

図10 AzaC *in utero*投与による胎児終脳における遺伝子発現変化(E14.5)

AzaCを妊娠10.5日マウスに腹腔内投与し、妊娠14.5日に胎児終脳を採取し、Perccellome手法を適用した網羅的遺伝子発現解析を行った。発現が変化した遺伝子群が認められなかった。

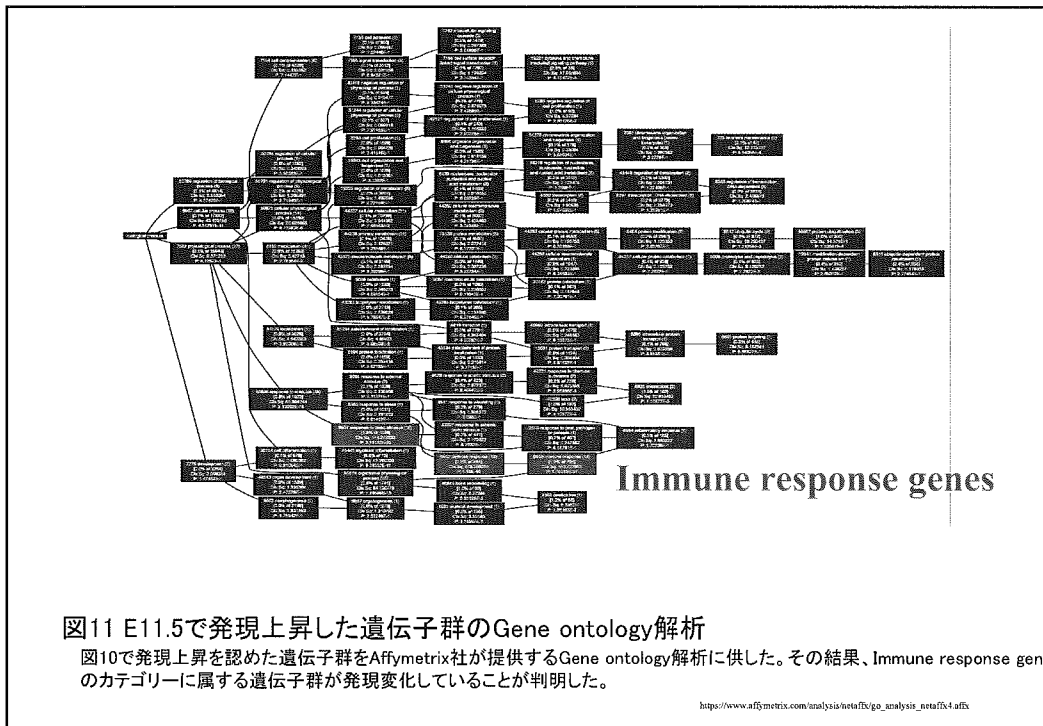
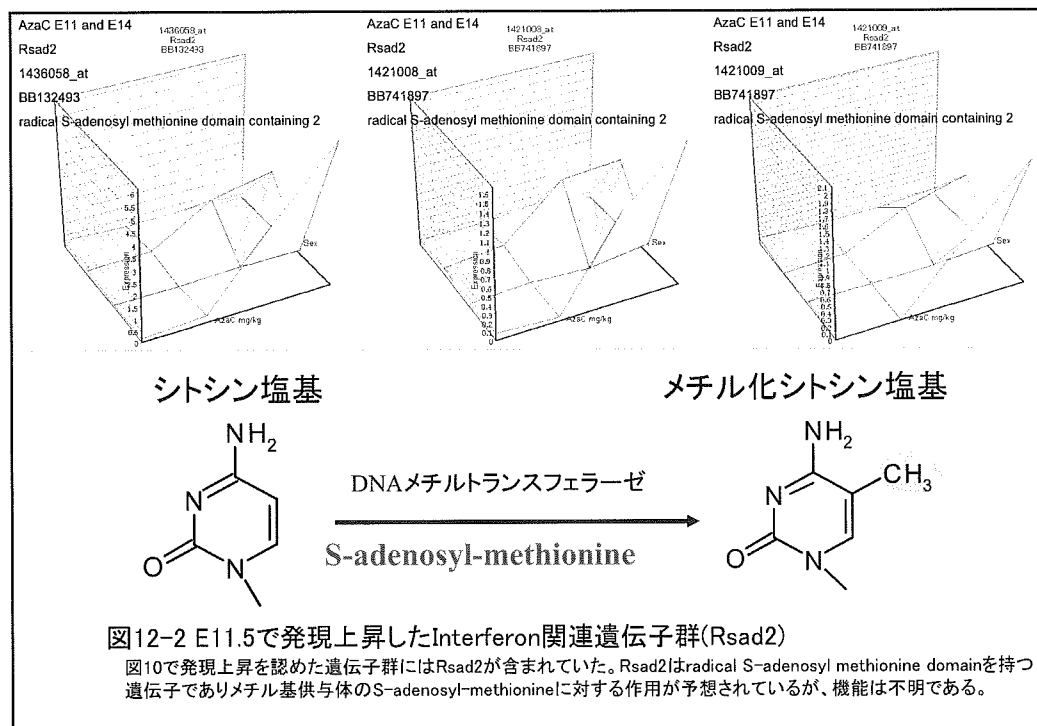
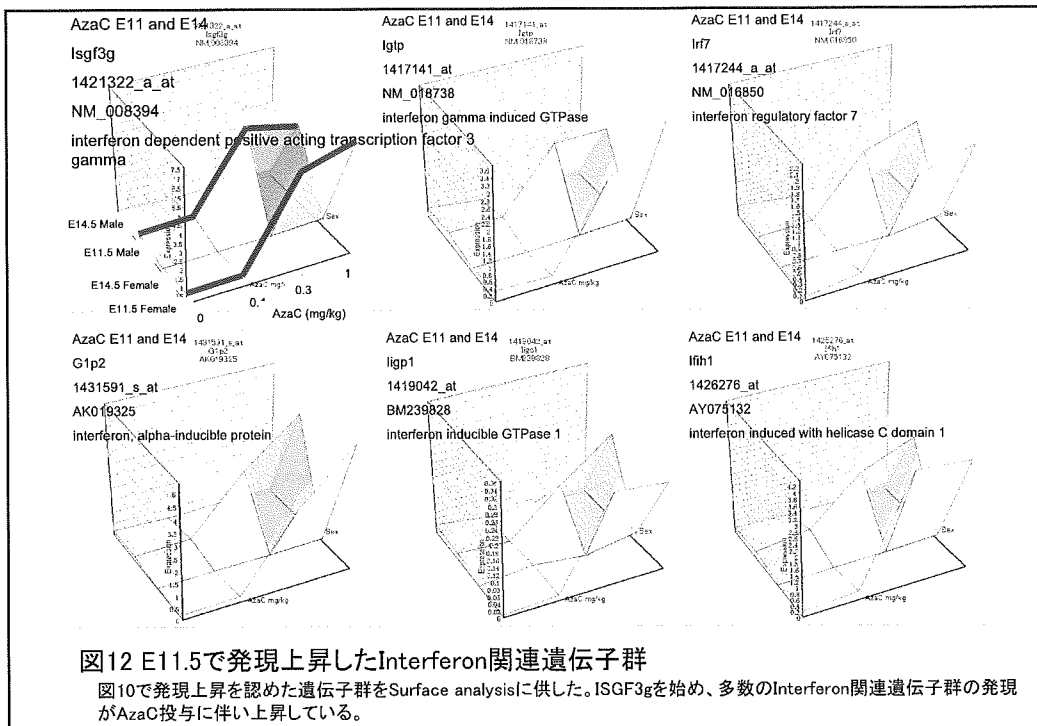
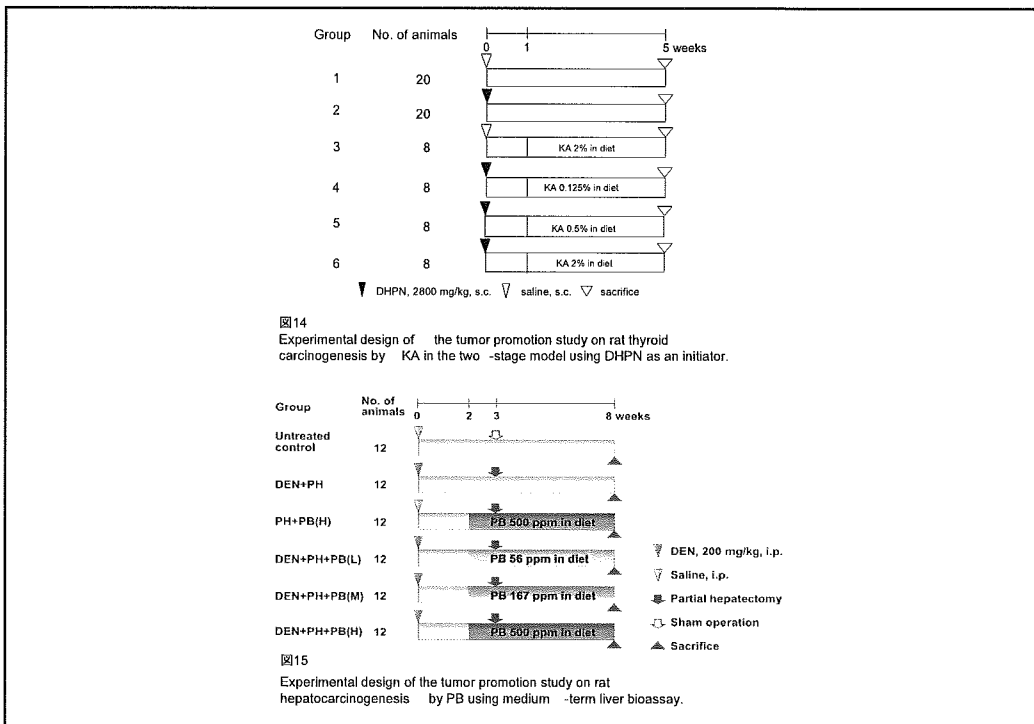
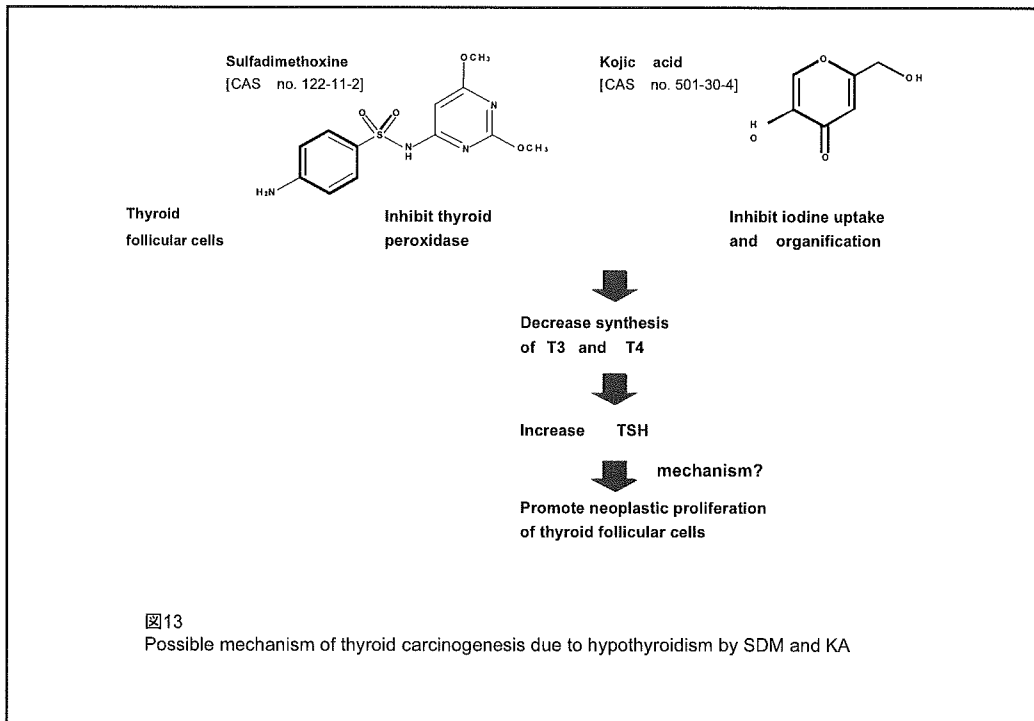


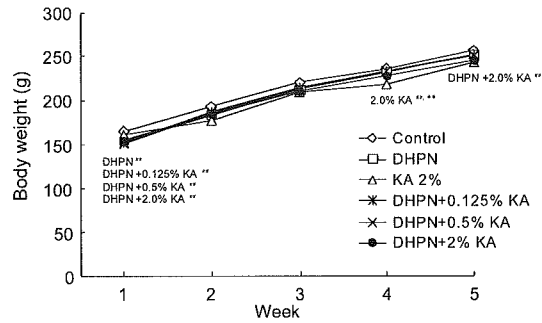
図11 E11.5で発現上昇した遺伝子群のGene ontology解析

図10で発現上昇を認めた遺伝子群をAffymetrix社が提供するGene ontology解析に供した。その結果、Immune response genのカテゴリーに属する遺伝子群が発現変化していることが判明した。

https://www.affymetrix.com/analysis/netafix/go_analysis_netafix4 affix







#, ## : Significantly different from the untreated group (# P<0.05, ##P<0.01).
 **: Significantly different from the DHPN group (P<0.01).

图16 Growth curve of male F344 rats treated with KA in the two-stage thyroid carcinogenesis model using DHPN as an initiator.

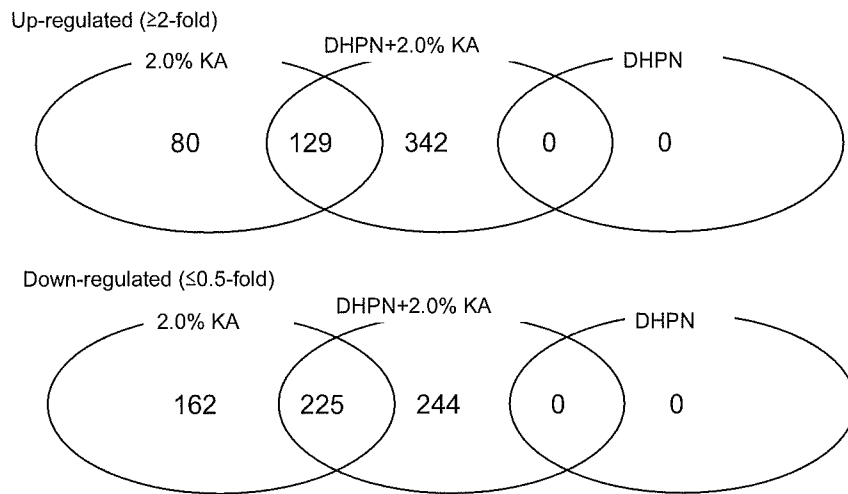


图17 Number of genes showing up- or down-regulation in response to DHPN+2.0% KA-treatment. Common genes between DHPN-initiated and 2.0% KA groups.

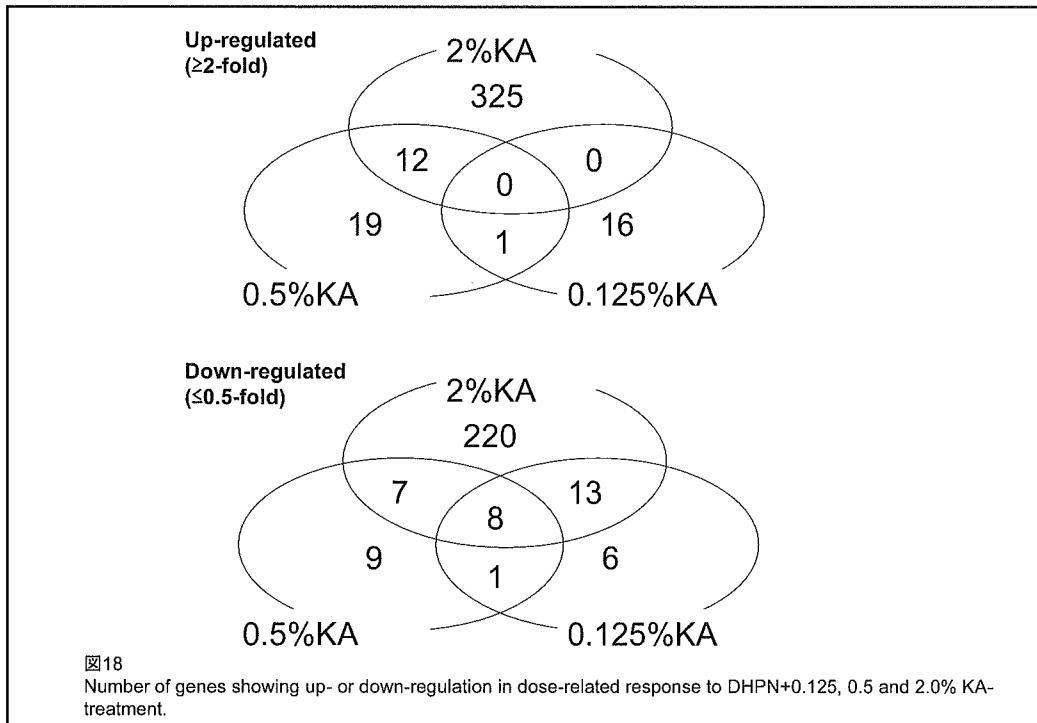


Table 1.
 Final body, absolute and relative thyroid weights of male F344 rats after 4-week KA-treatment in the two-stage thyroid carcinogenesis model using DHPN as an initiator.

	Group					
	Untreated	DHPN	KA 2%	DHPN+KA (%)		
				0.125	0.5	2
Final body weight (g)	253.1 ± 16.6 ^a	246.7 ± 16.2	237.0 ± 6.5	244.4 ± 10.9	246.2 ± 9.0	241.1 ± 7.9
Thyroid weight						
Absolute (mg)	9.6 ± 2.2	9.9 ± 2.5	53.2 ± 6.2 ^{***}	13.7 ± 2.1	21.3 ± 1.5 ^{***}	43.7 ± 13.1 ^{***}
Relative (mg/100g b.w.)	3.8 ± 1.0	4.0 ± 1.0	22.4 ± 2.5 ^{***}	5.6 ± 0.9	8.7 ± 0.6 ^{***}	18.0 ± 4.9 ^{***}

^a Mean ±SD

^{***}: Significantly different from the untreated group (P < 0.01).

^{**}: Significantly different from the DHPN group (P < 0.01).

Table 2.
 Incidence of histopathological lesions in the thyroid of male F344 rats treated with KA for 4 weeks after initiation with DHPN.

	Control	DHPN	2% KA	DHPN+KA (%)		
				0.125	0.5	2
No. of animals examined	4	4	8	8	8	8
Diffuse follicular cell hypertrophy (1/++/+++)	0	0	8(0/1/5/2)* ^a	0	8(0/8/0/0)* ^a	8(2/3/3/0)* ^a
Focal follicular cell hyperplasia (1/+/++/+++)	0	0	0	0	5(3/1/1)* ^a	7(0/4/3)* ^a

^a Grade of the lesion: ±, minimal; +, slight; ++, moderate; +++, severe.

^b Grade of the lesion was classified as the total number of lesions/section: ±.

*: Significantly different from the controls (P < 0.01).

^a: Significantly different from the DHPN group (P < 0.01).

^a 2 foci; +, 3-5 foci; ++, 6-14 foci; +++,

^a 15 foci.

Table 3.
List of genes showing dose-related up-regulation by KA in the two-stage thyroid carcinogenesis model (≥2-fold, p<0.05).

Accession No.	Gene symbol	Gene title	DHPN-KA (%)		
			0.125	0.5	2.0
from 0.5% (12 genes)					
NM053338.1	Rrad	Ras related associated with diabetes	1.8*	3.4	3.5
NM022589.1	Tspan 2	tetraspan 2	1.5	2.5	3.0
NM053716.1		fructose-1,6-biphosphatase 2	1.5	2.5	3.0
AB073753.1	Kerj6	potassium inwardly-rectifying channel, subfamily J, member 6	1.3	2.5	3.6
D45414.1	Ptprn	protein tyrosine phosphatase, receptor type, N	1.5	3.0	3.1
D1290720		EST	1.7	2.1	2.4
BF285731		EST	1.7	2.6	2.2
NM022297.1	Ddah1	dimethylarginine dimethylaminohydrolase 1	1.3	2.5	2.0
NM022513.1	Slut1b1	sulfotransferase family 1B, member 1	1.1	2.4	3.3
BE113640	Slc4a1	solute carrier family 4, member 1	1.7	3.0	2.6
A1639162		EST	1.7	2.1	2.8
BF389489		TBC1D12, TBC1 domain family, member 12 (predicted)	1.2	2.7	2.7

*: x fold, vs DHPN group.

Table 4.
List of genes showing dose-related up-regulation by KA in the two-stage thyroid carcinogenesis model (≤0.5 fold, p<0.05).

Accession No.	Gene Symbol	Gene title	DHPN-KA (%)		
			0.125	1.0	5.0
from 0.125% (8 genes)					
BF000470		EST	0.46*	0.42	0.19
BE107282		Ischemia related factor vof-16	0.22	0.19	0.38
AA850361		EST	0.35	0.44	0.42
BF545268		Complement receptor 2 (predicted)	0.44	0.46	0.46
AA899256		similar to eukaryotic translation initiation factor 4G1	0.37	0.45	0.21
BF282471	Lep2	Lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kD)	0.33	0.17	0.43
A1227800		kinesin-associated protein 3 (predicted)	0.19	0.43	0.23
BE116089		EST	0.43	0.48	0.37
from 0.5% (7 genes)					
A1169367		EST	0.6	0.48	0.51
AW531880		EST	0.53	0.29	0.24
AF109674.1		late gestation lung protein 1	0.61	0.45	0.44
AA996804		strongly similar to fibulin 1 (Mus musculus)	0.49	0.43	0.45
A1454854		TGFB inducible early growth response 3 (predicted)	0.95	0.31	0.13
A1502114	Abca1	ATP-binding cassette, sub-family A (ABC1), member 1	0.69	0.4	0.37
BE105697		EST	0.53	0.34	0.46

*: x fold, DHPN group.

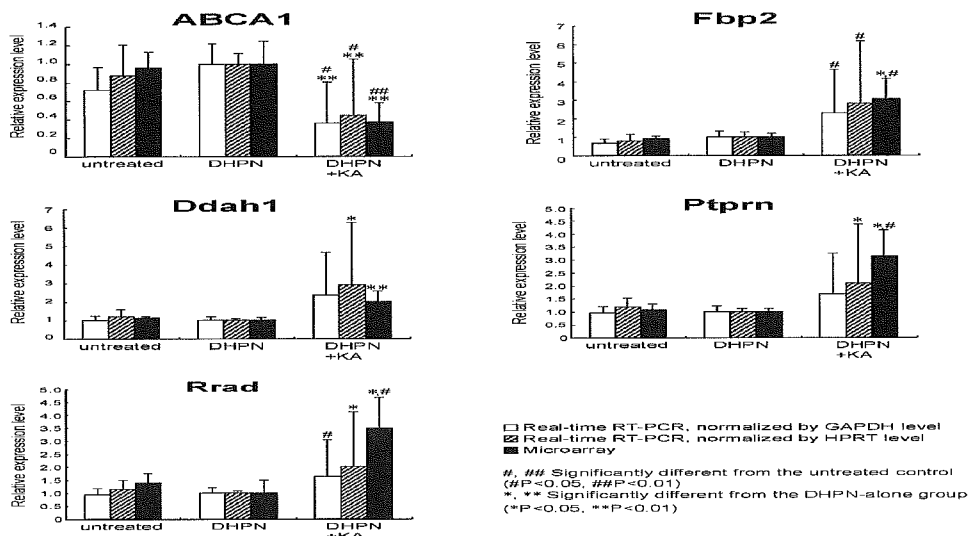


Figure 19. Relative expression level of genes showing dose-dependent changes detected by microarray analysis and real-time RT-PCR.

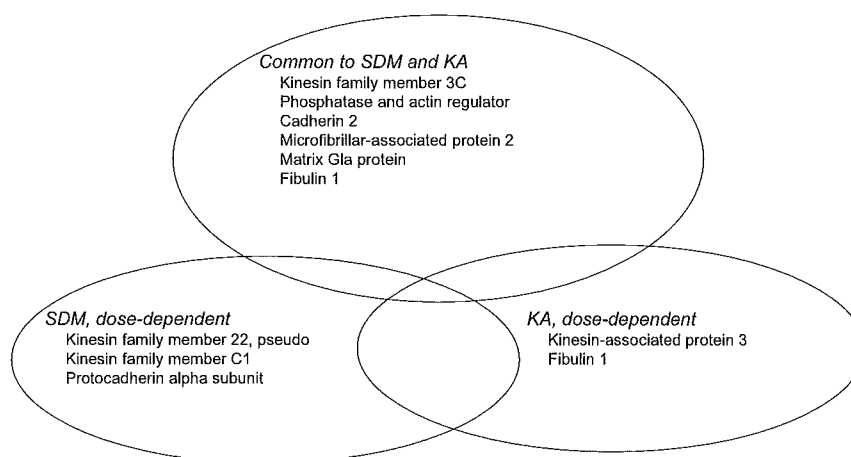
Table 5. Up-regulated genes common to the carcinogenic process by 1000 ppm-SDM and 20,000 ppm-KA (≥ 2 -fold, $p < 0.05$).

Accession No.	Gene symbol	Gene title	1000 ppm-SDM	ppm-KA	20,000 ppm-KA
NM012914.1	Atp2a3	ATPase, Ca ⁺⁺ transporting, ubiquitous	2.04	*	2.46
NM022858.1	Foxq1	HNF-3Forkhead homolog-1	2.06		2.98
NM053486.1	Kif3c	Kinesin family member 3C	2.04		2.43
BI286411		Immunoglobulin superfamily, member 11 (predicted)	2.31		2.25
BF415939		EST	2.99		5.04
BF417890		EST	2.93		2.40
BE396607		EST	2.27		2.25
AA996943		Phosphatase and actin regulator	1.96		2.01
AI070944		EST	2.32		3.72
NM012949.1		EST	2.18		9.22
NM130741.1	Lcn2	Lipocalin 2	2.46		2.83
NM022513.1	Slit1b1	Sulfotransferase family 1B, member 1	1.96		3.30
AI232643		Salute carrier family 25 (mitochondrial carrier, adenine nucleotide translocator), member 13	2.04		2.51
BF396595		EST	2.13		2.08
AI070875	Mgp	Matrix Gla protein	1.99		2.23
AA899386		EST	1.99		1.95
AI576190		EST	2.16		2.37
BE564059		EST	1.99		2.33

* : x fold, vs DHPN group

Table 6. Down-regulated genes common to the carcinogenic process by 1000 ppm-SDM and 20,000 ppm-KA (≤ 0.5 -fold, $p < 0.05$).

Accession No.	Gene symbol	Gene title	1000 ppm-SDM	ppm-KA	20,000 ppm-KA
NM031766.1	Cpz	Carboxypeptidase Z	0.41	*	0.37
NM031333.1	Cdh2	Cadherin 2	0.52		0.46
NM012703.1	Thrsp	Thyroid hormone responsive protein	0.49		0.22
BM386326	Mfap2	Microfibrillar-associated protein 2 (predicted)	0.46		0.40
AI176918	Fbln1	Fibulin 1 (predicted)	0.43		0.44
BI297183	Sox4	SRY-box containing gene 4 (predicted)	0.48		0.32
BE107282		Ischemia related factor-16	0.34		0.39
BF561454	Fgl2	Fibrinogen-like 2	0.47		0.33
AW914996		EST	0.47		0.48
AI072641		EST	0.48		0.30
BC381546		EST	0.33		0.46



☒20

Common functions involved in early process of thyroid carcinogenesis related to hypothyroidism

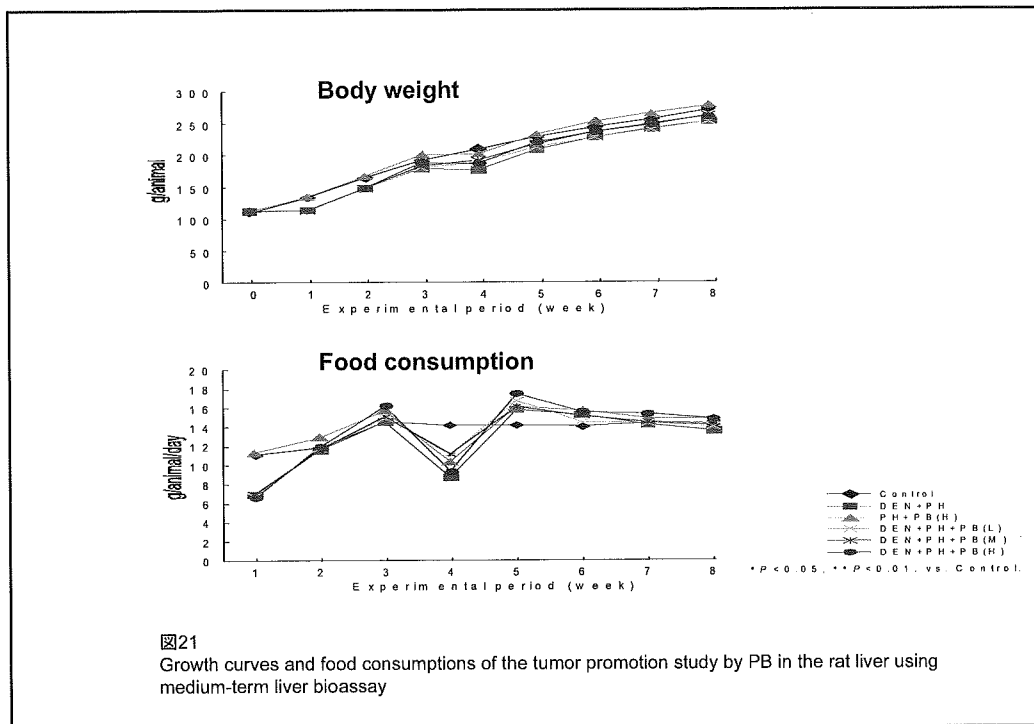


图21
Growth curves and food consumptions of the tumor promotion study by PB in the rat liver using medium-term liver bioassay

Table 7.
Final body and liver weights of rats treated with PB at the promotion stage in the medium-term liver bioassay.

Group	No. of effective animals	BW (g)	Liver (g)	Liver (g/100 g BW)
Control	12	267.1 ± 7.4	8.35 ± 0.47	3.12 ± 0.13
DEN+PH	11	249.0 ± 10.6**	7.36 ± 0.59**	2.96 ± 0.27
PH+PB(H)	10	271.8 ± 12.1**	10.29 ± 0.67**	3.78 ± 0.17**
DEN+PH+PB(L)	12	247.1 ± 25.9*	7.51 ± 1.08*	3.03 ± 0.17
DEN+PH+PB(M)	11	255.4 ± 12.2	8.55 ± 0.61**	3.35 ± 0.10*
DEN+PH+PB(H)	12	253.6 ± 7.7*	9.72 ± 0.71**	3.83 ± 0.24**

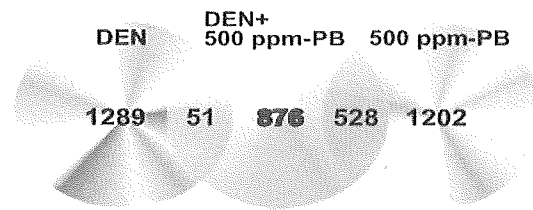
* P < 0.05, ** P < 0.01, vs. Control.
* P < 0.05, ** P < 0.01, vs. DEN+PH.

Table 8.
Final body and liver weights of rats treated with PB at the promotion stage in the medium-term liver bioassay.

	DEN+PH	DEN+PB (ppm)		
		56	167	500
No. of effective animals	11	12	11	12
Numbers (No./cm ²)	3.85 ± 2.04	4.61 ± 2.23	6.90 ± 3.16**	6.20 ± 2.66**
Area (mm ² /cm ²)	0.22 ± 0.13	0.31 ± 0.17	0.60 ± 0.24**	0.46 ± 0.26**

** P < 0.01, vs. DEN+PH.

≥ 2-fold



≤ 0.5-fold

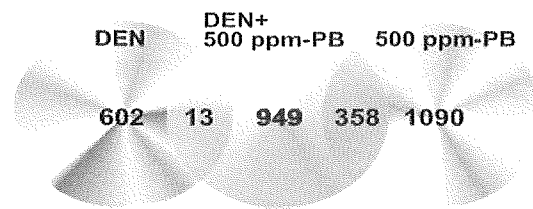


Figure 22

Genes showing altered expression specific to the tumor promotion process in the medium-term liver bioassay using rats

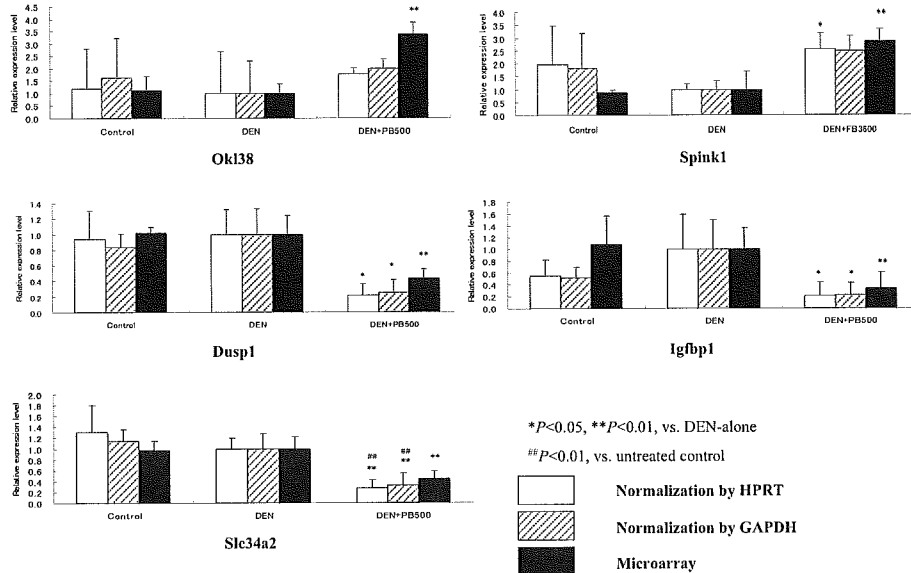
Table 9.

List of genes showing dose-related up-regulation by PB in the two-stage hepatocarcinogenesis model (≥2-fold, p<0.05).

Accession No.	Gene symbol	Gene title	DEN+PB (ppm)		
			56	167	500
From 56 ppm					
NM_031665.1	Stx6	Syntaxin 6	2.64	2.44	2.78
D31838.1	Wee1	Wee 1 tyrosine kinase	2.05	2.34	2.15
M35300.1	Spink1	Serine protease inhibitor, kazal type 1	2.35	2.14	2.70
AA943075		EST	2.87	2.85	2.92
M60388.1	Hemiferrin	Hemiferrin, transferrin-like protein	3.15	2.74	2.39
AW523578		Brain Ntub mRNA sequence	2.36	2.10	2.15
From 167 ppm					
AY081218.1	Ok38	Pregnancy-induced growth inhibitor	1.53	2.14	3.36
BG380736		EST, similar to PHD finger protein 20 (Mus musculus)	1.68	2.06	2.34
AI236937		EST, similar to anthrax toxin receptor 2 (Antx2; Mus musculus)	1.91	2.19	2.33
AI511380		EST, similar to outer dense fiber of sperm tails 2-like (Odf2l; Mus musculus)	1.83	2.02	2.20
AW435169		EST, similar to tripartite motif protein 24 (Trim24; Mus musculus)	1.51	2.11	2.46
BI277442		EST	1.63	2.03	2.25

Table 10.
List of genes showing dose-related down-regulation by PB in the two-stage hepatocarcinogenesis model (≤ 0.5 -fold, $p < 0.05$).

Accession No.	Gene symbol	Gene title	DEN+PB (ppm)		
			56	167	500
From 56 ppm					
NM_053380	Slc34a2	Solute carrier family 34, member 2	0.39	0.32	0.45
BE110276		EST	0.38	0.23	0.16
A1111456		EST	0.21	0.43	0.47
AA924641		EST	0.39	0.47	0.46
BF392017		EST	0.31	0.10	0.37
From 167 ppm					
U02553.1 (BE1101108)	Dusp1	Dual specificity phosphatase	0.66	0.45	0.47
NM_013144	Igfbp1	Insulin-like growth factor binding protein 1	0.57	0.43	0.34
U39571.1		Phosphatidylinositol 4-kinase	0.70	0.45	0.46
BM384131		EST, A1115348 protein (predicted)	0.52	0.49	0.43
AI071617		EST	0.56	0.47	0.47
AI176317		EST	0.56	0.40	0.49
AW141081		EST	0.65	0.39	0.41
L08447.1	Cd3dz	CD3 antigen, zeta polypeptide	0.52	0.48	0.44
BI285940		EST	0.53	0.45	0.38
BI285616		Adipose differentiation-related protein	0.53	0.47	0.49
AI044898		EST	0.58	0.50	0.50
AA956038		EST	0.53	0.43	0.41
BF565241		EST	0.60	0.48	0.42
BE120455		EST	0.57	0.44	0.40
BF404845		EST	0.53	0.42	0.39
AI045966		EST	0.87	0.48	0.45



23
Validation of expression levels of representative genes selected in the microarray analysis by real-time RT-PCR

別添 5
雑誌

発表者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
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