M2	–	ND	–
35	M/19	Control	M2	ND	–	–
36	M/20	Control	M2	ND	–	–
37	M/49	Control	M2	–	ND	ND
38	F/59	Control	M4	–	ND	ND
39	F/20	Control	M4	ND	–	–
40	F/61	Control	M4	–	ND	–
41	M/66	Control	M4	–	ND	ND
42	M/66	Control	M4	–	ND	ND
43	M/48	Control	M4	–	ND	ND
44	M/32	Control	M4	ND	–	–
45	M/36	Control	M4	ND	–	–
46	F/44	Control	M4eo	–	ND	ND
47	M/26	Control	M4eo	–	ND	ND
48	M/39	Control	M4eo	ND	ND	–
49	F/64	Control	M4eo	–	ND	ND
50	M/47	Control	M4eo	–	ND	–
51	F/20	Control	M4eo	ND	–	–
52	M/25	Control	M4eo	ND	–	ND
53	M/55	Control	M5a	–	ND	–
54	M/48	Control	M5a	ND	–	–
55	F/30	Control	M5a	–	ND	ND
56	F/25	Control	M5a	+	–	–
57	M/19	Control	M5a	ND	–	–
58	M/21	Control	M5b	ND	–	–
59	M/46	Control	M6	–	ND	ND
Total in control group						1/32
60	F/62	Secondary	M2	ND	–	–
61	M/24	Secondary	M5a	ND	+	–
Total in group of secondary (therapy-related) AML						1/2
Total				2/61 (3,3%)		

M — male; F — female; CW — clean-up worker of the Chernobyl accident; Victim — patient evacuated from the Chernobyl exclusion zone or lived in territories with a high contamination of radionuclide fallout; secondary — patient with secondary (therapy-related) AML after treatment with topoisomerase II inhibitors; (–) — negative case, (+) — positive case; ND — not determined due to lack of suitable material for the analysis.
*At diagnosis. † Case showed three MLL signals.

and 0.05 M $MgCl_2$/PBS at room temperature (RT), post-fixed in 1% paraformaldehyde/PBS, and dehydrated through an ethanol series. After denaturation for 4 min at 73 °C in 70% formamide/2x SSC, slides were dehydrated in ethanol series. The probe mixture was denatured at 73 °C for 5 min, added to denatured cells at 45–50 °C and covered. After overnight hybridization in a humidified chamber at 37 °C, slides were washed in 50% formamide/2x SSC, 2 x SSC, 0.2 x SSC at 42 °C, and 100 mM sodium phosphate pH 8.0/0.1% NP 40 at RT. Cells were counterstained with 4′, 6′-diamidino-2-phenylindole solution (150 ng/ml in 2 x SSC) and examined using a Zeiss Axioplan 2 fluorescence microscope (Zeiss, Jena, Germany) with image processing software ISIS3/V.3.04 (Metasystems, Altlussheim, Germany). At least 100 nuclei were analyzed for each case. A cut-off value of positive case was set at 10% of nuclei showing abnormality.

RT-PCR. Total RNA was isolated immediately after collection of bone marrow or peripheral blood by the guanidinium thiocyanate phenol-chloroform extraction method [19]. Complementary DNA (cDNA) was synthesized from 1 μg of total RNA, using random hexamer primers and with Moloney murine leukemia virus reverse transcriptase (Fermentas, Vilnius, Lithuania) and following the protocol supplied by the manufacturer.

Nested RT-PCR amplifications were performed for fusion transcripts of *MLL/AF4* and *MLL/AF9* using the following primers:

5′-CCGCCTCAGCCACCTAC-3′ (*MLL* outer primer),

5′-AGGACCGCCAAGAAAAGA-3′ (*MLL* inner primer),

5′- TGTCACTGAGCTGAAGGTCG-3′ (*AF4* outer primer),

5′-CGTTCCTTGCTGAGAATTTG-3′ (*AF4* inner primer),

5′-CAACGTTACCGCCATTTGAT-3′ (*AF9* outer primer),

5′-TCGTGATGTAGGGGTGAAGAAGCAG-3′ (*AF9* inner primer).

Briefly, in a volume of 25 μl, 3 μl of the first-strand cDNA mixture was added to a mixture containing 1 x PCR buffer, 2.5 mM $MgCl_2$, 0.2 mM each dNTP, 75 nM concentration outer primers, and 1.5 U Taq polymerase (Fermentas, Vilnius, Lithuania). PCR cycling consisted of 30 cycles at 94 °C for 40 s, 63 °C for 40 s, and 72 °C for 90 s. The second round of nested PCR was carried out under the same conditions using 3 μl of the first-round PCR product as the template, and 75 nM concentration inner primers. As a control for the integrity of the RNA, PCR reactions were also performed using primers for the *actin* gene.

***Statistical analysis*.** Differences in the prevalence of *MLL* translocations were analyzed by 2-sided Fisher's exact test for 2 x 2 tables using STATISTICA 4.5 (StatSoft, Tulsa, OK, USA).

RESULTS AND DISCUSSION

The presence of *MLL* gene abnormalities was examined by FISH in 41 AML patients. Of these, there were 23 radiation-associated, and 18 spontaneous cases (see Table). An abnormal pattern of hybridization was found in two cases. In case #25 three orange and green fused signals were detected in the majority of the leukemia cells indicative of the additional copy of the *MLL* gene. In case #56 the FISH revealed a pattern characteristic of the concomitant *MLL* translocation and deletion, i.e., one orange/green fusion and one isolated green signal. The remaining 39 cases showed a normal pattern of hybridization with two pairs of adjacent orange/green signals. The origin of the additional *MLL* gene copy in case #25 could be either polysomy of chromosome 11 or duplication of the *MLL* gene. To exclude trisomy 11 we performed a FISH study with the chromosome 11 centromeric probe, which revealed two signals in all scored cells, excluding trisomy and confirming duplication of the *MLL* gene in this case.

Thirty one case (8 with radiation-associated, 21 with spontaneous, and 2 with therapy-related AML after treatment with topoisomerase II inhibitors) was screened for *MLL/AF4* and/or *MLL/AF9* fusion products using RT-PCR. In 11 out of 61 samples FISH and RT-PCR was performed in parallel. There was no discrepancy between the results of these two assays. Translocation of the *MLL* gene by RT-PCR was found in only 1 AML patient. The *MLL/AF9* fusion product was detected in an AML secondary to the treatment with topoisomerase II inhibitors in case #61 (Figure).

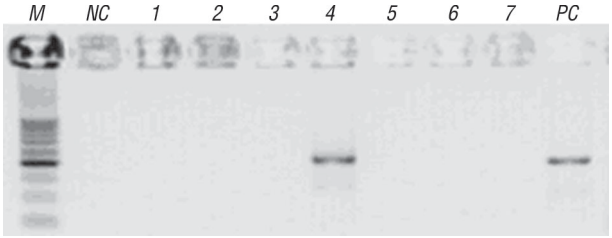

Figure. Representative example of an RT-PCR amplification of *MLL/AF9* fusion transcript from seven patients. M — molecular weight 100 bp ladder (Sigma, Saint Louis, USA); NC — negative control, where reagents without template were used; lines 1–7, set of samples analyzed for *MLL/AF9* translocation; line 4 — DNA from case #61; PC — patient with *MLL/AF9* translocation used as positive control

Thus, the overall frequency of *MLL* translocations in all patients was 3.3% (2/61 cases). We did not find any *MLL* gene translocation in the group of radiation-associated AML, but detected one in the control group with spontaneous AML (0/25 and 1/28 cases respectively). It is difficult to compare frequency of *MLL* translocation in these groups with the group of patient with therapy-related AML (1/2 cases) because of its small number, but the difference for radiation-associated AML cases was on the borderline of statistical significance ($P = 0.07$).

It seems that recurrent chromosomal translocations of the *MLL* gene, characteristic for the disease *de novo* and therapy-related AML after treatment with topoisomerase II inhibitors [20], are not common among the AML patients exposed to ionizing radiation due to the Chernobyl accident. This is in accordance with the prevalence of *MLL* translocations in unselected AML cases of 2.8% [4]. *MLL* gene translocations do not appear to play an important role in radiation-induced leukemo-

genesis. Moreover, radiation-induced leukemia is cytogenetically different from those that occur after therapeutic application of topoisomerase II inhibitors, where non-random rearrangements involving the *MLL* locus on chromosome 11 were observed. Nevertheless, our data support the hypothesis of Smith et al. [21], postulated that radiation may act as many other DNA-damaging agents and similar to alkylating agents, in contributing to therapy-related bone marrow dysfunction. Indeed, the only *MLL* gene rearrangement found in radiation-associated AML cases in our study was a gene duplication in a patient evacuated from the Chernobyl exclusion zone.

The genomic amplification of oncogene is a frequent event in solid tumors, but is rarely observed in hematogical malignancies [22]. The estimated incidence of cytogenetically detectable gene amplification in AML is approximately 1%. A rough estimate of the incidence of 11q23 segmental amplifications in all myeloid disorders, including not only AML and MDS but also chronic myeloproliferative disorders was given by Reddy et al. [23] as 4/690 (0.57%). This is dramatically different to leukemia cases diagnosed after mutagene exposure. Here duplication or amplification of chromosome band 11q23 with 3–7 copies of the *MLL* gene was detected by FISH in 12 out of 70 unselected patients (17%) who developed MDS or AML following a preceding chemotherapy with alkylating agents [24, 25].

Our findings exclude *MLL* gene translocations as an important factor in the etiology of radiation-induced leukemogenesis, but support the assumption that loss and gain of chromosomal material could be of importance in the leukemogenesis of AML patients with the history of radiation exposure due to the Chernobyl accident. Further study of the consistent cytogenetic changes induced by ionizing radiation will lead to the ascertainment of important genes and gene products that are involved in radiation-induced leukemogenesis.

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ПЕРЕСТРОЙКИ ГЕНА *MLL* ПРИ РАДИАЦИОННО-АССОЦИИРОВАННЫХ ОСТРЫХ МИЕЛОИДНЫХ ЛЕЙКОЗАХ

***Цель*: несмотря на то, что острые миелоидные лейкозы (ОМЛ), возникающие после воздействия ионизирующей радиации, рассматривают как вторичные, почти ничего неизвестно о молекулярных механизмах радиационного лейкемогенеза. Цель исследования — анализ частоты транслокаций гена *MLL* при радиационно-ассоциированных ОМЛ по сравнению со спонтанными ОМЛ. *Методы*: были проанализированы образцы субстратных клеток, полученные при первичной диагностике ОМЛ у 61 пациента, для выявления перестроек *MLL* с использованием флуоресцентной *in situ* гибридизации и/или ОТ-ПЦР. 27 пациентов подверглись воздействию ионизирующего облучения вследствие Чернобыльской катастрофы, 32 — со спонтанным ОМЛ не были облучены и у 2 было диагностировано заболевание, развившееся в связи с предшествующим лечением ингибиторами топоизомеразы II. *Результаты*: транслокации гена *MLL* обнаружены в группах больных со спонтанным и вызванным терапией ОМЛ (1/32 и 1/2 случаев соответственно). Единственной аномалией *MLL* в группе радиационно-ассоциированных ОМЛ была дупликация гена. *Выводы*: полученные нами данные исключают вовлечение транслокаций гена *MLL* в радиационно-индуцированный лейкемогенез, но поддерживают гипотезу о значимости потерь и прироста хромосомного материала в развитии ОМЛ у пациентов, подвергшихся воздействию ионизирующего облучения вследствие Чернобыльской катастрофы.**

***Ключевые слова*: острый миелоидный лейкоз, ионизирующая радиация, Чернобыльская катастрофа, *MLL*, транслокация, дупликация.**