別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
A.H. Hashimoto, K. Amanuma, K. Masumura, T. Nohmi and Y.Aoki	in vivo mutagenesis caused by diesel exhaust in the testis of *gpt* delta transgenic mice	Genes Environ.	31	1-8	2009
Y. Aoki., A.H. Hashimoto, K. Amanuma and M. Matsumoto	Potency of air pollutants at DNA adduct formation and assessment by in vivo mutagenesis.	DNA adduct formation, detection and mutagenesisv		143-153	2010
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N. Niimi, A. Sassa, A. Katafuchi, P. Gruz, H. Fujimoto, RR. Bonala, F. Johnson, T. Ohta and T. Nohmi,	The steric gate amino acid tyrosine 112 is required for efficient mismatched-primer extension by human DNA polymerase kappa	Biochemistry	48	4239-4246	2009
A. Shibata, D. Maeda, H. Ogino, M. Tsutsumi, T. Nohmi, H. Nakagama, T. Sugimura, H. Teraoka and M. Masutani	Role of Parp-1 in suppressing spontaneous deletion mutation in the liver and brain of mice atadolescence and advanced age	Mutat. Res.	664	20–27	2009
DA. Eastmond, A. Hartwig, D. Anderson, WA. Anwar, MC. Cimino, I. Dobrev, GR. Douglas, T. Nohmi, DH. Phillips and C. Vickers	Mutagenicity testing for chemical risk assessment: update of the WHO/IPCS Harmonized Scheme,	Mutagenesis	24	341-349	2009

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H. Fukuda, T. Takamura-Enya, Y. Masuda, T. Nohmi, C. Seki, K. Kamiya, T. Sugimura, C. Masutani, F. Hanaoka and H. Nakagama	Translesional DNA synthesis through a C8-guanyl adduct of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in vitro: REV1 inserts dC opposite the lesion, and DNA polymerase kappa potentially catalyzes extension reaction from the 3'-dC terminus	J. Biol. Chem..	284	25585-25592	2009
Y. Totsuka, T. Higuchi, T. Imai, A. Nishikawa, T. Nohmi, T. Kato, S. Masuda, N. Kinae, K. Hiyoshi, S. Ogo, M. Kawanishi, T. Yagi, T. Ichinose, N. Fukumori, M. Watanabe, T. Sugimura and K. Wakabayashi	Genotoxicity of nano/microparticles in in vitro micronuclei, in vivo comet and mutation assay systems	Part. Fibre. Toxicol.	6	23-33	2009
H. Nagayoshi, A. Matsumoto, R. Nishi, T. Kawamoto, M. Ichiba and T. Matsuda	Increased formation of gastric N^2-ethylidene-2'-deoxyguanosine DNA adducts in aldehyde dehydrogenase-2 knockout mice treated with ethanol	Mutat. Res.	673	74-77	2009
A. Katafuchi, A. Sassa, N. Niimi, P. Gruz, H. Fujimoto, C. Masutani, F. Hanaoka, T. Ohta and T. Nohmi	Critical amino acids in human DNA polymerases {eta} and {kappa} involved in erroneous incorporation of oxidized nucleotides	Nucleic Acids Res.	38	859-867	2010
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N. Okudaira, Y. Uehara, K. Fujiwara, N. Kagawa, A. Ootsuyama, T. Norimura, K. Saeki, T. Nohmi, K. Masumura, T. Matsumoto, Y. Oghiso, K. Tanaka, K. Ichinohe, S. Nakamura, S. Tanaka and T.Ono	Radiation dose-rate effect on mutation induction in spleen and liver of gpt delta mice	Radiat. Res..	173	138-147	2010
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松田, 永吉, 椙村, 周	液体クロマトグラフィータンデム質量分析法を用いた DNA 損傷研究法	J. Mass Spectrom. Soc. Jpn.	57	301-304	2009
松田, 足立, 周	アダクトミクス-DNA およびタンパク質付加体の網羅的解析	実験医学増刊	27	2481-2488	2009
Y. Takashima, M. Sakuraba, T. Koizumi, H. Sakamoto, M. Hayashi and M. Honma,	Dependence of DNA double strand break repair pathways on cell cycle phase in human lymphoblastoid cells	Environ Mol Mutagen.	50	815-822	2009
J. Wang, J.R. Sawyer, L. Chen, T. Chen, M. Honma, N. Mei and M.M. Moore	The mouse lymphoma assay detects recombination, deletion, and aneuploidy	Toxicol Sci.	109	96-105	2009
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J. Kawahara, C. Tanaka, C. Tanaka, Y. Aoki and J. Yonemoto	Estimation of the respiratory ventilation rate of preschool children in daily life	J. Air Waste Manag. Assoc.	61	46-54	2011
J. Kawahara, S. Tanaka, C. Tanaka, Y. Aoki and J. Yonemoto	Estimation of daily inhalation rate in preschool children using a tri-axial accelerometer: a pilot study	Sci. Total Environ.	409	3073-3077	2011
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M. Hori, S. Yonekura, T. Nohmi, P. Gruz, H. Sugiyama, S. Yonei and Q.-M. Zhang-Akiyama	Error-prone translesion DNA synthesis by Escherichia coli DNA polymerase IV (DinB) on templates containing 1,2-dihydro-2-oxoadenine	J. Nucleic Acids	2010	Article I.D. 807579	2010
A. Sheh, C.W. Lee, K. Masumura, B.H. Rickman, T. Nohmi, G. N. Wogan, J.G. Fox and D.B. Schauer	Mutagenic potency of Helicobacter pylori in the gastric mucosa of mice is determined by sex and duration of infection	Proc. Natl. Acad. Sci. U.S.A.,	107	15217–15222	2010
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T. Nohmi and M. Bignami	Nucleotide pool damage and its biological consequences	Mutat. Res.	703	1-1	2010
A. Katafuchi and T. Nohmi	DNA polymeraseds involved in the incorporation of oxidized nucleotides into DNA: the efficiency and template base preference	Mutat. Res.	703	24-31	2010
M. Yasui, N. Koyama, T. Koizumi, K. Senda-Murata, Y. Takashima, M. Hayashi, K. Sugimoto, and M. Honma	Live cell imaging of micronucleus formation and development	Mutat. Res.	692	12-18	2010
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K. Kato, E. Yamamura, M. Kawanishi, T. Yagi, T. Matsuda, A. Sugiyama and Y. Uno	Application of the DNA adductome approach to assess the DNA-damaging capability of in vitro micronucleus test-positive compounds	Mutat. Res.	721	21-26	2011
P.H. Chou, S. Kageyama, S. Matsuda, K. Kanemoto, Y. Sasada, M. Oka, K. Shinmura, H. Mori, K. Kawai, H. Kasai, H. Sugimura and T. Matsuda	Detection of lipid peroxidation-induced DNA adducts caused by 4-oxo-2(E)-nonenal and 4-oxo-2(E)-hexenal in human autopsy tissues	Chem Res Toxicol	23	1442-1448	2010
T. Matsuda	Anticipated Mutation Assay Using Single-molecule Real-time (SMRT TM) Sequencing Technology	Genes and Environment	32	21-24	2010

H. Takemura, H. Nagayoshi, T. Matsuda, H. Sakakibara, M. Morita, A. Matsui, T. Ohura and K. Shimoi	Inhibitory effects of chrysoeriol on DNA adduct formation with benzo[a]pyrene in MCF-7 breast cancer cells	Toxicology	274	42-48	2010
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A. Furuhama, K. Hasunuma, Y. Aoki, Y. Yoshioka and H. Shiraishi	Application of chemical reaction mechanistic domains to an ecotoxicity QSAR model, the KAshinhou Tool for Ecotoxicity (KATE)	SAR QSAR Environ. Res.	22	505-523	2011
J. Kawahara, C. Tanaka, C. Tanaka, Y. Aoki and J. Yonemoto	Estimation of daily inhalation rate in preschool children using a tri-axial accelerometer: a pilot study	Sci. Total Environ.	409	3073-3077	2011
青木康展	改正「化審法」の施行	ファルマシア	47	895-870	2011
T.-H. Lim, R. Fujikane, S. Sano, R. Sakagami, Y. Nakatsu, T. Tsuzuki, M. Sekiguchi and A. Hidaka	Activation of AMP-activated protein kinase by MAPO1 and FLCN induces apoptosis triggered by alkylated base mismatch in DNA	DNA Repair	11	259-266	2012
T. Tsuzuki, J, Piao, T. Isoda, K. Sakumi, Y. Nakabeppu and Y. Nakatsu	Oxidative stress-induced tumorigenesis in the small intestine of various types of DNA repair-deficient mice	Health Physics	100	293-294	2011
大野みずき, 續輝久	DNA 修復酵素遺伝子-酸化的 DNA 損傷の修復系を中心として-	疾患モデルマウス表現型解析指南ー標準解析から専門解析まで		pp. 339-345, pp. 466-467	2011
T. Kamigaito, T. Noguchi, K. Narumi, R. Takashima, S. Hamada, H. Sanada, M. Hasuko, H. Hayashi, K. Masumura and T. Nohmi	Evaluation of the in vivo mutagenicity of nickel subsulfide in the lung of F344 gpt delta transgenic rats exposed by intratracheal instillation: A collaborative study for the gpt delta transgenic rat mutation assay	Genes and Environ.	34	18-24	2012

H. Sui, R. Ohta, T. Shiragiku, A. Akahori, K. Suzuki, M.Nakajima, H. Hayashi, K. Masumura and T. Nohmi	Evaluation of in vivo mutagenicity by 2,4-diaminotoluene and 2,6-diaminotoluene in liver of F344 gpt delta transgenic rat dosed for 28 days: a collaborative study of the gpt delta transgenic rat mutation assay	Genes and Environ.	18	25-33	2012
Y. Kawamura, H. Hayashi, O. Tajima, S. Yamada, T. Takayanagi, H. Hori, W. Fujii, K. Masumura and T. Nohmi	Evaluation of the genotoxicity of aristolochic acid in the kidney and liver of F344 gpt delta transgenic rat using a 28-day repeated-dose protocol: a collaborative study of the gpt delta transgenic rat mutation assay	Genes and Environ.	18	34-44	2012
M. Jin, A. Kijima, Y. Suzuki, D. Hibi, T. Inoue, Y. Ishii, T. Nohmi, A. Nishikawa, K. Ogawa and T. Umemura M.	Comprehensive toxicity study of safrole using a medium-term animal model with gpt delta rats	Toxicol.	290	312-321	2011
N. Toyoda-Hokaiwado1, Y. Yasui, M. Takamune, M. Yamada, M. Muramatsu, K. Masumura, M., T. Ohta, T. Tanaka and T. Nohmi	Modulatory effects of capsaicin on N-diethylnitrosamine (DEN)-induced mutagenesis in Salmonella typhimurium YG7108 and DEN-induced hepatocarcinogenesis in gpt delta transgenic rats	Genes and Environ.	33	160-166	2011
N. Toyoda-Hokaiwado1, Y. Yasui, M. Muramatsu, K. Masumura, M. Takamune, M. Yamada, T. Ohta, T. Tanaka and T. Nohmi	Chemopreventive effects of silymarin against 1,2-dimethylhydrazine plus dextran sodium sulfate-induced inflammation-associated carcinogenicity and genotoxicitiy in the colon of gpt delta rats	Carcinogenesis	32	1512-1517	2011
D. Hibi, Y. Suzuki, Y. Ishii, M. Jin, M. Watanabe, Y. Sugita-Konishi, T. Yanai, T. Nohmi, A. Nishikawa and T. Umemura	Site-specific in vivo mutagenicity in the kidney of gpt delta rats given a carcinogenic dose of ochratoxin A,	Toxicol. Sci.	122	406-414	2011

A. Yamamoto, Y. Sakamoto, K. Masumura, M. Honma and T. Nohmi	Involvement of mismatch repair proteins in adaptive responses induced by N-methyl-N'-nitro-N-nitroso guanidine against γ -induced genotoxicity in human cells	Mutat. Res.	713	56-63	2011
N. Koyama, M. Yasui, A. Kimura, S. Takami, T. Suzuki, K. Masumura, T. Nohmi, S. Masuda, N. Kinae, T. Matsuda, T. Imai and M. Honma	Acrylamide genotoxicity in young versus adult gpt delta male rats	Mutagenesis	26	525-529	2011
A. Sassa, T. Ohta, T. Nohmi, M. Honma and M. Yasui	Mutational specificities of brominated DNA adducts catalyzed by human DNA polymerases	J. Mol. Boil.	406	679-686	2011
P. Hakulinen, A. Yamamoto, N. Koyama, W. Kumita, M. Yasui and M. Honma	Induction of TK mutations in human lymphoblastoid TK6 cells by the rat carcinogen 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX)	Mutat. Res.	725	43-49	2011
H. Sugimura, H. Tao, M. Suzuki, H. Mori, M. Tsuboi, S. Matsuura, M. Goto, K. Shinmura, T. Ozawa, F. Tanioka, N. Sato, Y. Matsushima, S. Kageyama, K. Funai, P.H. Chou and T. Matsuda	Genetic susceptibility to lung cancer	Front Biosci (Schol Ed)	3	1463-1477	2011
K. Shinmura, M. Goto, M. Suzuki, H. Tao, H. Yamada, H. Igarashi, S. Matsuura, M. Maeda, H. Konno, T. Matsuda and H. Sugimura	Reduced expression of MUTYH with suppressive activity against mutations caused by 8-hydroxyguanine is a novel predictor of a poor prognosis in human gastric cancer	J Pathol	225	414-423	2011
S. Matsuda, S. Matsui, Y. Shimizu and T. Matsuda	Genotoxicity of colloidal fullerene C(60)	Environ Sci Technol	45	4133-4138	2011
K. Kato, E. Yamamura, M. Kawanishi, T. Yagi, T. Matsuda, A. Sugiyama and Y. Uno	Application of the DNA adductome approach to assess the DNA-damaging capability of in vitro micronucleus test-positive compounds	Mutat. Res.	721	21-26	2011

平成 23 年度厚生労働科学研究費補助金 食品の安全確保推進研究事業

第二回 遺伝毒性発がん物質の閾値に関する国際シンポジウム

International Symposium on Genotoxic and Carcinogenic Thresholds

プログラム・抄録集
Program & Abstracts

2011 年 11 月 23 日（水/祝） November 23, 2011

一橋記念講堂 Hitotsubashi Memorial Hall, Tokyo

Welcome to the 2nd International Symposium on Genotoxic and Carcinogenic Thresholds

Since the disaster at the Fukushima No. 1 nuclear power plant in March 2011, people became concerned about adverse effects of radiation, in particular those of low dose radiation strongly. The effects of radiation on chromosome DNA are events of probability, and thus it is thought that radiation poses cancer risk to humans even at very low doses. Likewise, genotoxic compounds, which interact with DNA and induce mutations, are assumed to have no thresholds for their action. These compounds are used to be called "radiomimetic compounds". Hence, genotoxic carcinogens, which induce cancer via genotoxic mechanisms, are regulated based on a paradigm that they have no thresholds for the cancer risk. Recently, however, the paradigm has been challenged by research on analyzes of carcinogenicity and genotoxicity of chemicals at low doses. Organisms including humans possess various self-defense mechanisms, such as detoxication metabolism, DNA repair, error-free translesion DNA synthesis, and apoptosis etc., which may suppress genotoxicity of chemicals at low doses and reduce the mutation frequency to spontaneous levels. These self defense mechanisms may constitute "apparent" or "practical" thresholds for genotoxic carcinogens.

In this symposium, six and four experts of genotoxicity and chemical carcinogenicity are invited from inside and outside of Japan, respectively, to discuss genotoxicity and carcinogenicity at low doses and the regulatory policies. This symposium follows the precedent symposia "International symposium – threshold of carcinogenicity and genotoxicity" in Kobe in Japan in 2006, and "The 1st International symposium on genotoxic and carcinogenic threshold" in Tokyo in 2008. It is our hope that presentation and discussion in this symposium will be beneficial to all the participants.

Takehiko Nohmi Ph.D.

Meeting Co-chairperson
Head, Division of Genetics and Mutagenesis
National Institute of Health Sciences, Japan

はじめに「第二回　遺伝毒性発がん物質の閾値に関する国際シンポジウム」

本年(2011年)3月に起きた福島第一原子力発電所の事故以来、放射線のヒトに対する影響、特に低線量放射線の影響について強い関心が集まっています。放射線の染色体 DNA に対する影響は確率的事象であり、放射線はどのように低線量であってもヒトに対して発がんリスクを負わせるもの考えられています。同様に、DNA に作用して突然変異を起こす遺伝毒性物質の作用に閾値はないと考えられています。遺伝毒性物質は、かつては「放射線類似作用物質」と呼ばれていました。このため、遺伝毒性のメカニズムに基づいて発がん性を示す遺伝毒性発がん物質は、その発がんリスクに閾値はないというパラダイムに基づいて規制が行われています。しかし近年、低用量域での化学物質の発がん作用、遺伝毒性作用の解析研究から、「遺伝毒性発がん物質の作用に閾値はない」というパラダイムは挑戦を受けています。ヒトを含む生物には、さまざまな生体防御機構（例えば解毒代謝、DNA 修復、トランスリージョン DNA 合成、アポトーシス等）が備わっており、これらが化学物質の低用量域での遺伝毒性を抑制し、変異頻度を自然突然変異のレベルに減少させることが考えられます。こうしたメカニズムは、遺伝毒性発がん物質の「みかけの」あるいは「実際的な」閾値を形成するかもしれません。

本シンポジウムでは、遺伝毒性、化学発がん分野の専門家を日本国内から6名、国外から4名招へいし、低用量域での遺伝毒性作用、発がん作用と、行政的な規制のあり方について発表と討論を行います。このシンポジウムは、2006年3月に神戸で開催された国際シンポジウム「環境因子、特に遺伝毒性発がん物質の閾値：安全と安心の接点をめざして」、2008年7月に東京で開催された「第一回遺伝毒性発がん物質の閾値に関する国際シンポジウム」に続くものです。シンポジウムでの発表と討論の内容が、全ての参加者にとって有益なものとなることを願ってやみません。

能美健彦

シンポジウム世話人
国立医薬品食品衛生研究所　変異遺伝部　部長

参加者へのご案内

1. 同時通訳について

   シンポジウム期間中、日英同時通訳（双方向）を行なっております。

2. 質疑・討論について

   質疑は、個別の発表終了後、挙手のうえ、場内のスタンドマイクでお願いいたします。ご質問等は、お名前とご所属を述べてから手短にご発言くださいますようお願いいたします。同時通訳は、質問に対しても行われます。皆様の活発なご発言、ご討論をお願いいたします。

3. 飲食・喫煙について

   会場内での食事、喫煙、撮影、録音はご遠慮ください。喫煙場所は１階の入り口を入ってすぐの左手にございます。

4. クローク

   用意してございません。お手回り品はご自身でお持ちください。

5. シンポジウム本部

   講堂を出て左に進まれますと、案内板がいくつかございます。その指示に従ってお進みください。吹き抜け部分の向こう側にございます。

Program

The 2nd International Symposium on Genotoxic and Carcinogenic Thresholds

November 23, 2011
Hitotsubashi Memorial Hall
National Center of Sciences Building
Hitotsubashi 2-1-2, Chiyoda-ku, Tokyo 101-0003, Japan

9:50 Opening Address

Takehiko Nohmi (Meeting Co-chairperson)

10:00 – 12:00 Session 1

Chair: Shoji Fukushima & Samuel M. Cohen

10:00 Genotoxic thresholds: identification of mutations in vivo and mechanistic studies in vitro

Takehiko Nohmi (National Institute of Health Sciences, Japan)

10:30 Threshold of genotoxic carcinogens: it is central concerns of carcinogenic risk assessment

Shoji Fukushima (Japan Bioassay Research Center, Japan)

11:00 Lessons Learned From 40,000-Animal Cancer Dose-Response Studies

George S. Bailey (Oregon State University, U.S.A.)

11:30 Urinary Bladder Carcinogenesis by DNA Reactive and Non-Reactive Chemicals: Non-linearity's and Thresholds

Samuel M. Cohen (University of Nebraska Medical Center, U.S.A.)

12:00 – 13:30 Lunch

13:30 – 15:30 Session 2

Chair: Teruhisa Tsuzuki & Elmar Gocke

13:30 A threshold for the murine T-cell lymphoma induction by N-ethyl-N-nitrosourea and/or radiation

Shizuko Kakinuma (National Institute of Radiological Sciences, Japan)

14:00 Exposure to ethylating agents: Where do the thresholds for mutagenic/clastogenic effects arise?

Elmar Gocke (F. Hoffmann-La Roche Ltd., Switzerland)

14:30 Oxidative stress-induced tumorigenesis in the small intestine of Mutyh-deficient mice: the effect of low-level exposure to $KBrO_3$

Teruhisa Tsuzuki (Kyushu University, Japan)

15:00 How do thresholds for mutagenicity and clastogenicity arise for DNA damaging agents?

George E. Johnson (Swansea University, U.K.)

15:30 – 16:00 Coffee Break

16:00 – 17:30 Session 3

Chair: Yasunobu Aoki & George S. Bailey

16:00 Health risk assessment of air pollutants: Air pollutant genotoxicity and its enhancement on suppression of phase II drug-metabolizing enzymes

Yasuhobu Aoki (National Institute for Environmental Studies, Japan)

16:30 Toxicity testing strategy based on the concept of the threshold of toxicological concern (TTC)

Akihiko Hirose (National Institute of Health Sciences, Japan)

17:00 Closing Remarks

Shoji Fukushima (Meeting Co-chairperson)

第二回 遺伝毒性発がん物質の閾値に関する国際シンポジウム

平成23年11月23日(水・祝)

学術総合センター, 一橋記念講堂

9:50　世話人挨拶（開会の辞）

能美 健彦

10:00 – 12:00　セッション 1　　座長　福島 昭治, Samuel M. Cohen

10:00　Genotoxic thresholds: the underlying mechanisms in vitro and in vivo

能美 健彦（国立医薬品食品衛生研究所・変異遺伝部）

10:30　Threshold of genotoxic carcinogens: it is central concerns of carcinogenic risk assessment

福島 昭治（日本バイオアッセイ研究センター）

11:00　Cancer and biomarker response at ultra-low carcinogen dose: A 42,000 animal study

George S. Bailey (Oregon State University, U.S.A.)

11:30　Urinary Bladder Carcinogenesis by DNA Reactive and Non-DNA Reactive Chemicals: Non-linearities and Thresholds

Samuel M. Cohen (University of Nebraska Medical Center, U.S.A.)

12:00 – 13:30　　****** 昼 食 *****

13:30 – 15:30　セッション 2　　座長　續 輝久, Elmar Gocke

13:30　A threshold for the murine T-cell lymphoma induction by N-ethyl-N-nitrosourea and/or radiation

柿沼 志津子（放射線医学総合研究所）

14:00　Exposure to ethylating agents: Where do the thresholds for mutagenic/clastogenic effects arise?

Elmar Gocke (F. Hoffmann-La Roche Ltd., Switzerland)

14:30　Oxidative stress-induced tumorigenesis in the small intestine of Mutyh-deficient mice: the effect of low-level exposure to $KBrO_3$

續 輝久（九州大学大学院）

15:00 Investigating DNA repair as the genotoxic threshold mechanism for DNA reactive compounds

George E. Johnson (Swansea University, U.K.)

15:30 – 16:00 ****** 休 憩 ******

16:00 – 17:30 セッション 3 座長 青木 康展, George S. Bailey

16:00 Enhanced genotoxicity under the phase II drug-metabolizing enzyme deficient condition

青木 康展（国立環境研究所）

16:30 Toxicity testing strategy based on the concept of the threshold of toxicological concern (TTC)

広瀬 明彦（国立医薬品食品衛生研究所・総合評価研究室）

17:00 閉会の辞

福島 昭治（日本バイオアッセイ研究センター）

Abstracts

Genotoxic thresholds: identification of mutations *in vivo* and mechanistic studies *in vitro*

Takehiko Nohmi[1], Kenichi Masumura[1], Petr Gruz[1], Naomi Toyoda-Hokaiwado[1], Makiko Takamune[1], Naoko Niimi[1], Tetsuya Suzuki[1], Yuki Kanemaru[1], Manabu Yasui[1], Masami Yamada[1], Masamitsu Honma[1], Noritaka Adachi[2], and Akiyoshi Nishikawa[3]

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Currently, genotoxic carcinogens are regulated based on an assumption that carcinogens with genotoxic properties have no thresholds for their risk on humans. However, there are several issues to be discussed on the policy. The first is a practical issue: how to identify genotoxicity of chemicals. At present, bacterial reverse mutation assay (Ames test) is most widely used for identification of chemicals that interact with DNA and induce mutations. However, there is a gap between results of in vitro and in vivo mutagenicity tests. The second is a mechanistic issue. Organisms including humans possess defense mechanisms against toxic compounds including genotoxic chemicals. Therefore, the defense mechanisms may reduce the level of mutations induced by the chemicals to the level of spontaneous mutations, thereby generating "practical thresholds" for genotoxic compounds. We address these two issues by in vivo and in vitro approaches.

In in vivo studies, we have established transgenic mice and rats, i.e., gpt delta mice and rats, for identification of mutagenicity of chemicals in targets organs of carcinogens. These transgenic rodents allow to detect mutagenicity of chemicals in any organs of mice and rats and the mutations can be identified at sequence levels. We present basic features of gpt delta mice (C57BL/6J background) and rats (Sprague Dawley and Fischer 344 background), and discuss their significance in regulatory toxicology.

In in vitro studies, we have established human cells expressing genetically modified specialized DNA polymerases (Pol), i.e., Pol ζ and Pol κ, involved in translesion DNA synthesis (TLS).TLS is a process where Pols continue DNA synthesis across DNA lesions. The process may be error free or error prone. In either case, TLS rescues damaged cells from genotoxic effects of chemicals by continuing chromosome replication. The established human cells expressing modified specialized DNA polymerases displayed different sensitivity to mutagenicity and cytotoxicity of chemical carcinogens such as benzo[a]pyrene diolepoxide or hydrogen peroxide. We are examining the possibility whether TLS is involved in generation of "practical thresholds" against genotoxic carcinogens. In addition, we report an endeavor to introduce single DNA adduct, i.e., 8-oxo-7,8-dihydro-2'-deoxyguanosine , into a specific site of human chromosome. These experiments could answer the question of whether formation of DNA adducts in the chromosome inevitably leads to induction of mutations or not.

Threshold of genotoxic carcinogens: it is central concerns of carcinogenic risk assessment

Shoji Fukushima[1], Min Wei[2], Anna Kakehashi[2], and Hideki Wanibuchi[2]

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The presence or absence of a carcinogenic threshold will determine the reliability of risk assessment of chemical carcinogen when extrapolated from high dose rodent testing. Therefore, it is essential to verify scientifically whether the non-threshold concept is valid, especially for genotoxic carcinogens. Herein, we present low-dose carcinogenicity data based on medium-term rat liver bioassays for 3 genotoxic heptocarcinogens: 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and 2-amino-3-methylimidazo [4,5-f]quinoline (IQ), heterocyclic amines contained in seared meat and fish; N-nitrosodiethylamine (DEN), a N-nitrosocompound synthesized in the stomach through the reaction of secondary amines and nitrites. Very low doses of MeIQx induced formation of DNA-MeIQx adducts; somewhat higher doses caused elevation of 8-hydroxy-2'-deoxyquanosine (8-OHdG) levels, gene mutations and initiation activity; and the more higher dose induced formation of glutathione S-transferase placental form (GST-P) positive foci in the liver, a well-known preneoplastic lesion marker in rat hepatocarcinogenesis. Similarly, only the higher doses of IQ caused an increase in the number of GST-P positive foci in the liver, the lower doses had no effect. Furthermore, the finding that $p21^{Cip/WAF1}$ was significantly induced in the liver at doses well below those required for IQ mediated carcinogenic effects, suggests that induction of $p21^{Cip/WAF1}$ is one of the mechanisms responsible for no-effect doses for IQ carcinogenicity. We also demonstrated that low doses of DEN did not induce either GST-P positive foci formation or gene mutation in the liver. Moreover, concurrent administration of low doses of MeIQx with DEN that had no effects on GST-P positive foci formation still did not increase the GST-P positive foci formation compared to the MeIQx alone, DEN alone and non-treatment control groups, while concurrent administration of high dose of MeIQx with DEN showed at least an additive effect. Based on the above findings of existence of no-effect doses for markers that cells typically acquire as they move through the initiation and promotion stages of carcinogenesis, we argue strongly for the existence of a threshold, at least a practical threshold, for the carcinogenic effects of these three genotoxic carcinogens in the rat.