A systems biological study on the identification of safe and effective molecular targets for reduction of ultraviolet B-induced skin pigmentation

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Supplementary Materials

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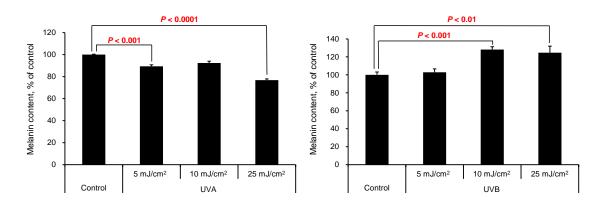
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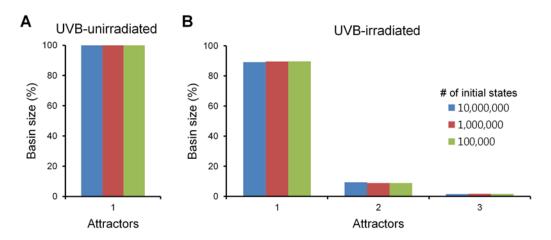
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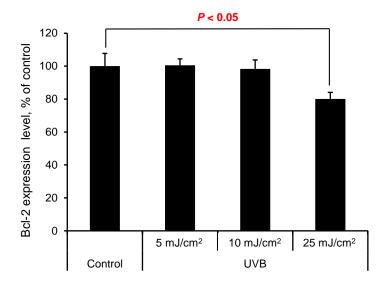
Supplementary Figure S1. The effect of UVA or UVB irradiation on the melanin content in human melanocytes.

Graphs of the melanin content in normal human melanocytes exposed to UVA or UVB irradiation at the indicated doses. Human melanocytes were cultured in 6-well plate and exposed to the indicated doses of UVA or UVB. After incubation, the melanocytes were harvested and dissolved in 1N NaOH solution. The melanin content was determined from absorbance (OD 475) measured by using microplate reader. The data represent the means + SD of three biological replicates. P-values were determined by Student's t test; t < 0.05 was considered statistically significant.



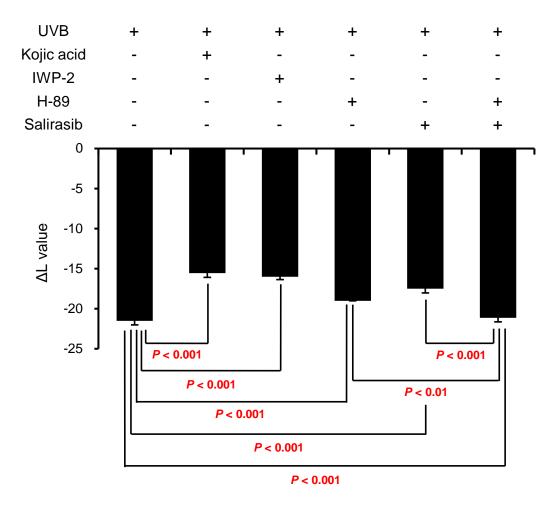
Supplementary Figure S2. The estimated basin sizes for different sampling numbers of initial network states.

The distributions of the estimated basin sizes are very similar regardless of the sampling number of initial states.



Supplementary Figure S3. The effect of UVB irradiation on the Bcl-2 expression level in human melanocytes.

Graphs of the Bcl-2 expression level in normal human melanocytes exposed to UVB irradiation at the indicated doses. Human melanocytes were cultured in 6-well plate and exposed to the indicated doses of UVB. After incubation, the melanocytes were harvested and lysed. Bcl-2 expression level was measured by using human Bcl-2 ELISA kit (Abcam, Cambridge, U.K.). The data represent the means + SD of three biological replicates. P-values were determined by Student's t test; t considered statistically significant.



Supplementary Figure S4. Effects of inhibition of beta-catenin, Ras, PKA, or a combination of Ras and PKA on the UVB-induced skin pigmentation.

Graphs of the Δ L values of the MelanoDerms exposed to IWP-2 (a beta-catenin inhibitor, 20 μ M), H-89 (a PKA inhibitor, 10 μ M), salirasib (a Ras inhibitor, 50 μ M), or a combined treatment with H-89 (10 μ M) and salirasib (50 μ M) upon UVB irradiation (10 mJ/cm²). MelanoDerms exposed to a combined treatment with H-89 and salirasib showed the Δ L value lower than those treated with either H-89 or salirasib alone. 1% kojic (70.37 mM) acid was used as a positive control. MelanoDerms were grown at the air-liquid interface and the maintenance medium was replenished every 2 days. After a 9-day of exposure to the chemicals, pigmentation of the skin equivalents was assessed by comparing the change in L* value, a value of CIE 1976 (L*,a*,b*) color space representing the brightness. The data represent the means + SD of at least three biological replicates. *P*-values were determined by Student's *t* test; *P* < 0.05 was considered statistically significant. See Table S4 for the simulation results of changes in UVB-induced melanin synthesis with respect to the inhibition of beta-catenin, Ras, PKA, or a combination of Ras and PKA.

II. Supplementary TablesSupplementary Table S1. The 113 links comprising the melanogenesis network.

Link index	Cellular type	Source	Interaction	Target	Reference
1	Extracellular Signal	UVB	+	ASK1	1-3
2	Extracellular Signal	UVB	+	EGFR	1
3	Extracellular Signal	UVB	+	IL-1	4
4	Extracellular Signal	UVB	-	PTEN	1,5,6
5	Keratinocytes	Melanin	-	IL-1	See the note [§] .
6	Keratinocytes	ERK	-	PTEN	6
7	Keratinocytes	Akt	-	PTEN	6
8	Keratinocytes	Melanin	+	PTEN	See the note [§] .
9	Keratinocytes	Melanin	-	EGFR	See the note [§] .
10	Keratinocytes	EGFR	+	PI3K	7
11	Keratinocytes	Akt	-	ASK1	8
12	Keratinocytes	Melanin	-	ASK1	See the note [§] .
13	Keratinocytes	EGFR	+	SG	9-11
14	Keratinocytes	ERK	-	SG	9,12
15	Keratinocytes	PI3K	+	PDK1	13,14
16	Keratinocytes	PTEN	-	PDK1	15
17	Keratinocytes	ASK1	+	MKK6	16
18	Keratinocytes	Akt	-	MKK4	17
19	Keratinocytes	ASK1	+	MKK4	16
20	Keratinocytes	SG	+	Ras	18
21	Keratinocytes	PDK1	+	Akt	14,19
22	Keratinocytes	MKK6	+	p38	20
23	Keratinocytes	MKK4	+	JNK	20
24	Keratinocytes	Akt	-	Raf	21
25	Keratinocytes	Ras	+	Raf	22
26	Keratinocytes	Akt	-	GSK3b	23
27	Keratinocytes	GSK3b	-	b-catenin	24
28	Keratinocytes	Raf	+	MEK	25-27
29	Keratinocytes	Akt	+	MDM2	28
30	Keratinocytes	GSK3b	-	NFAT	29,30
31	Keratinocytes	b-catenin	+	COX-2	31
32	Keratinocytes	GSK3b	-	COX-2	32
33	Keratinocytes	NFAT	+	COX-2	33
34	Keratinocytes	p38	+	COX-2	34
35	Keratinocytes	MEK	+	ERK	35,36
36	Keratinocytes	p38	-	ERK	37,38
37	Keratinocytes	ERK	+	p53	39

38	Keratinocytes	MDM2	-	p53	40
39	Keratinocytes	p38	+	p53	41
40	Keratinocytes	ERK	+	RSK	42,43
41	Keratinocytes	Akt	+	Bcl-2	44,45
42	Keratinocytes	ERK	+	Bcl-2	46
43	Keratinocytes	JNK	-	Bcl-2	47,48
44	Keratinocytes	b-catenin	+	Bcl-2	49
45	Keratinocytes	GSK3b	+	Bcl-2	50,51
46	Keratinocytes	p38	-	Bcl-2	52
47	Keratinocytes	p53	-	Bcl-2	53-55
48	Keratinocytes	RSK	+	Bcl-2	43,56,57
49	Keratinocytes	IL-1	+	ET-1	58
50	Keratinocytes	p53	+	ET-1	59,60
51	Keratinocytes	IL-1	+	SCF	61
52	Keratinocytes	p53	+	SCF	59
53	Keratinocytes	p53	+	a-MSH	59
54	Keratinocytes	COX-2	+	PGE2	62,63
55	Keratinocytes	IL-1	+	PGE2	62,63
56	Paracrine	ET-1	+	ETR	64
57	Paracrine	SCF	+	c-Kit	65,66
58	Paracrine	a-MSH	+	MC1R	67
59	Paracrine	PGE2	+	EP4	68
60	Melanocytes	ETR	+	PKC	64
61	Melanocytes	c-Kit	+	SG	69
62	Melanocytes	ERK	-	SG	9,12
63	Melanocytes	MC1R	+	AC	70,71
64	Melanocytes	Akt	-	ASK1	8
65	Melanocytes	PKC	+	PI3K	72
66	Melanocytes	Ras	+	PI3K	73
67	Melanocytes	cAMP	-	PI3K	74
68	Melanocytes	SG	+	Ras	18
69	Melanocytes	cAMP	+	Ras	75
70	Melanocytes	EP4	+	cAMP	68
71	Melanocytes	AC	+	cAMP	76
72	Melanocytes	PDE	-	cAMP	77,78
73	Melanocytes	ASK1	+	MKK4	16
74	Melanocytes	Akt	-	MKK4	17
75	Melanocytes	PI3K	+	PDK1	13,14
76	Melanocytes	PKC	+	Raf	79
77	Melanocytes	Ras	+	Raf	22,26
78	Melanocytes	cAMP	+	PKA	76

79	Melanocytes	ASK1	+	MKK6	16
80	Melanocytes	PDK1	+	Akt	14,19
81	Melanocytes	Raf	+	MEK	25-27
82	Melanocytes	PKA	+	PDE	80,81
83	Melanocytes	MKK6	+	p38	20
84	Melanocytes	Akt	-	GSK3b	23
85	Melanocytes	MEK	+	ERK	35,36
86	Melanocytes	p38	-	ERK	37
87	Melanocytes	p38	+	MSK	43,82
88	Melanocytes	ERK	+	MSK	43,82
89	Melanocytes	MKK4	+	JNK	20
90	Melanocytes	Akt	+	MDM2	28
91	Melanocytes	ERK	+	RSK	42,43
92	Melanocytes	p38	+	p53	41
93	Melanocytes	MDM2	-	p53	40
94	Melanocytes	MITFprotein	-	p53	83
95	Melanocytes	GSK3b	-	b-catenin	24
96	Melanocytes	PKA	+	CREB	76
97	Melanocytes	Akt	+	CREB	45,84
98	Melanocytes	MSK	+	CREB	43
99	Melanocytes	Akt	+	Bcl-2	44,45
100	Melanocytes	p38	-	Bcl-2	52
101	Melanocytes	ERK	+	Bcl-2	46
102	Melanocytes	JNK	-	Bcl-2	47,48
103	Melanocytes	RSK	+	Bcl-2	43,56,57
104	Keratinocytes	b-catenin	+	Bcl-2	49
105	Keratinocytes	GSK3b	+	Bcl-2	50,51
106	Melanocytes	p53	-	Bcl-2	53-55
107	Melanocytes	CREB	+	Bcl-2	45,85
108	Melanocytes	MITFprotein	+	Bcl-2	86
109	Melanocytes	b-catenin	+	MITFmRNA	87
110	Melanocytes	CREB	+	MITFmRNA	88
111	Melanocytes	ERK	+	MITFprotein	89-91
112	Melanocytes	MITFmRNA	+	MITFprotein	92
113	Melanocytes	MITFprotein	+	Melanin	92

Links 5, 8, 9, and 12 were included to represent the photoprotective role of epidermal melanin against UVB irradiation.

IL-1, interleukin 1; PTEN, phosphatase and tensin homolog; EGFR, epidermal growth factor receptor; PI3K, phosphatidylinositol 3-kinase; ASK1, apoptosis signal-regulating kinase 1; SG, the growth factor receptor–bound protein 2 (Grb2) and Son of Sevenless (SOS) complex; PDK1,

phosphoinositide-dependent kinase 1; MKK6, mitogen-activated protein kinase (MAPK) 6; MKK4, mitogen-activated protein kinase (MAPK) 4; JNK, c-Jun N-terminal kinase; GSK3b, Glycogen synthase kinase-3 beta; b-catenin, beta-catenin; ERK, extracellular signal-regulated kinase; MEK, MAPK/ERK kinase; MDM2, mouse double minute 2 homolog; NFAT, nuclear factor of activated T-cells; COX-2, cyclooxygenase (COX-2); RSK, ribosomal s6 kinase; ETR, endothelin receptor; MC1R, melanocortin 1 receptor; EP4, prostaglandin E receptor 4; PKC, protein kinase C; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; PDE, phosphodiesterase; MSK, mitogen- and stress-activated kinase and CREB, cAMP response element-binding protein.

Supplementary Table S2. Logic tables of the Boolean network model.

Node index]	Logic table	e		Remarks
index		Melanin	UVB	IL-1_	K	
	_	0	0	0	<u> </u>	IL-1 activation in human
1		0	1	1		keratinocytes is augmented by
		1	0	0		UVB irradiation.
		1	1	0		
	Melanin	UVB	Akt_K EF	RK_K	PTEN_K	
	0	0	0	0	1	
	0	0	0	1	0	
	0	0	1	0	0	LIVID imp disting inhibits DTENI
	0	0	1	1	0	UVB irradiation inhibits PTEN function by promoting its
	0	1	0	0	0	phosphorylation.
	0	1	0	1	0	Phosphorylation of PTEN
	0	1	1	0	0	downregulates its lipid
2	0	1	1	1	0	phosphatase function and protein
2	1	0	0	0	1	stability.
						UVB induced ERK/AKT-
	1	0	0	1	0	dependent PTEN suppression
	1	0	1	0	0	promotes survival of epidermal
	1	0	1	1	0	keratinocytes.
	1	1	0	0	1	
	1	1	0	1	0	
	1	1	1	0	0	
	1	1	1	1	0	
	M	elanin	UVB	EGF	R_K_	
		0	0	()	UVB irradiation induces
3		0	1	1		phosphorylation of EGFR and
		1	0	()	increases its kinase activity.
		1	1	(
					,	
4		EG		K_K 0		EGFR-mediated phosphorylation
7				1		of Gab1 results in PI3K activation

1		Melanin	UVB	Akt_K	ASK1_K	
1	•	0	0	0	0	
1		0	0	1	0	LIVP irradiction induces ASV1
Akt phosphorylates and negatively regulates ASK1 activity.		0	1	0	1	
1	5	0	1	1	0	
1		1	0	0	0	
		1	0	1	0	10811110011011111011111
BRK		1	1	0	0	
		1	1	1	0	
O		ED V	V ECI	ED V SC	V	EGFR interacts with and activates
Activates downstream Ras. Activated ERK phosphorylates						SG complex, which in turn
1						activates downstream Ras.
1	O					Activated ERK phosphorylates
PTEN_K						Sos and promotes disassociation
PTEN_R PISK_R PDK1_K PDK1_K PDK1_K O 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		1		1)	of the SG complex.
activates the downstream Akt kinase. 7						PI3K promotes the binding of
1		PTE	N_K PI31	K_K PDK1	_K	PDK1 with PIP3, which in turn
PTEN acts as a phosphatase to dephosphorylate PIP3, resulting in the deactivation of PDK1. ASK1_K		0) (0 0		activates the downstream Akt
1	7	C)	1 1		kinase.
the deactivation of PDK1. ASK1_K MKK6_K ASK1 phosphorylates and activates MKK6. ASK1_K AKL_K MKK4_K ASK1 activates MKK4 upon UVB irradiation. ASK1_K AKL_K MKK4_K ASK1 activates MKK4 upon UVB irradiation. Akt negatively regulates MKK4 activity by means of phosphorylation. SG_K Ras_K SG complex catalyzes the exchange of GDP with GTP and induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 phosphorylates Akt to promote its activation.		1	1 (0 0		PTEN acts as a phosphatase to
ASK1_K MKK6_K ASK1 phosphorylates and activates MKK6. ASK1_K AKL_K MKK4_K ASK1 activates MKK4 upon UVB irradiation. ASK1_K AKL_K MKK4_K ASK1 activates MKK4 upon UVB irradiation. Akt negatively regulates MKK4 activity by means of phosphorylation. SG_K Ras_K SG complex catalyzes the exchange of GDP with GTP and induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 phosphorylates Akt to promote its activation.		1	1	1 0		dephosphorylate PIP3, resulting in
ASK1 phosphorylates and activates MKK6. ASK1 phosphorylates and activates MKK6. ASK1 activates MKK4 upon UVB irradiation. Akt negatively regulates MKK4 1 0 1 activity by means of phosphorylation. SG_K Ras_K SG complex catalyzes the exchange of GDP with GTP and induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 phosphorylates Akt to promote its activation.						the deactivation of PDK1.
8 0 0 activates MKK6. ASK1_K Akt_K MKK4_K ASK1 activates MKK4 upon UVB irradiation. 9 0 1 0 Akt negatively regulates MKK4 1 0 1 activity by means of phosphorylation. 10 0 0 phosphorylation. SG complex catalyzes the exchange of GDP with GTP and induces Ras activation. induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 phosphorylates Akt to promote its activation.			ASK1_K	MKK6_K		ASK1 phosphorylates and
ASK1_K Akt_K MKK4_K ASK1 activates MKK4 upon UVB 0 0 0 0 irradiation. Akt negatively regulates MKK4 1 0 1 activity by means of 1 1 0 phosphorylation. SG_K Ras_K SG complex catalyzes the exchange of GDP with GTP and induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 11 0 phosphorylates Akt to promote its activation.	8		0	0		activates MKK6.
9 0 0 0 0 Akt negatively regulates MKK4 1 0 1 activity by means of 1 1 0 phosphorylation. SG_K Ras_K SG complex catalyzes the exchange of GDP with GTP and induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 phosphorylates Akt to promote its			1	1		
9 0 1 0 Akt negatively regulates MKK4 1 0 1 activity by means of 1 1 0 phosphorylation. SG_K Ras_K SG complex catalyzes the exchange of GDP with GTP and induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 11 0 phosphorylates Akt to promote its		ASK1	_K Ak	t_K MKF	K4_K	•
activity by means of phosphorylation. SG_K Ras_K SG complex catalyzes the exchange of GDP with GTP and induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 0 0 0 phosphorylates Akt to promote its activation.		0		0)	
phosphorylation. SG_K Ras_K SG complex catalyzes the exchange of GDP with GTP and induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 0 0 0 phosphorylates Akt to promote its activation.	9	0		1 ()	
SG_K Ras_K SG complex catalyzes the exchange of GDP with GTP and induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 0 0 phosphorylates Akt to promote its activation.		1		0	1	activity by means of
10 0 0 0 exchange of GDP with GTP and induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 11 0 0 0 phosphorylates Akt to promote its activation.		1		1 ()	phosphorylation.
1 1 induces Ras activation. PDK1_K Akt_K Upon UVB irradiation, PDK1 11 0 0 phosphorylates Akt to promote its			SG_K	Ras_K		SG complex catalyzes the
PDK1_K Akt_K Upon UVB irradiation, PDK1 11 0 0 phosphorylates Akt to promote its	10	_	0	0		exchange of GDP with GTP and
11 0 0 phosphorylates Akt to promote its			1	1		induces Ras activation.
activation			PDK1_K	Akt_K		Upon UVB irradiation, PDK1
1 activation.	11	_	0	0	•	phosphorylates Akt to promote its
			1	1		activation.

MKK6_K p38_K UVB-induced active MKK6 phosphorylates and activates p38.			
1	12		
13	12		phosphorylates and activates p38.
1		MKK4_K JNK_K	Active MKK4 directly
Ras_K	13	0 0	
Ras directly interacts with and activates Raf. 1		1 1	its activation.
14		Ras_K Akt_K Raf_K	Ras directly interacts with and
Akt phosphorylates and inhibits 1		0 0 0	activates Raf.
AKL GSK3b_K O 1 O SK3b_K O 1 O SK3b_K O 1 O SK3b_K O 1 O SK3b_K O SK3b_K O O 1 O O O MEK activation. Akt promotes nuclear localization and activation of MDM2 by means of phosphorylation.	14		Akt phosphorylates and inhibits
AK_K GSK3b_K O O			Ser/Thr kinase Raf.
15 0 1 kinase activity of GSK3b. GSK3b_K b-catenin_K 0 1 and promotes its degradation. 16 Raf_K MEK_K 17 0 0 MEK activation. 18 Akt_K MDM2_K 0 0 and activation of MDM2 by means of phosphorylation.			
1 0 GSK3b_K b-catenin_K 0 1 and promotes its degradation. 1 0 Raf_K MEK_K 0 0 0 MEK activation. Akt_K MDM2_K 0 0 and activation of MDM2 by means of phosphorylation.	15		
16 O 1 and promotes its degradation. Raf_K MEK_K Raf phosphorylates and promotes O 0 0 MEK activation. 1 1 Akt_K MDM2_K Akt promotes nuclear localization and activation of MDM2 by means of phosphorylation.	13		kinase activity of GSK3b.
16 10 Raf_K MEK_K 0 0 Raf phosphorylates and promotes MEK activation. 11 11 Akt_K MDM2_K 0 0 0 and activation of MDM2 by means 1 1 of phosphorylation.		GSK3b_K b-catenin_K	GSK3b phosphorylates b-catenin
1 0 Raf_K MEK_K 0 0 0 MEK activation. 1 1 Akt_K MDM2_K 0 0 and activation of MDM2 by means of phosphorylation.	16	0 1	
17 0 0 0 MEK activation. 1 1 Akt_K MDM2_K 0 0 0 and activation of MDM2 by means 1 1 1 of phosphorylation.		1 0	
Akt_K MDM2_K Akt promotes nuclear localization and activation of MDM2 by means of phosphorylation.		Raf_K MEK_K	Raf phosphorylates and promotes
Akt_K MDM2_K Akt promotes nuclear localization and activation of MDM2 by means of phosphorylation.	17	0 0	MEK activation.
18 0 0 0 and activation of MDM2 by means 1 1 1 of phosphorylation.			Akt promotes puglear localization
of phosphorylation.	10		•
<u> </u>	18		·
		· 1 ·	NFAT phosphorylation by active
GSK3b_K NFAT_K GSK3b suppresses its nuclear		GSK3b_K NFAT_K	
19 0 1 translocation, which reduces its	19		translocation, which reduces its
DNA hinding activity		1 0	DNA binding activity.

	b-catenin_K	GSK3b_K	p38_K	NFAT_K	COX-2_K	
	0	0	0	0	0	
	0	0	0	1	1	p38, NFAT, or b-catenin is needed
	0	0	1	0	1	for the transcriptional activation of
	0	0	1	1	0	COX-2, hence forming an OR
	0	1	0	1	0	_
20	0	1	1 1	0	0	relation.
	1	0	0	0	1	Inhibition of COX-2 by GSK3b is
	1	0	0 1	1 0	1 1	dominant to the positive
	1	0	1	1	1	regulators.
	1	1	0	0	0	
	1 1	1	0 1	1 0	0	
	1	1	1	1	0	
	N	MEK_K	p38_K	ERK_F	Χ	MEK phosphorylates and activate
		0	0	0		ERK.
21		0	1	0		When both MEK and p38 are
		1	0	1		activated, dephosphorylation of
		1	1	0		ERK occurs.
						ERK or p38 kinase phosphorylate
	MDM				53_K	p53 protein in response to UVB
	0	0	()	0	irradiation, leading to its
	0	0		1	1	activation.
	0	1	()	1	
22	0	1		1	1	The nuclear localization of p53,
	1	0	()	0	which is necessary for its
	1	0	1	1	0	transcriptional activation, is
	1	1	()	0	inhibited by direct binding of p53
	1	1	1	1	0	to MDM2.
		ERK_I	RSI	K_K		RSK is directly phosphorylated by
23		0)		ERK, which promotes its kinase
		1		1		activity.

	JNK_K 0	p53_K 0	p38_K 0	b-catenin_K	GSK3b_K	Akt_K 0	ERK_K 0	RSK_K 0	Bcl-2_K	
	0	0	0	0	0	0	0	1	1	
	0	0	0	0	0	0	1	0	1	
	0	0	0	0	0	0	1	1	1	
	0	0	0	0	0	1	0	0	1	
	0	0	0	0	0	1	0	1	1	
	0	0	0	0	0	1	1	0	1	
	0	0	0	0	0	1	1	1	1	
	0	0	0	0	1	0	0	0	1	
	0	0	0	0	1	0	1	0	1	
	0	0	0	0	1	0	1	1	1	Phosphorylation of BAD (a Bcl-
	0	0	0	0	1	1	0	0	1	antagonist) by Akt, ERK, or RSI
	0	0	0	0	1	1	0	1	1	is needed for the full activation of
	0	0	0	0	1	1	1	0	1	
	0	0	0	0	1	1	1	1	1	Bcl-2 protein.
	0	0	0	1	0	0	0	0	1	Beta-catenin and GSK3-beta
	0	0	0	1 1	0	0	0	0	1	upregulates Bcl-2 expression
	0	0	0	1	0	0	1	1	1	level.
	0	0	0	1	0	1	0	0	1	The activity of Bcl-2 is suppress
24	0	0	0	1	0	1	0	1	1	
	0	0	0	1	0	1	1	0	1	if any of its negative regulators i
	0	0	0	1	0	1	1	1	1	activated.
	0	0	0	1	1	0	0	0	1	Hence, the activation condition
	0	0	0	1	1	0	0	1	1	Bcl-2_M is
	0	0	0	1 1	1	0	1	0	1	'AND(OR(Akt_K,ERK_K,RSK
	0	0	0	1	1	1	0	0	1	
	0	0	0	1	1	1	0	1	1	, b-catenin_K, GSK3b_K),
	0	0	0	1	1	1	1	0	1	NOT(OR(p53_K, JNK_K,
	0	0	0	1	1	1	1	1	1	p38_K)))'.
	0	0	1	0	0	0	0	0	0	
	0	0	1	0	0	0	0	1	0	
	0	0	1	0	0	0	1	0	0	
	0	0	1	0	0	0	1	1	0	
	0	0	1	0	0	1	0	0	0	
	0	0	1	0	0	1	1	0	0	
	0	0	1	0	0	1	1	1	0	
	0	0	1	0	1	0	0	0	0	
	0	0	1	0	1	0	0	1	0	
	0	0	1	0	1	0	1	0	0	
	0	0	1	0	1	0	1	1	0	

	0	0	1	0	1	1	0	1	0	
	0	0	1	0	1	1	1	0	0	
	0	0	1	0	1	1	1	1	0	
	0	0	1	1	0	0	0	0	0	
	0	0	1	1	0	0	0	1	0	
	0	0	1	1	0	0	1	0	0	
	0	0	1	1 1	0	0	1	0	0	
	0	0	1	1	0	1	0	1	0	
	0	0	1	1	0	1	1	0	0	
	0	0	1	1	0	1	1	1	0	
	0	0	1	1	1	0	0	0	0	
	0	0	1	1	1	0	0	1	0	
	0	0	1	1	1	0	1	0	0	
	0	0	1	1	1	0	1	1	0	Phosphorylation of BAD (a Bcl-2
	0	0	1	1	1	1	0	0	0	antagonist) by Akt, ERK, or RSK
	0	0	1	1	1	1	0	1	0	is needed for the full activation of
	0	0	1	1	1	1	1	0	0	
	0	0	1	1	1	1	1	1	0	Bcl-2 protein.
	0	1	0	0	0	0	0	0	0	Beta-catenin and GSK3-beta
	0	1	0	0	0	0	1	0	1	upregulates Bcl-2 expression
	0	1	0	0	0	0	1	1	0	level.
	0	1	0	0	0	1	0	0	1	The activity of Bcl-2 is suppressed
24	0	1	0	0	0	1	0	1	0	
	0	1	0	0	0	1	1	0	0	if any of its negative regulators is
	0	1	0	0	0	1	1	1	0	activated.
	0	1	0	0	1	0	0	0	0	Hence, the activation condition for
	0	1	0	0	1	0	0	1	1	Bcl-2_M is
	0	1	0	0	1	0	1	0	1	'AND(OR(Akt_K,ERK_K,RSK_K
	0	1	0	0	1	0	0	0	0	
	0	1	0	0	1	1	0	1	0	, b-catenin_K, GSK3b_K),
	0	1	0	0	1	1	1	0	0	NOT(OR(p53_K, JNK_K,
	0	1	0	0	1	1	1	1	0	p38_K)))'.
	0	1	0	1	0	0	0	0	0	
	0	1	0	1	0	0	0	1	1	
	0	1	0	1	0	0	1	0	1	
	0	1	0	1	0	0	1	1	0	
	0	1	0	1	0	1	0	0	1	
	0	1	0	1	0	1	0	1	0	
	0	1	0	1	0	1	1	0	0	
	0	1	0	1	0	1	1	1	0	
	0	1	0	1	1	0	0	0	0	
	0	1	0	1	1 1	0	0	1	1	
	0	1	0	1	1	0	1 1	0	0	
	0	1	0	1	1	1	0	0	1	
	0	1	0	1	1	1	0	1	0	

	0	1	0	1	1	1	1	0	0	
	0	1	0	1	1	1	1	1	0	
	0	1	1	0	0	0	0	0	0	
	0	1	1	0	0	0	0	1	0	
	0	1	1	0	0	0	1	0	0	
	0	1	1	0	0	0	1	1	0	
	0	1	1	0	0	1	0	0	0	
	0	1	1	0	0	1	0	1	0	
	0	1	1	0	0	1	1	0	0	
	0	1	1 1	0	0	1	1	0	0	
	0	1	1	0	1	0	0	1	0	
	0	1	1	0	1	0	1	0	0	
	0	1	1	0	1	0	1	1	0	
	0	1	1	0	1	1	0	0	0	
	0	1	1	0	1	1	0	1	0	Phosphorylation of BAD (a Bcl-2
	0	1	1	0	1	1	1	0	0	antagonist) by Akt, ERK, or RSK
	0	1	1	0	1	1	1	1	0	is needed for the full activation of
	0	1	1	1	0	0	0	0	0	
	0	1	1	1	0	0	0	1	0	Bcl-2 protein.
	0	1	1	1	0	0	1	0	0	Beta-catenin and GSK3-beta
	0	1	1	1	0	0	1	1	0	upregulates Bcl-2 expression
	0	1	1	1	0	1	0	0	0	level.
	0	1	1	1	0	1	0	1	0	
24	0	1	1	1	0	1	1	0	0	The activity of Bcl-2 is suppressed
	0	1	1	1	0	1	1	1	0	if any of its negative regulators is
	0	1	1	1	1	0	0	0	0	activated.
	0	1	1	1	1	0	0	1	0	Hence, the activation condition for
	0	1	1	1	1	0	1	0	0	
	0	1	1	1	1	1	0	0	0	Bcl-2_M is 'AND(OR(Akt_K,
	0	1	1	1	1	1	0	1	0	ERK_K, RSK_K, b-catenin_K,
	0	1	1	1	1	1	1	0	0	GSK3b_K), NOT(OR(p53_K,
	0	1	1	1	1	1	1	1	0	JNK_K, p38_K)))'.
	1	0	0	0	0	0	0	0	0	VI (II_II, p30_II//) .
	1	0	0	0	0	0	0	1	1	
	1	0	0	0	0	0	1	0	1	
	1	0	0	0	0	0	1	1	0	
	1	0	0	0	0	1	0	0	1	
	1	0	0	0	0	1	0	1	0	
	1	0	0	0	0	1	1	0	0	
	1	0	0	0	0	1	1	1	0	
	1	0	0	0	1	0	0	0	0	
	1	0	0	0	1	0	0	1	1	
	1	0	0	0	1	0	1	0	1	
	1	0	0	0	1	0	1	1	0	
	1	0	0	0	1	1	0	0	1	
	1	0	0	0	1	1	0	1	0	
-	1	0	0	0	1	1	1	0	0	

	1	0	0	0	1	1	1	1	0	
	1	0	0	1	0	0	0	0	0	
	1	0	0	1	0	0	0	1	1	
	1	0	0	1	0	0	1	0	1	
	1	0	0	1	0	0	1	1	0	
	1	0	0	1	0	1	0	0	1	
	1	0	0	1	0	1	0	1	0	
	1	0	0	1 1	0	1 1	1	0	0	
	1	0	0	1	1	0	0	0	0	
	1	0	0	1	1	0	0	1	1	
	1	0	0	1	1	0	1	0	1	
	1	0	0	1	1	0	1	1	0	
	1	0	0	1	1	1	0	0	1	
	1	0	0	1	1	1	0	1	0	DI 1 1 C CDAD (D 12
	1	0	0	1	1	1	1	0	0	Phosphorylation of BAD (a Bcl-2
	1	0	0	1	1	1	1	1	0	antagonist) by Akt, ERK, or RSK
	1	0	1	0	0	0	0	0	0	is needed for the full activation of
	1	0	1	0	0	0	0	1	0	Bcl-2 protein.
	1	0	1	0	0	0	1	0	0	
	1	0	1	0	0	0	1	1	0	Beta-catenin and GSK3-beta
	1	0	1	0	0	1	0	0	0	upregulates Bcl-2 expression
	1	0	1	0	0	1 1	0	0	0	level.
24	1	0	1	0	0	1	1	1	0	The activity of Bcl-2 is suppressed
21	1	0	1	0	1	0	0	0	0	if any of its negative regulators is
	1	0	1	0	1	0	0	1	0	
	1	0	1	0	1	0	1	0	0	activated.
	1	0	1	0	1	0	1	1	0	Hence, the activation condition for
	1	0	1	0	1	1	0	0	0	Bcl-2_M is 'AND(OR(Akt_K,
	1	0	1	0	1	1	0	1	0	ERK_K, RSK_K, b-catenin_K,
	1	0	1	0	1	1	1	0	0	GSK3b_K), NOT(OR(p53_K,
	1	0	1	0	1	1	1	1	0	
	1	0	1	1	0	0	0	0	0	JNK_K, p38_K)))'.
	1	0	1	1 1	0	0	0	0	0	
	1	0	1	1	0	0	1	1	0	
	1	0	1	1	0	1	0	0	0	
	1	0	1	1	0	1	0	1	0	
	1	0	1	1	0	1	1	0	0	
	1	0	1	1	0	1	1	1	0	
	1	0	1	1	1	0	0	0	0	
	1	0	1	1	1	0	0	1	0	
	1	0	1	1	1	0	1	0	0	
	1	0	1	1	1	0	1	1	0	
	1	0	1	1	1	1	0	0	0	
	1	0	1	1	1	1	0	1	0	
	1	0	1	1	1	1	1	0	0	
	1	0	1	1	1	1	1	1	0	

	1	1	0	0	0	0	0	0	0	
	1	1	0	0	0	0	0	1	0	
	1	1	0	0	0	0	1	0	0	
	1	1	0	0	0	0	1	1	0	
	1	1	0	0	0	1	0	0	0	
	1	1	0	0	0	1	0	1	0	
	1	1	0	0	0	1	1	0	0	
	1	1	0	0	0	1	1	1	0	
	1	1	0	0	1	0	0	0	0	
	1	1	0	0	1	0	1	0	0	
	1	1	0	0	1	0	1	1	0	
	1	1	0	0	1	1	0	0	0	
	1	1	0	0	1	1	0	1	0	
	1	1	0	0	1	1	1	0	0	
	1	1	0	0	1	1	1	1	0	Phosphorylation of BAD (a Bcl-2
	1	1	0	1	0	0	0	0	0	antagonist) by Akt, ERK, or RSK
	1	1	0	1	0	0	0	1	0	is needed for the full activation of
	1	1	0	1	0	0	1	0	0	Bcl-2 protein.
	1	1	0	1	0	0	1	1	0	
	1	1	0	1	0	1	0	0	0	Beta-catenin and GSK3-beta
	1	1	0	1	0	1	0	1	0	upregulates Bcl-2 expression
	1	1	0	1	0	1	1	0	0	level.
2.4	1	1	0	1	0	1	1	1	0	The activity of Bcl-2 is suppressed
24	1	1	0	1	1	0	0	0	0	
	1	1	0	1	1	0	0	0	0	if any of its negative regulators is
	1	1	0	1	1	0	1	1	0	activated.
	1	1	0	1	1	1	0	0	0	Hence, the activation condition for
	1	1	0	1	1	1	0	1	0	Bcl-2_M is 'AND(OR(Akt_K,
	1	1	0	1	1	1	1	0	0	
	1	1	0	1	1	1	1	1	0	ERK_K, RSK_K, b-catenin_K,
	1	1	1	0	0	0	0	0	0	GSK3b_K), NOT(OR(p53_K,
	1	1	1	0	0	0	0	1	0	JNK_K, p38_K)))'.
	1	1	1	0	0	0	1	0	0	
	1	1	1	0	0	0	1	1	0	
	1	1	1	0	0	1	0	0	0	
	1	1	1	0	0	1	0	1	0	
	1	1	1	0	0	1	1	0	0	
	1	1	1	0	0	1	1	1	0	
	1	1	1	0	1	0	0	0	0	
	1	1	1	0	1	0	0	0	0	
	1	1	1	0	1	0	1	1	0	
	1	1	1	0	1	1	0	0	0	
	1	1	1	0	1	1	0	1	0	
	1	1	1	0	1	1	1	0	0	
	1	1	1	0	1	1	1	1	0	
	1	1	1	1	0	0	0	0	0	

										Phosphorylation of BAD (a Bcl-2
										antagonist) by Akt, ERK, or RSK
	1	1	1	1	0	0	0	1	0	is needed for the full activation of
	1	1	1	1	0	0	1	0	0	Bcl-2 protein.
	1	1	1	1 1	0	0	0	0	0	Beta-catenin and GSK3-beta
	1	1	1	1	0	1	0	1	0	upregulates Bc1-2 expression
	1	1	1	1	0	1	1	0	0	level.
2.4	1	1	1	1	0	1	1	1	0	The activity of Bcl-2 is suppressed
24	1	1	1	1	1	0	0	0	0	if any of its negative regulators is
	1	1	1	1	1	0	1	0	0	
	1	1	1	1	1	0	1	1	0	activated.
	1	1	1	1	1	1	0	0	0	Hence, the activation condition for
	1	1	1	1	1	1	0	0	0	Bcl-2_M is 'AND(OR(Akt_K,
	1	1	1	1	1	1	1	1	0	ERK_K, RSK_K, b-catenin_K,
									ı	GSK3b_K), NOT(OR(p53_K,
										JNK_K, p38_K)))'.
			IL-	1_K	p53_K	ET-	1_K			
			(0	0		0			IL-1 or p53 is needed for ET-1
25			(0	1		1			expression and activation, hence
]	1	0		1			forming an OR relation.
			:	1	1		1			
			IL-1	1_K	p53_K	SC	F_K			
			(0	0		0			IL-1 or p53 is needed for SCF
26			(0	1		1			production and activation, hence
				1	0		1			forming an OR relation.
				1	1		1			
				p53 _.		SH_K				p53 increases the transcriptional
27				0		0				activity of a-MSH upon UVB
<i>4</i> /				1		1				irradiation.
			IL-1_		COX2_K		E2_K			COX-2 promotes PGE2
			0		0		0			production in response to UVB
28			0		1		0			irradiation in an IL-1 dependent
			1		0		0			manner.
			1		1		1			mannet.
				ET-1	K ET	R_M	_			ET-1 interacts with and activates
			_							
29				0		0				ETR.

		SCF_K	c-Kit_M		
30	-	0	0	•	SCF binds to and activates c-Kit.
		1	1		
		a-MSH_K	MC1R_M		Binding of a-MSH to the MC1R
31		0	0	ı	stimulates activation of MC1R and
		1	1		its downstream signaling proteins.
			<u> </u>		EP4 is a G protein-coupled
		PGE2_K	EP4_M	i	receptor which activates cAMP
32		0	0		signaling in response to PGE2
		1	1		stimulation.
		ETR_M	PKC_M		ET-1 bound active ETR activates
33	•	0	0		PKC.
		1	1		
	DI	RK_M c-Ki	t_M SG_	M	c-Kit interacts with SG complex,
	El	0 0			which in turn activates
34		0 1			downstream Ras.
34		1 0			Activated ERK phosphorylates
		1 1			Sos and promotes disassociation
		1 1	I "		of the SG complex.
		MC1R_M	AC_M	ı	a-MSH-bound activated MC1R
35		0	0		stimulates AC activation.
		1	1		
		Akt_M	ASK1_M		Akt phosphorylates and negatively
36		0	1		regulates ASK1 activity.
		1	0		regulates ribiti activity.
	PKC_M	cAMP_M	Ras_M	PI3K_M	
	0	0	0	0	
	0	0	1	1	Ras interacts directly with the catalytic subunit of PI3K in a
	0	1	0	0	GTP-dependent manner.
37	0	1	1	0	cAMP inhibits PI3K activation,
	1	0	0	1	which in turn inactivates
	1	0	1	1	downstream Akt kinase.
	1	1	0	0	
	1	1	1	0	
	=	-	-		

	SG_N	M cAMF	P_M Ras	_M	SG complex catalyzes the	
	0	0	()	exchange of GDP with GTP and	
38	0	1	1		induces Ras activation.	
	1	0			SG does not participate in the	
					cAMP-dependent Ras activation,	
	1	1	1		hence forming an OR relation.	
	PDE_M	EP4_M	AC_M	cAMP_M		
	0	0	0	0	The activation of EP4 or AC is	
	0	0	1	1		
	0	1	0	1	required for the conversion of ATF to cAMP.	
39	0	1	1	1	PDE hydrolyzes and inhibits the	
	1	0	0	0	cAMP activity, which is dominant	
	1	0	1	0	to the positive regulators.	
	1	1	0	0	. 0	
	1	1	1	0		
	ASK1_	M Akt_	M MKK	4_M		
	0	0			ASK1 activates MKK4.	
40	0	1	()	Akt negatively regulates MKK4	
	1	0			activity by means of	
	1	1			phosphorylation.	
		PI3K_M	PDK1_M		PI3K promotes the binding of	
41		0	0	ı	PDK1 with PIP3, which in turn	
		1	1		activates downstream kinases.	
					Ras directly interacts with and	
	Ras_l	M PKC	M Raf	_M	activates Raf.	
	0	0	0		Ras binding of Raf promotes	
42	0	1	1		conformational changes of Raf	
	1	0	1		that relieve Raf autoinhibition.	
	1	1	1		PKC phosphorylation rescues the	
			I		inhibition of Raf by ERK.	
	C	AMP_M	PKA_M		cAMP activates PKA by binding	
12		0		=	to its regulatory subunits, causing	
43			0		their dissociation from catalytic	
		1	1		subunits.	

	ASK1	MKK	Κ6_M	
44	0	()	ASK1 phosphorylates and activates and MKK6.
	1	1	1	activates and witted.
	PDK	1_M Akt	_M	PDK1 phosphorylates Akt to
45	0	0		promote its activation.
	1	. 1		•
	Raf_	MEK	K_M	Raf phosphorylates MEK, and
46	0			promotes its activation.
	1			
47	PKA 0			Phosphorylation of PDE by PKA
47	1			enhances its activity.
	MKK			
48	0			MKK6 phosphorylates and activates p38.
	1	. 1		activates p36.
	Akt_	M GSK3b	<u>_M</u>	AKT inhibits kinase activity of
49	0	1		GSK3b by phosphorylating
	1	0		GSK3b at serine 9.
	MEK_M	p38_M	ERK_M	MEK phosphorylates and activates
	0	0	0	ERK.
50	0	1	0	When both MEK and p38 are
	1	0	1	activated, dephosphorylation of ERK occurs.
	1	1	0	ERK OCCUIS.
	p38_M	ERK_M	MSK_M	
	0	0	0	The MCV and and
51	0	1	1	The MSK activation requires phosphorylation by ERK or p38.
	1	0	1	rsphory muon by Exert or pool.
	1	1	1	
_	МКК	X4_M JNK_		Active MKK4 phosphorylates
52	(0		JNK and promotes its activation.
	1	1 1		<u>-</u>

53		0 1	MDM2_M 0 1		Akt promotes nuclear localization and activation of MDM2 by means of phosphorylation.
54		0 1	RSK_M 0 1		RSK is directly phosphorylated by ERK, which promotes its kinase activity.
55	MDM2_M M 0 0 0 0 1 1 1	0 0 1 1 0 0 0 1	p38_M 0 1 0 1 0 1 0 1 1 1 1 1 1	p53_M 0 1 0 0 0 0 0 0 0 0	p38 phosphorylates p53 protein at in response to UVB irradiation, leading to p53 activation. The nuclear localization of p53, which is necessary for its transcriptional activation, is inhibited by direct binding of p53 to MDM2.
56		GSK3b_M 0 1	b-catenin_M 1 0	-	GSK3b phosphorylates b-catenin and promotes its degradation.
57	Akt_M 0 0 0 1 1 1 1	PKA_M 0 0 1 1 0 0 1	MSK_M 0 1 0 1 0 1 0 1	CREB_M 0 1 1 1 1 1 1 1	Akt, PKA, or MSK stimulates CREB activity via a serine 133- dependent mechanism.

	p53_M	JNK_M	p38_M	GSK3b M	b-catenin_M	Akt M	ERK M	RSK_M	CREB M	MITFprotein_M	Bcl-2_M	
	0	0	0	0	0	0	0	0	0	0	0	
	0	0	0	0	0	0	0	0	0	1	0	
	0	0	0	0	0	0	0	0	1	0	0	
	0	0	0	0	0	0	0	0	0	0	0	
	0	0	0	0	0	0	0	1	0	1	1	
	0	0	0	0	0	0	0	1	1	0	1	
	0	0	0	0	0	0	0	1	1	1	1	
	0	0	0	0	0	0	1	0	0	0	0	
	0	0	0	0	0	0	1	0	1	0	1	
	0	0	0	0	0	0	1	0	1	1	1	
	0	0	0	0	0	0	1	1	0	0	0	
	0	0	0	0	0	0	1	1	1	0	1	
	0	0	0	0	0	0	1	1	1	1	1	CREB or MITF is required for the
	0	0	0	0	0	1	0	0	0	0	0	transcriptional activation of Bcl-2
	0	0	0	0	0	1	0	0	0	0	1	gene.
	0	0	0	0	0	1	0	0	1	1	1	-
	0	0	0	0	0	1	0	1	0	0	0	Phosphorylation of BAD (a Bcl-2
	0	0	0	0	0	1	0	1	0	1	1	antagonist) by Akt, ERK, or RSK
	0	0	0	0	0	1	0	1	1	0	1	is needed for the full activation of
	0	0	0	0	0	1	1	0	0	0	0	
	0	0	0	0	0	1	1	0	0	1	1	Bcl-2 protein.
	0	0	0	0	0	1	1	0	1	0	1	Beta-catenin and GSK3-beta
	0	0	0	0	0	1	1	1	0	0	1	upregulates Bcl-2 expression
	0	0	0	0	0	1	1	1	0	1	1	
7 0	0	0	0	0	0	1	1	1	1	0	1	level.
58	0	0	0	0	0	0	0	0	0	0	0	Bcl-2 activity is suppressed if any
	0	0	0	0	1	0	0	0	0	1	0	of its negative regulators is
	0	0	0	0	1	0	0	0	1	0	0	
	0	0	0	0	1	0	0	0	0	0	0	activated.
	0	0	0	0	1	0	0	1	0	1	1	Hence, the activation condition for
	0	0	0	0	1	0	0	1	1	0	1	Bcl-2_M is
	0	0	0	0	1	0	0	1	1	1	1	
	0	0	0	0	1	0	1	0	0	0	0	'AND(OR(MITFprotein_M,
	0	0	0	0	1	0	1	0	1	0	1	CREB_M), OR(Akt_M, ERK_M,
	0	0	0	0	1	0	1	0	1	1	1	RSK_M, b-catenin_M,
	0	0	0	0	1	0	1	1	0	0	0	
	0	0	0	0	1	0	1	1	1	0	1	GSK3b_M), NOT(OR(p53_M,
	0	0	0	0	1	0	1	1	1	1	1	JNK_M, p38_M)))'.
	0	0	0	0	1	1	0	0	0	0	0	
	0	0	0	0	1	1	0	0	0	0	1	
	0	0	0	0	1	1	0	0	1	1	1	
	0	0	0	0	1	1	0	1	0	0	0	
	0	0	0	0	1	1	0	1	0	0	1	
	0	0	0	0	1	1	0	1	1	1	1	
	0	0	0	0	1	1	1	0	0	0	0	
	0	0	0	0	1	1	1	0	0	1	1	
	0	0	0	0	1	1	1	0	1	0	1	
	0	0	0	0	1	1	1	1	0	0	1	
	0	0	0	0	1	1	1	1	0	1	1	
	0	0	0	0	1	1	1	1	1	0	1	
	Ü	Ü	v	Ü		•	•		٠.		I '	

	0	0	0	1	0	0	0	0	0	0	0	
	0	0	0	1	0	0	0	0	0	0	0	
	0	0	0	1	0	0	0	0	1	1	0	
	0	0	0	1	0	0	0	1	0	0	0	
	0	0	0	1	0	0	0	1	0	0	1	
	0	0	0	1	0	0	0	1	1	1	1	
	0	0	0	1	0	0	1	0	0	0	0	
	0	0	0	1	0	0	1	0	0	0	1	
	0	0	0	1	0	0	1	0	1	1	1	
	0	0	0	1	0	0	1	1	0	0	0	
	0	0	0	1	0	0	1	1	0	0	1	
	0	0	0	1	0	0	1	1	1	1	1	CDED or MITE is required for the
	0	0	0	1	0	1	0	0	0	0	0	CREB or MITF is required for the
	0	0	0	1	0	1	0	0	0	0	1	transcriptional activation of Bcl-2
	0	0	0	1	0	1	0	0	1	1	1	gene.
	0	0	0	1	0	1	0	1	0	0	0	Phosphorylation of BAD (a Bcl-2
	0	0	0	1	0	1	0	1	0	0	1	
	0	0	0	1	0	1	0	1	1	1	1	antagonist) by Akt, ERK, or RSK
	0	0	0	1	0	1	1	0	0	0	0	is needed for the full activation of
	0	0	0	1	0	1	1	0	1	0	1	Bcl-2 protein.
	0	0	0	1	0	1	1	0	1	1	1	Beta-catenin and GSK3-beta
	0	0	0	1	0	1	1	1	0	1	1	upregulates Bcl-2 expression
	0	0	0	1	0	1	1	1	1	0	1	level.
58	0	0	0	1	0	0	0	0	0	0	0	
30	0	0	0	1	1	0	0	0	0	1	0	Bcl-2 activity is suppressed if any
	0	0	0	1	1	0	0	0	1	0	0	of its negative regulators is
	0	0	0	1	1	0	0	0	0	0	0	activated.
	0	0	0	1	1	0	0	1	0	1	1	Hence, the activation condition for
	0	0	0	1	1	0	0	1	1	1	1	Bcl-2_M is
	0	0	0	1	1	0	1	0	0	0	0	
	0	0	0	1	1	0	1	0	0	0	1	'AND(OR(MITFprotein_M,
	0	0	0	1	1	0	1	0	1	1	1	CREB_M), OR(Akt_M, ERK_M,
	0	0	0	1	1	0	1	1	0	0	0	RSK_M, b-catenin_M,
	0	0	0	1	1	0	1	1	1	0	1	GSK3b_M), NOT(OR(p53_M,
	0	0	0	1	1	0	1 0	0	1	0	0	JNK_M, p38_M)))'.
	0	0	0	1	1	1	0	0	0	1	1	5141K_1VI, p36_1VI))).
	0	0	0	1	1	1	0	0	1	0	1	
	0	0	0	1	1	1	0	0	1	0	0	
	0	0	0	1	1	1	0	1	0	1	1	
	0	0	0	1	1	1	0	1	1	0	1	
	0	0	0	1	1	1	0	0	0	0	0	
	0	0	0	1	1	1	1	0	0	1	1	
	0	0	0	1	1	1	1	0	1	0	1	
	0	0	0	1	1	1	1	0	0	0	1	
	0	0	0	1	1	1	1	1	0	1	1	
	0	0	0	1	1	1	1	1	1	0	1 1	
	0	0	1	0	0	0	0	0	0	0	0	
									26		•	

	0	0	1	0	0	0	0	0	0	1	0	
	0	0	1	0	0	0	0	0	1	0	0	
	0	0	1	0	0	0	0	0	1	1	0	
	0	0	1	0	0	0	0	1	0	0	0	
	0	0	1	0	0	0	0	1	0	1	0	
	0	0	1	0	0	0	0	1	1	0	0	
	0	0	1	0	0	0	0	1	1	1	0	
	0	0	1	0	0	0	1	0	0	0	0	
	0	0	1	0	0	0	1	0	0	1	0	
	0	0	1	0	0	0	1	0	1	0	0	
	0	0	1	0	0	0	1	0	1	1	0	
	0	0	1	0	0	0	1	1	0	0	0	
	0	0	1	0	0	0	1	1	0	1	0	
	0	0	1	0	0	0	1	1	1	0	0	
	0	0	1	0	0	0	1	1	1	1	0	
	0	0	1	0	0	1	0	0	0	0	0	CDED MIDE: 1.16 d
	0	0	1	0	0	1	0	0	0	1	0	CREB or MITF is required for the
	0	0	1	0	0	1	0	0	1	0	0	4
		0	1		0	1	0		1		0	transcriptional activation of Bcl-2
	0			0				0		1		cono
	0	0	1	0	0	1	0	1	0	0	0	gene.
	0	0	1	0	0	1	0	1	0	1	0	Dhoophorylation of DAD (a Pol 2
	0	0	1	0	0	1	0	1	1	0	0	Phosphorylation of BAD (a Bcl-2
	0	0	1	0	0	1	0	1	1	1	0	antagonist) by Akt, ERK, or RSK
	0	0	1	0	0	1	1	0	0	0	0	antagonist) by Akt, EKK, of KSK
	0	0	1	0	0	1	1	0	0	1	0	is needed for the full activation of
	0	0	1	0	0	1	1	0	1	0	0	is needed for the full activation of
							-					Bcl-2 protein.
	0	0	1	0	0	1	1	0	1	1	0	Bei-2 protein.
	0	0	1	0	0	1	1	1	0	0	0	Beta-catenin and GSK3-beta
	0	0	1	0	0	1	1	1	0	1	0	Deta eatenin and GBR3 beta
	0	0	1	0	0	1	1	1	1	0	0	upregulates Bcl-2 expression
	0	0	1	0	0	1	1	1	1	1	0	apregulates Bel 2 empression
	0	0	1	0	1	0	0	0	0	0	0	level.
58	0	0	1	0	1	0	0	0	0	1	0	
36												Bcl-2 activity is suppressed if any
	0	0	1	0	1	0	0	0	1	0	0	
	0	0	1	0	1	0	0	0	1	1	0	of its negative regulators is
	0	0	1	0	1	0	0	1	0	0	0	
	0	0	1	0	1	0	0	1	0	1	0	activated.
	0	0	1	0	1	0	0	1	1	0	0	
	0	0	1	0	1	0	0	1	1	1	0	Hence, the activation condition for
	0	0	1	0	1	0	1	0	0	0	0	
		0	1	0	1	0	1		0			Bcl-2_M is
	0							0		1	0	
	0	0	1	0	1	0	1	0	1	0	0	'AND(OR(MITFprotein_M,
	0	0	1	0	1	0	1	0	1	1	0	
	0	0	1	0	1	0	1	1	0	0	0	CREB_M), OR(Akt_M, ERK_M,
	0	0	1	0	1	0	1	1	0	1	0	DOM MALE AND
	0	0	1	0	1	0	1	1	1	0	0	RSK_M, b-catenin_M,
	0	0	1	0	1	0	1	1	1	1	0	CCIZ2L M) NOT(OD(=52 M
	0	0	1	0	1	1	0	0	0	0	0	GSK3b_M), NOT(OR(p53_M,
												INK M n38 M)))'
	0	0	1	0	1	1	0	0	0	1	0	JNK_M, p38_M)))'.
	0	0	1	0	1	1	0	0	1	0	0	
	0	0	1	0	1	1	0	0	1	1	0	
	0	0	1	0	1	1	0	1	0	0	0	
	0	0	1	0	1	1	0	1	0	1	0	
	0	0	1	0	1	1	0	1	1	0	0	
	0	0	1	0	1	1	0	1	1	1	0	
	0	0	1	0	1	1	1	0	0	0	0	
	0	0	1	0	1	1	1	0	0	1	0	
	0	0	1	0	1	1	1	0	1	0	0	
	0	0	1	0	1	1	1	0	1	1	0	
	0	0	1	0	1	1	1	1	0	0	0	
	0	0	1	0	1	1	1	1	0	1	0	
	0	0	1	0	1	1	1	1	1	0	0	
		0			1		1					
	0		1	0		1		1	1	1	0	
	0	0	1	1	0	0	0	0	0	0	0	
	0	0	1	1	0	0	0	0	0	1	0	

	0	0	1	1	0	0	0	0	1	0	0
	0	0	1	1	0	0	0	0	1	1	0
	0	0	1	1	0	0	0	1	0	0	0
	0	0	1	1	0	0	0	1	0	1	0
	0	0	1	1	0	0	0	1	1	0	0
	0	0	1	1	0	0	0	1	1	1	0
	0	0	1	1	0	0	1	0	0	0	0
	0	0	1	1	0	0	1	0	0	1	0
	0	0	1	1	0	0	1	0	1	0	0
	0	0	1	1	0	0	1	0	1	1	0
	0	0	1	1	0	0	1	1	0	0	0
	0	0	1	1	0	0	1	1	0	1	0
	0	0	1	1	0	0	1	1	1	0	0
	0	0	1	1	0	0	1	1	1	1	0
			-				-				
	0	0	1	1	0	1	0	0	0	0	0
	0	0	1	1	0	1	0	0	0	1	CREB or MITF is required for the
	0	0	1	1	0	1	0	0	1	0	
	0	0	1	1	0	1	0	0	1	1	transcriptional activation of Bcl-2
	0	0	1	1	0	1	0	1	0	0	0
	0	0	1	1	0	1	0	1	0	1	o gene.
	0	0	1	1	0	1	0	1	1	0	
	0	0	1	1	0	1	0	1	1	1	Phosphorylation of BAD (a Bcl-2
	0	0	1	1	0	1	1	0	0	0	onto conjet) by Alet EDV on DCV
	0	0	1	1	0	1	1	0	0	1	antagonist) by Akt, ERK, or RSK
		0		1	0	1			1		
	0						1	0		0	
	0	0	1	1	0	1	1	0	1	1	Bcl-2 protein.
	0	0	1	1	0	1	1	1	0	0	
	0	0	1	1	0	1	1	1	0	1	Beta-catenin and GSK3-beta
	0	0	1	1	0	1	1	1	1	0	
	0	0	1	1	0	1	1	1	1	1	o upregulates Bcl-2 expression
	0	0	1	1	1	0	0	0	0	0	0
	0	0	1	1	1	0	0	0	0	1	level.
58	0	0	1	1	1	0	0	0	1	0	0
20	0	0	1	1	1	0	0	0	1	1	Bcl-2 activity is suppressed if any
	0	0	1	1	1	0	0	1	0	0	
	0	0	1	1	1	0	0	1	0	1	of its negative regulators is
			1		1		0		1		
	0	0		1		0		1		0	
	0	0	1	1	1	0	0	1	1	1	Hence, the activation condition for
	0	0	1	1	1	0	1	0	0	0	o Tience, the activation condition to
	0	0	1	1	1	0	1	0	0	1	Bcl-2_M is
	0	0	1	1	1	0	1	0	1	0	0 DC1 2_1V1 15
	0	0	1	1	1	0	1	0	1	1	⁰ 'AND(OR(MITFprotein_M,
	0	0	1	1	1	0	1	1	0	0	0
	0	0	1	1	1	0	1	1	0	1	CREB_M), OR(Akt_M, ERK_M
	0	0	1	1	1	0	1	1	1	0	0
	0	0	1	1	1	0	1	1	1	1	RSK_M, b-catenin_M,
			-								
	0	0	1	1	1	1	0	0	0	0	GSK3b_M), NOT(OR(p53_M,
	0	0	1	1	1	1	0	0	0	1	0
	0	0	1	1	1	1	0	0	1	0	⁰ JNK_M, p38_M)))'.
	0	0	1	1	1	1	0	0	1	1	0
	0	0	1	1	1	1	0	1	0	0	0
	0	0	1	1	1	1	0	1	0	1	0
	0	0	1	1	1	1	0	1	1	0	0
	0	0	1	1	1	1	0	1	1	1	0
	0	0	1	1	1	1	1	0	0	0	0
	0		1	1	1		1		0		
		0				1		0		1	0
	0	0	1	1	1	1	1	0	1	0	0
	0	0	1	1	1	1	1	0	1	1	0
	0	0	1	1	1	1	1	1	0	0	0
	0	0	1	1	1	1	1	1	0	1	0
	0	0	1	1	1	1	1	1	1	0	0
	0	0	1	1	1	1	1	1	1	1	0
	0	1	0	0	0	0	0	0	0	0	0
	0	1	0	0	0	0	0	0	0	1	0
	0	1	0	0	0	0	0	0	1	0	0
	U	1	v	v	U	v	U	U	1	U	, v

	0	1	0	0	0	0	0	0	1	1	0	
	0	1	0	0	0	0	0	1	0	0	0	
	0	1	0	0	0	0	0	1	0	1	0	
	0	1	0	0	0	0	0	1	1	0	0	
	0	1	0	0	0	0	0	1	1	1	0	
	0	1	0	0	0	0	1	0	0	0	0	
	0	1	0	0	0	0	1	0	0	1	0	
		-										
	0	1	0	0	0	0	1	0	1	0	0	
	0	1	0	0	0	0	1	0	1	1	0	
	0	1	0	0	0	0	1	1	0	0	0	
	0	1	0	0	0	0	1	1	0	1	0	
	0	1	0	0	0	0	1	1	1	0	0	
	0	1	0	0	0	0	1	1	1	1	0	
	0	1	0	0	0	1	0	0	0	0	0	
	0	1	0	0	0	1	0	0	0	1	0	
	0	1	0	0	0	1	0	0	1	0	0	CREB or MITF is required for the
	0	1	0	0	0	1	0	0	1	1	0	CRED of WITT is required for the
	0	1	0	0	0	1	0	1	0	0	0	transcriptional activation of Bcl-2
	0	1	0	0	0	1	0	1	0	1	0	transcriptional activation of Bei-2
	0	1	0	0	0	1	0	1	1		0	gene.
										0		gene.
	0	1	0	0	0	1	0	1	1	1	0	Phosphorylation of BAD (a Bcl-2
	0	1	0	0	0	1	1	0	0	0	0	Thosphorylation of BAD (a Bel-2
	0	1	0	0	0	1	1	0	0	1	0	antagonist) by Akt, ERK, or RSK
	0	1	0	0	0	1	1	0	1	0	0	antagonist) by 1 kt, LKK, of KSK
	0	1	0	0	0	1	1	0	1	1	0	is needed for the full activation of
	0	1	0	0	0	1	1	1	0	0	0	is needed for the full detivation of
												Bcl-2 protein.
	0	1	0	0	0	1	1	1	0	1	0	Bei-2 protein.
	0	1	0	0	0	1	1	1	1	0	0	Beta-catenin and GSK3-beta
	0	1	0	0	0	1	1	1	1	1	0	Beta catemin and GBRS beta
	0	1	0	0	1	0	0	0	0	0	0	upregulates Bcl-2 expression
	0	1	0	0	1	0	0	0	0	1	0	apregulates Bel 2 expression
	0	1	0	0	1	0	0	0	1	0	0	level.
50									1			10 (01)
58	0	1	0	0	1	0	0	0		1	0	Bcl-2 activity is suppressed if any
	0	1	0	0	1	0	0	1	0	0	0	Bei 2 detivity is suppressed if any
	0	1	0	0	1	0	0	1	0	1	0	of its negative regulators is
	0	1	0	0	1	0	0	1	1	0	0	01 110 11084111 0 1084141010 10
	0	1	0	0	1	0	0	1	1	1	0	activated.
	0	1	0	0	1	0	1	0	0	0	0	
	0	1	0	0	1	0	1	0	0	1	0	Hence, the activation condition for
		1										
	0	1	0	0	1	0	1	0	1	0	0	Bcl-2_M is
	0	1	0	0	1	0	1	0	1	1	0	
	0	1	0	0	1	0	1	1	0	0	0	'AND(OR(MITFprotein_M,
	0	1	0	0	1	0	1	1	0	1	0	
	0	1	0	0	1	0	1	1	1	0	0	CREB_M), OR(Akt_M, ERK_M,
	0	1	0	0	1	0	1	1	1	1	0	
		,									0	RSK_M, b-catenin_M,
	0	1	0	0	1	1	0	0	0	0		
	0	1	0	0	1	1	0	0	0	1	0	GSK3b_M), NOT(OR(p53_M,
	0	1	0	0	1	1	0	0	1	0	0	
	0	1	0	0	1	1	0	0	1	1	0	JNK_M, p38_M)))'.
	0	1	0	0	1	1	0	1	0	0	0	1 _ ///
	0	1	0	0	1	1	0	1	0	1	0	
	0	1	0	0	1	1	0	1	1	0	0	
	-											
	0	1	0	0	1	1	0	1	1	1	0	
	0	1	0	0	1	1	1	0	0	0	0	
	0	1	0	0	1	1	1	0	0	1	0	
	0	1	0	0	1	1	1	0	1	0	0	
	0	1	0	0	1	1	1	0	1	1	0	
	0	1	0	0	1	1	1	1	0	0	0	
	0											
	0	1	0	0	1	1	1	1	0	1	0	
	0	1	0	0	1	1	1	1	1	0	0	
	0	1	0	0	1	1	1	1	1	1	0	
	0	1	0	1	0	0	0	0	0	0	0	
	0	1	0	1	0	0	0	0	0	1	0	
	0	1	0	1	0	0	0	0	1	0	0	
	0	1	0	1	0	0	0	0	1	1	0	
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CREB or MITF is required for the transcriptional activation of Bcl-2 gene. Phosphorylation of BAD (a Bcl-2 antagonist) by Akt, ERK, or RSK is needed for the full activation of Bcl-2 protein. Beta-catenin and GSK3-beta upregulates Bcl-2 expression level. Bcl-2 activity is suppressed if any of its negative regulators is activated. Hence, the activation condition for Bcl-2 M is AND(OR(MITF) protein, M, CREB_M), OR(Akt_M, ERK, M, RSK_M, b-catenin_M, GSK3b_M), NOT(OR(p53_M, JNK_M, p38_M))).													
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CREB or MITF is required for the transcriptional activation of Bel-2 gene. Phosphorylation of BAD (a Bel-2 antagonist) by Akt, ERK, or RSK is needed for the full activation of Bel-2 protein. Beta-catenin and GSK3-beta upregulates Bel-2 expression level. Bel-2 activity is suppressed if any of its negative regulators is activated. Hence, the activation condition for Bel-2_M is 'AND/OR(MITF/protein_M, CREB_M), OR(Akt_M, ERK_M, RSK_M, b-catenin_M, GSK3b_M), NOT(OR(p53_M, JNK_M, p38_M))).			1		1					1			
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Bel-2 protein. Beta-catenin and GSK3-beta upregulates Bel-2 expression level. Bel-2 activity is suppressed if any of its negative regulators is activated. Hence, the activation condition for Bel-2_M is 'AND(OR(MITFprotein_M, CREB_M), OR(Akt_M, ERK_M, RSK_M, b-catenin_M, GSK3b_M), NOT(OR(p53_M, JNK_M, p38_M)))'.			1										is needed for the full activation of
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Beta-catenin and GSK3-beta upregulates Bcl-2 expression level. 1													Bei-2 protein.
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level Bcl-2 activity is suppressed if any of its negative regulators is activated.			1										upregulates Bcl-2 expression
58			1		-								lovel
Bel-2 activity is suppressed if any of its negative regulators is activated.	70		1		-								level.
of its negative regulators is activated. I	58												Bcl-2 activity is suppressed if any
of this negative regulators is activated. of the control of the c			-										
activated.													of its negative regulators is
Hence, the activation condition for background in the condition for a conditio													
Hence, the activation condition for			1					-					activated.
			1					-					Hence the activation condition for
Bc1-2_M is			1					-					Tience, the activation condition for
			-										Bcl-2 M is
0		0	1								0		
0		0	1								1		'AND(OR(MITFprotein_M,
0		0	1										CDED MO OD (AL, M. EDIZ M.
RSK_M, b-catenin_M, RSK_M, b-		0	1	0	1	1	0				1		CREB_M), OR(ART_M, ERK_M,
0		0	1								0		RSK M h-catenin M
0		0	1	0	1	1	1	0	0	0	1	0	
0		0	1								0		GSK3b_M), NOT(OR(p53_M,
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0 1 0 1 1 0		0	1	0	1		1				0		JNK_M, p38_M)))'.
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	0		1	0	0	1	0	0	1	1	0	
	0	1	1	0	0	1	0	1	0	0	0	CREB or MITF is required for the
	0	1	1	0	0	1	0	1	0	1	0	
	0	1	1	0	0	1	0	1	1	0	0	transcriptional activation of Bcl-2
	0	1	1	0	0	1	0	1	1	1	0	gana
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	0	1	1	0	0	1	1	0	0	1	0	Phosphorylation of BAD (a Bcl-2
	0	1	1	0	0	1	1	0	1	0	0	
	0	1	1	0	0	1	1	0	1	1	0	antagonist) by Akt, ERK, or RSK
	0	1	1	0	0	1	1	1	0	0	0	
	0	1	1	0	0	1	1	1	0	1	0	is needed for the full activation of
	0	1	1	0	0	1	1	1	1	0	0	Bcl-2 protein.
	0	1	1	0	0	1	1	1	1	1	0	Bei-2 protein.
	0	1	1	0	1	0	0	0	0	0	0	Beta-catenin and GSK3-beta
	0	1	1	0	1	0	0	0	0	1	0	
	0	1	1	0	1	0	0	0	1	0	0	upregulates Bcl-2 expression
	0	1	1	0	1	0	0	0	1	1	0	11
~ 0	0	1	1	0	1	0	0	1	0	0	0	level.
58	0	1	1	0	1	0	0	1	0	1	0	Bcl-2 activity is suppressed if any
	0	1	1	0	1	0	0	1	1	0	0	
	0	1	1	0	1	0	0	1	1	1	0	of its negative regulators is
	0	1	1	0	1	0	1	0	0	0	0	
	0	1	1	0	1	0	1	0	0	1	0	activated.
	0	1	1	0	1	0	1	0	1	0	0	Hence, the activation condition for
	0	1	1	0	1	0	1	0	1	1	0	Tience, the activation condition for
	0	1	1	0	1	0	1	1	0	0	0	Bcl-2_M is
	0	1	1	0	1	0	1	1	0	1	0	
	0	1	1	0	1	0	1	1	1	0	0	'AND(OR(MITFprotein_M,
	0	1	1	0	1	0	1	1	1	1	0	CDED M) OD(AL M EDV M
	0	1	1	0	1	1	0	0	0	0	0	CREB_M), OR(Akt_M, ERK_M,
	0	1	1	0	1	1	0	0	0	1	0	RSK_M, b-catenin_M,
	0	1	1	0	1	1	0	0	1	0	0	
	0	1	1	0	1	1	0	0	1	1	0	GSK3b_M), NOT(OR(p53_M,
	0	1	1	0	1	1	0	1	0	0	0	
	0	1	1	0	1	1	0	1	0	1	0	JNK_M, p38_M)))'.
	0	1	1	0	1	1	0	1	1	0	0	
	0	1	1	0	1	1	0	1	1	1	0	
	0	1	1	0	1	1	1	0	0	0	0	
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	0		1	1	0	1	0	1	0	0	0	
	0				0	1	0	1	0	1	0	CREB or MITF is required for the
	0	1		1	0	1	0	1	1	0	0	
	0	1	1	1	0	1	0	1	1	1	0	transcriptional activation of Bcl-2
	0	1	1	1	0	1	1	0	0	0	0	gana
	0	1	1	1	0	1	1	0	0	1	0	gene.
	0	1	1	1	0	1	1	0	1	0	0	Phosphorylation of BAD (a Bcl-2
	0	1	1	1	0	1	1	0	1	1	0	
	0	1	1	1	0	1	1	1	0	0	0	antagonist) by Akt, ERK, or RSK
	0	1	1	1	0	1	1	1	0	1	0	. 1 10 4 011 4 4 6
	0	1	1	1	0	1	1	1	1	0	0	is needed for the full activation of
	0	1	1	1	0	1	1	1	1	1	0	Bcl-2 protein.
	0	1	1	1	1	0	0	0	0	0	0	Bei-2 protein.
	0	1	1	1	1	0	0	0	0	1	0	Beta-catenin and GSK3-beta
	0	1	1	1	1	0	0	0	1	0	0	
	0	1	1	1	1	0	0	0	1	1	0	upregulates Bcl-2 expression
	0	1	1	1	1	0	0	1	0	0	0	level.
5 0	0	1	1	1	1	0	0	1	0	1	0	level.
58	0	1	1	1	1	0	0	1	1	0	0	Bcl-2 activity is suppressed if any
	0	1	1	1	1	0	0	1	1	1	0	
	0	1	1	1	1	0	1	0	0	0	0	of its negative regulators is
	0	1	1	1	1	0	1	0	0	1	0	
	0	1	1	1	1	0	1	0	1	0	0	activated.
	0	1	1	1	1	0	1	0	1	1	0	Hence, the activation condition for
	0	1	1	1	1	0	1	1	0	0	0	Hence, the activation condition for
	0	1	1	1	1	0	1	1	0	1	0	Bcl-2_M is
	0	1	1	1	1	0	1	1	1	0	0	
	0	1	1	1	1	0	1	1	1	1	0	'AND(OR(MITFprotein_M,
	0	1	1	1	1	1	0	0	0	0	0	CDED M) OD(AL M EDIZ M
	0	1	1	1	1	1	0	0	0	1	0	CREB_M), OR(Akt_M, ERK_M,
	0	1	1	1	1	1	0	0	1	0	0	RSK_M, b-catenin_M,
	0	1	1	1	1	1	0	0	1	1	0	
	0	1	1	1	1	1	0	1	0	0	0	GSK3b_M), NOT(OR(p53_M,
	0	1	1	1	1	1	0	1	0	1	0	
	0	1	1	1	1	1	0	1	1	0	0	JNK_M, p38_M)))'.
	0	1	1	1	1	1	0	1	1	1	0	
	0	1	1	1	1	1	1	0	0	0	0	
	0	1	1	1	1	1	1	0	0	1	0	
	0	1	1	1	1	1	1	0	1	0	0	
	0	1	1	1	1	1	1	0	1	1	0	
	0	1	1	1	1	1	1	1	0	0	0	
	0	1	1	1	1	1	1	1	0	1	0	
	0	1	1	1	1	1	1	1	1	0	0	
	0	1	1	1	1	1	1	1	1	1	0	
	1	0	0	0	0	0	0	0	0	0	0	
	1	0	0	0	0	0	0	0	0	1	0	
	1	0	0	0	0	0	0	0	1	0	0	
	1	0	0	0	0	0	0	0	1	1	0	
	1	0	0	0	0	0	0	1	0	0	0	
	1	0	0	0	0	0	0	1	0	1	0	
	1	0	0	0	0	0	0	1	1	0	0	

	1	0	0	0	0	0	0	1	1	1	0	
	1	0	0	0	0	0	1	0	0	0	0	
	1	0	0	0	0	0	1	0	0	1	0	
	1	0	0	0	0	0	1	0	1	0	0	
	1	0	0	0	0	0	1	0	1	1	0	
	1	0	0	0	0	0	1	1	0	0	0	
	1	0	0	0	0	0	1	1	0	1	0	
	1	0	0	0	0	0	1	1	1	0	0	
	1	0	0	0	0	0	1	1	1	1	0	
	1	0	0	0	0	1	0	0	0	0	0	
	1	0	0	0	0	1	0	0	0	1	0	
	1	0	0	0	0	1	0	0	1	0	0	
	1	0	0	0	0	1	0	0	1	1	0	
	1	0	0	0	0	1	0	1	0	0	0	
	1	0	0	0	0	1	0	1	0	1	0	
	1	0	0	0	0	1	0	1	1	0	0	
	1	0	0	0	0	1	0	1	1	1	0	CREB or MITF is required for the
	1	0	0	0	0	1	1	0	0	0	0	transcriptional activation of Bcl-2
	1	0	0	0	0	1	1	0	0	1	0	transcriptional activation of Bei-2
	1	0	0	0	0	1	1	0	1	0	0	gene.
	1	0	0	0	0	1	1	0	1	1	0	
	1	0	0	0	0	1	1	1	0	0	0	Phosphorylation of BAD (a Bcl-2
	1	0	0	0	0	1	1	1	0	1	0	
	1	0	0	0	0	1	1	1	1	0	0	antagonist) by Akt, ERK, or RSK
	1	0	0	0	0	1	1	1	1	1	0	is needed for the full activation of
	1	0	0	0	1	0	0	0	0	0	0	is needed for the full activation of
	1	0	0	0	1	0	0	0	0	1	0	Bcl-2 protein.
	1	0	0	0	1	0	0	0	1	0	0	
	1	0	0	0	1	0	0	0	1	1	0	Beta-catenin and GSK3-beta
	1	0	0	0	1	0	0	1	0	0	0	unragulates Pol 2 averagion
	1	0	0	0	1	0	0	1	0	1	0	upregulates Bcl-2 expression
	1	0	0	0	1	0	0	1	1	0	0	level.
58	1	0	0	0	1	0	0	1	1	1	0	
30	1	0	0	0	1	0	1	0	0	0	0	Bcl-2 activity is suppressed if any
	1	0	0	0	1	0	1	0	0	1	0	C'
	1	0	0	0	1	0	1	0	1	0	0	of its negative regulators is
	1	0	0	0	1	0	1	0	1	1	0	activated.
	1	0	0	0	1	0	1	1	0	0	0	
	1	0	0	0	1	0	1	1	0	1	0	Hence, the activation condition for
	1	0	0	0	1	0	1	1	1	0	0	
	1	0	0	0	1	0	1	1	1	1	0	Bcl-2_M is
	1	0	0	0	1	1	0	0	0	0	0	'AND(OR(MITFprotein_M,
	1	0	0	0	1	1	0	0	0	1	0	AND(OR(MITT protein_M,
	1	0	0	0	1	1	0	0	1	0	0	CREB_M), OR(Akt_M, ERK_M,
	1	0	0	0	1	1	0	0	1	1	0	
	1	0	0	0	1	1	0	1	0	0	0	RSK_M, b-catenin_M,
	1	0	0	0	1	1	0	1	0	1	0	CCIVAL MONOT(OD (152 M
	1	0	0	0	1	1	0	1	1	0	0	GSK3b_M), NOT(OR(p53_M,
	1	0	0	0	1	1	0	1	1	1	0	JNK_M, p38_M)))'.
	1	0	0	0	1	1	1	0	0	0	0	· ·, F- ·///
	1	0	0	0	1	1	1	0	0	1	0	
	1	0	0	0	1	1	1	0	1	0	0	
	1	0	0	0	1	1	1	0	1	1	0	
	1	0	0	0	1	1	1	1	0	0	0	
	1	0	0	0	1	1	1	1	0	1	0	
	1	0	0	0	1	1	1	1	1	0	0	
	1	0	0	0	1	1	1	1	1	1	0	
	1	0	0	1	0	0	0	0	0	0	0	
	1	0	0	1	0	0	0	0	0	1	0	
	1	0	0	1	0	0	0	0	1	0	0	
	1	0	0	1	0	0	0	0	1	1	0	
	1	0	0	1	0	0	0	1	0	0	0	
	1	0	0	1	0	0	0	1	0	1	0	
	1	0	0	1	0	0	0	1	1	0	0	
	1	0	0	1	0	0	0	1	1	1	0	
											<u> </u>	

	1	0	0	1	0	0	1	0	0	0	0	
	1	0	0	1	0	0	1	0	0	1	0	
	1	0	0	1	0	0	1	0	1	0	0	
	1	0	0	1	0	0	1	0	1	1	0	
	1	0	0	1	0	0	1	1	0	0	0	
	1	0	0	1	0	0	1	1	0	1	0	
	1	0	0	1	0	0	1	1	1	0	0	
	1	0	0	1	0	0	1	1	1	1	0	
	1	0	0	1	0	1	0	0	0	0	0	
	1	0	0	1	0	1	0	0	0	1	0	
	1	0	0	1	0	1	0	0	1	0	0	
	1	0	0	1	0	1	0	1	0	0	0	
	1	0	0	1	0	1	0	1	0	1	0	
	1	0	0	1	0	1	0	1	1	0	0	
	1	0	0	1	0	1	0	1	1	1	0	CDED on MITE is no swine of four the
	1	0	0	1	0	1	1	0	0	0	0	CREB or MITF is required for the
	1	0	0	1	0	1	1	0	0	1	0	transcriptional activation of Bcl-2
	1	0	0	1	0	1	1	0	1	0	0	
	1	0	0	1	0	1	1	0	1	1	0	gene.
	1	0	0	1	0	1	1	1	0	0	0	Phosphorylation of BAD (a Bcl-2
	1	0	0	1	0	1	1	1	0	1	0	
	1	0	0	1	0	1	1	1	1	0	0	antagonist) by Akt, ERK, or RSK
	1	0	0	1	0	1	1	1	1	1	0	
	1	0	0	1	1	0	0	0	0	0	0	is needed for the full activation of
	1	0	0	1	1	0	0	0	0	0	0	Bcl-2 protein.
	1	0	0	1	1	0	0	0	1	1	0	
	1	0	0	1	1	0	0	1	0	0	0	Beta-catenin and GSK3-beta
	1	0	0	1	1	0	0	1	0	1	0	upregulates Bcl-2 expression
	1	0	0	1	1	0	0	1	1	0	0	upregulates Bel-2 expression
	1	0	0	1	1	0	0	1	1	1	0	level.
58	1	0	0	1	1	0	1	0	0	0	0	D-1-2 tiit i 1:f
	1	0	0	1	1	0	1	0	0	1	0	Bcl-2 activity is suppressed if any
	1	0	0	1	1	0	1	0	1	0	0	of its negative regulators is
	1	0	0	1	1	0	1	0	1	1	0	
	1	0	0	1	1	0	1	1	0	0	0	activated.
	1	0	0	1	1	0	1	1	0	1	0	Hence, the activation condition for
	1	0	0	1	1	0	1	1	1	0	0	
	1	0	0	1	1	0	0	1	0	1	0	Bcl-2_M is
	1	0	0	1	1	1	0	0	0	0	0	
	1	0	0	1	1	1	0	0	1	0	0	'AND(OR(MITFprotein_M,
	1	0	0	1	1	1	0	0	1	1	0	CREB_M), OR(Akt_M, ERK_M,
	1	0	0	1	1	1	0	1	0	0	0	
	1	0	0	1	1	1	0	1	0	1	0	RSK_M, b-catenin_M,
	1	0	0	1	1	1	0	1	1	0	0	GSK3b_M), NOT(OR(p53_M,
	1	0	0	1	1	1	0	1	1	1	0	
	1	0	0	1	1	1	1	0	0	0	0	JNK_M, p38_M)))'.
	1	0	0	1	1	1	1	0	0	1	0	
	1	0	0	1	1	1	1	0	1	0	0	
	1	0	0	1	1	1	1	0	1	1	0	
	1	0	0	1	1	1	1	1	0	0	0	
	1	0	0	1	1	1	1	1	0	1	0	
	1	0	0	1	1	1	1	1	1	0	0	
	1	0	1	0	0	0	0	0	0	0	0	
	1	0	1	0	0	0	0	0	0	1	0	
	1	0	1	0	0	0	0	0	1	0	0	
	1	0	1	0	0	0	0	0	1	1	0	
	1	0	1	0	0	0	0	1	0	0	0	
	1	0	1	0	0	0	0	1	0	1	0	
	1	0	1	0	0	0	0	1	1	0	0	
	1	0	1	0	0	0	0	1	1	1	0	
	1	0	1	0	0	0	1	0	0	0	0	

	1	0	1	0	0	0	1	0	0	1	0	
	1	0	1	0	0	0	1	0	1	0	0	
	1	0	1	0	0	0	1	0	1	1	0	
	1	0	1	0	0	0	1	1	0	0	0	
	1	0	1	0	0	0	1	1	0	1	0	
	1	0	1	0	0	0	1	1	1	0	0	
	1	0	1	0	0	0	1	1	1	1	0	
		0	1	0	0	1	0	0	0	0	0	
	1											
	1	0	1	0	0	1	0	0	0	1	0	
	1	0	1	0	0	1	0	0	1	0	0	
	1	0	1	0	0	1	0	0	1	1	0	
	1	0	1	0	0	1	0	1	0	0	0	
	1	0	1	0	0	1	0	1	0	1	0	
			1		0	1	0				0	
	1	0		0				1	1	0		
	1	0	1	0	0	1	0	1	1	1	0	
	1	0	1	0	0	1	1	0	0	0	0	CREB or MITF is required for the
	1	0	1	0	0	1	1	0	0	1	0	CREB of WITT is required for the
	1	0	1	0	0	1	1	0	1	0	0	transprintional activation of Pal 2
	1	0	1	0	0	1	1	0	1	1	0	transcriptional activation of Bcl-2
							-					gana
	1	0	1	0	0	1	1	1	0	0	0	gene.
	1	0	1	0	0	1	1	1	0	1	0	Dhashamilation of DAD (a Pal 2
	1	0	1	0	0	1	1	1	1	0	0	Phosphorylation of BAD (a Bcl-2
	1	0	1	0	0	1	1	1	1	1	0	antagonist) by Alet EDV or DSV
	1	0	1	0	1	0	0	0	0	0	0	antagonist) by Akt, ERK, or RSK
	1	0	1		1	0	0		0			is needed for the full activation of
	1			0				0		1	0	is needed for the full activation of
	1	0	1	0	1	0	0	0	1	0	0	D-1-2
	1	0	1	0	1	0	0	0	1	1	0	Bcl-2 protein.
	1	0	1	0	1	0	0	1	0	0	0	D 1.001/2.1 .
	1	0	1	0	1	0	0	1	0	1	0	Beta-catenin and GSK3-beta
	1	0	1	0	1	0	0	1	1	0	0	1 (D 12)
	•		1									upregulates Bcl-2 expression
	1	0	1	0	1	0	0	1	1	1	0	1 1
	1	0	1	0	1	0	1	0	0	0	0	level.
58	1	0	1	0	1	0	1	0	0	1	0	D 10
	1	0	1	0	1	0	1	0	1	0	0	Bcl-2 activity is suppressed if any
	1	0	1	0	1	0	1	0	1	1	0	
	-											of its negative regulators is
	1	0	1	0	1	0	1	1	0	0	0	
	1	0	1	0	1	0	1	1	0	1	0	activated.
	1	0	1	0	1	0	1	1	1	0	0	
	1	0	1	0	1	0	1	1	1	1	0	Hence, the activation condition for
	1	0	1	0	1	1	0	0	0	0	0	
												Bcl-2_M is
	1	0	1	0	1	1	0	0	0	1	0	
	1	0	1	0	1	1	0	0	1	0	0	'AND(OR(MITFprotein_M,
	1	0	1	0	1	1	0	0	1	1	0	
	1	0	1	0	1	1	0	1	0	0	0	CREB_M), OR(Akt_M, ERK_M,
	1	0	1	0	1	1	0	1	0	1	0	
												RSK_M, b-catenin_M,
	1	0	1	0	1	1	0	1	1	0	0	
	1	0	1	0	1	1	0	1	1	1	0	GSK3b_M), NOT(OR(p53_M,
	1	0	1	0	1	1	1	0	0	0	0	
	1	0	1	0	1	1	1	0	0	1	0	JNK_M, p38_M)))'.
	1	0	1	0	1	1	1	0	1	0	0	<u> </u>
							1					
	1	0	1	0	1	1	-	0	1	1	0	
	1	0	1	0	1	1	1	1	0	0	0	
	1	0	1	0	1	1	1	1	0	1	0	
	1	0	1	0	1	1	1	1	1	0	0	
	1	0	1	0	1	1	1	1	1	1	0	
	1	0	1	1	0	0	0	0	0	0	0	
	1	0	1	1	0	0	0	0	0	1	0	
	1	0	1	1	0	0	0	0	1	0	0	
	1	0	1	1	0	0	0	0	1	1	0	
	1	0	1	1	0		0		0		0	
						0		1		0		
	1	0	1	1	0	0	0	1	0	1	0	
	1	0	1	1	0	0	0	1	1	0	0	
	1	0	1	1	0	0	0	1	1	1	0	
	1	0	1	1	0	0	1	0	0	0	0	
	1	0	1	1	0	0	1	0	0	1	0	
		,					•	-	•	•		

	1	0	1	1	0	0	1	0	1	0	0	
	1	0	1	1	0	0	1	0	1	1	0	
			1									
	1	0	1	1	0	0	1	1	0	0	0	
	1	0	1	1	0	0	1	1	0	1	0	
	1	0	1	1	0	0	1	1	1	0	0	
	1	0	1	1	0	0	1	1	1	1	0	
			-				-					
	1	0	1	1	0	1	0	0	0	0	0	
	1	0	1	1	0	1	0	0	0	1	0	
	1	0	1	1	0	1	0	0	1	0	0	
	1	0	1	1	0	1	0	0	1	1	0	
		0		1	0	1	0		0		0	
	1		1					1		0		
	1	0	1	1	0	1	0	1	0	1	0	
	1	0	1	1	0	1	0	1	1	0	0	
	1	0	1	1	0	1	0	1	1	1	0	
	1	0	1	1	0	1	1	0	0	0	0	
	1	0	1	1	0	1	1	0	0	1	0	
	-		•									CREB or MITF is required for the
	1	0	1	1	0	1	1	0	1	0	0	
	1	0	1	1	0	1	1	0	1	1	0	transcriptional activation of Bcl-2
	1	0	1	1	0	1	1	1	0	0	0	
	1	0	1	1	0	1	1	1	0	1	0	gene.
		0	1	1	0	1	1				0	8
	1							1	1	0		Phosphorylation of BAD (a Bcl-2
	1	0	1	1	0	1	1	1	1	1	0	Thosphorylation of Brib (a Ber 2
	1	0	1	1	1	0	0	0	0	0	0	antagonist) by Akt, ERK, or RSK
	1	0	1	1	1	0	0	0	0	1	0	untugomst) by rikt, Ekik, or Kok
	1	0	1	1	1	0	0	0	1	0	0	is needed for the full activation of
				1								is needed for the full activation of
	1	0	1		1	0	0	0	1	1	0	Bcl-2 protein.
	1	0	1	1	1	0	0	1	0	0	0	BCI-2 protein.
	1	0	1	1	1	0	0	1	0	1	0	Beta-catenin and GSK3-beta
	1	0	1	1	1	0	0	1	1	0	0	Deta-catemin and USK5-beta
	1	0	1	1	1	0	0	1	1	1	0	
	•		•	-			Ü					upregulates Bcl-2 expression
	1	0	1	1	1	0	1	0	0	0	0	1 1
	1	0	1	1	1	0	1	0	0	1	0	level.
58	1	0	1	1	1	0	1	0	1	0	0	5.10
	1	0	1	1	1	0	1	0	1	1	0	Bcl-2 activity is suppressed if any
	1	0	1	1	1		1	1	0			
	1		1			0				0	0	of its negative regulators is
	1	0	1	1	1	0	1	1	0	1	0	
	1	0	1	1	1	0	1	1	1	0	0	activated.
	1	0	1	1	1	0	1	1	1	1	0	
	1	0	1	1	1	1	0	0	0	0	0	Hence, the activation condition for
		-										
	1	0	1	1	1	1	0	0	0	1	0	Bcl-2_M is
	1	0	1	1	1	1	0	0	1	0	0	
	1	0	1	1	1	1	0	0	1	1	0	'AND(OR(MITFprotein_M,
	1	0	1	1	1	1	0	1	0	0	0	The Descentage of the Control of the
	1	0	1	1	1	1	0	1	0	1	0	CREB_M), OR(Akt_M, ERK_M,
			•									CILED_IVI), OIK(I IKL_IVI, EIKIL_IVI,
	1	0	1	1	1	1	0	1	1	0	0	RSK_M, b-catenin_M,
	1	0	1	1	1	1	0	1	1	1	0	13511_1, 0 000011111_1,
	1	0	1	1	1	1	1	0	0	0	0	GSK3b_M), NOT(OR(p53_M,
	1	0	1	1	1	1	1	0	0	1	0	551256_141), 1401 (OK(p35_141,
	1	0	1	1	1	1	1	0	1	0	0	JNK_M, p38_M)))'.
												51115_141, p30_141///.
	1	0	1	1	1	1	1	0	1	1	0	
	1	0	1	1	1	1	1	1	0	0	0	
	1	0	1	1	1	1	1	1	0	1	0	
	1	0	1	1	1	1	1	1	1	0	0	
	1	0	1	1	1	1	1	1	1	1	0	
	1											
	1	1	0	0	0	0	0	0	0	0	0	
	1	1	0	0	0	0	0	0	0	1	0	
	1	1	0	0	0	0	0	0	1	0	0	
	1	1	0	0	0	0	0	0	1	1	0	
	1	1	0	0	0	0	0	1	0		0	
	1									0		
	1	1	0	0	0	0	0	1	0	1	0	
	1	1	0	0	0	0	0	1	1	0	0	
	1	1	0	0	0	0	0	1	1	1	0	
	1	1	0	0	0	0	1	0	0	0	0	
	1	1	0	0	0	0	1	0	0	1	0	
			-									
	1	1	0	0	0	0	1	0	1	0	0	

	1	1	0	0	0	0	1	0	1	1	0	
	1	1	0	0	0	0	1	1	0	0	0	
	1		0	0	0	0	1	1	0	1	0	
	1	1										
	1	1	0	0	0	0	1	1	1	0	0	
	1	1	0	0	0	0	1	1	1	1	0	
	1	1	0	0	0	1	0	0	0	0	0	
	1	1	0	0	0	1	0	0	0	1	0	
	1	1	0	0	0	1	0	0	1	0	0	
	1	1	0	0	0	1	0	0	1	1	0	
		1	0	0	0	1	0	1	0	0	0	
	1	1	0	0	0	1	0	1	0	1	0	
	1	1	0	0	0	1	0	1	1	0	0	
	1	1	0	0	0	1	0	1	1	1	0	
	1	1	0	0	0	1	1	0	0	0	0	
	1	1	0	0	0	1	1	0	0	1	0	
	1	1	0	0	0	1	1	0	1	0	0	
	1	1	0	0	0	1	1	0	1	1	0	CREB or MITF is required for the
	1	1	0	0	0	1	1	1	0	0	0	transcriptional activation of Bcl-2
	1	1	0	0	0	1	1	1	0	1	0	
	1	1	0	0	0	1	1	1	1	0	0	gene.
	1	1	0	0	0	1	1	1	1	1	0	DI
	1	1	0	0	1	0	0	0	0	0	0	Phosphorylation of BAD (a Bcl-2
	1	1	0	0	1	0	0	0	0	1	0	
		1	0	0	1	0	0	0	1	0	0	antagonist) by Akt, ERK, or RSK
												. 1 10 4 011 4 4 0
	1	1	0	0	1	0	0	0	1	1	0	is needed for the full activation of
	1	1	0	0	1	0	0	1	0	0	0	D 10
	1	1	0	0	1	0	0	1	0	1	0	Bcl-2 protein.
	1	1	0	0	1	0	0	1	1	0	0	Data and an A CCV2 hada
	1	1	0	0	1	0	0	1	1	1	0	Beta-catenin and GSK3-beta
	1	1	0	0	1	0	1	0	0	0	0	umma aulatas Dal 2 ayummasian
		1	0	0	1	0	1	0	0	1	0	upregulates Bcl-2 expression
												level.
	1	1	0	0	1	0	1	0	1	0	0	ievei.
58	1	1	0	0	1	0	1	0	1	1	0	Bcl-2 activity is suppressed if any
	1	1	0	0	1	0	1	1	0	0	0	Dei-2 activity is suppressed if any
	1	1	0	0	1	0	1	1	0	1	0	of its negative regulators is
	1	1	0	0	1	0	1	1	1	0	0	of its negative regulators is
	1	1	0	0	1	0	1	1	1	1	0	activated.
		1		0	1		0				0	activated.
	1		0			1		0	0	0		Hence, the activation condition for
	1	1	0	0	1	1	0	0	0	1	0	Tience, the activation condition for
	1	1	0	0	1	1	0	0	1	0	0	Bcl-2_M is
	1	1	0	0	1	1	0	0	1	1	0	BCI-2_IVI IS
	1	1	0	0	1	1	0	1	0	0	0	'AND(OR(MITFprotein_M,
	1	1	0	0	1	1	0	1	0	1	0	THAD (OR (MITTI protein_IM;
	1	1	0	0	1	1	0	1	1	0	0	CREB_M), OR(Akt_M, ERK_M,
												CREB_IVI), OR(/IRI_IVI, ERIX_IVI,
	1	1	0	0	1	1	0	1	1	1	0	RSK_M, b-catenin_M,
	1	1	0	0	1	1	1	0	0	0	0	
	1	1	0	0	1	1	1	0	0	1	0	GSK3b_M), NOT(OR(p53_M,
	1	1	0	0	1	1	1	0	1	0	0	
	1	1	0	0	1	1	1	0	1	1	0	JNK_M, p38_M)))'.
	1	1	0	0	1	1	1	1	0	0	0	— ¬ r - ~—///
	1	1	0	0	1	1	1	1	0	1	0	
	1	1	0	0	1	1	1	1	1	0	0	
	1	1	0	0	1	1	1	1	1	1	0	
	1	1	0	1	0	0	0	0	0	0	0	
	1	1	0	1	0	0	0	0	0	1	0	
	1	1	0	1	0	0	0	0	1	0	0	
	1	1	0	1	0	0	0	0	1	1	0	
	1	1	0	1	0	0	0	1	0	0	0	
	1	1	0	1	0	0	0	1	0	1	0	
	1	1	0	1	0	0	0	1	1	0	0	
	1	1	0	1	0	0	0	1	1	1	0	
	1	1	0	1	0	0	1	0	0	0	0	
	1	1	0	1	0	0	1	0	0	1	0	
	1	1	0	1	0	0	1	0	1		0	
										0		
	1	1	0	1	0	0	1	0	1	1	0	

	1	1	0	1	0	0	1	1	0	0	0	
	1	1	0	1	0	0	1	1	0	1	0	
	1	1	0	1	0	0	1	1	1	0	0	
	1	1	0	1	0	0	1	1	1	1	0	
	1	1	0	1	0	1	0	0	0	0	0	
	1	1	0	1	0	1	0	0	0	1	0	
	1	1	0	1	0	1	0	0	1	0	0	
	1	1	0	1	0	1	0	0	1	1	0	
	1	1	0	1	0	1	0	1	0	0	0	
	1	1	0	1	0	1	0	1	0	1	0	
	1	1	0	1	0	1	0	1	1	0	0	
	1	1	0	1	0	1	0	1	1	1	0	
	1	1	0	1	0	1	1	0	0	0	0	
	1	1	0	1	0	1	1	0	0	1	0	
	1	1	0	1	0	1	1	0	1	0	0	
	1	1	0	1	0	1	1	0	1	1	0	CREB or MITF is required for the
	1	1	0	1	0	1	1	1	0	0	0	CREB of WITT is required for the
	1	1	0	1	0	1	1	1	0	1	0	transcriptional activation of Bcl-2
	1	1	0	1	0	1	1	1	1	0	0	
	1	1	0	1	0	1	1	1	1	1	0	gene.
	1	1	0	1	1	0	0	0	0	0	0	Dhaanhamilation of DAD (a Dal 2
	1	1	0	1	1	0	0	0	0	1	0	Phosphorylation of BAD (a Bcl-2
	1	1	0	1	1	0	0	0	1	0	0	antagonist) by Akt, ERK, or RSK
	1	1	0	1	1	0	0	0	1	1	0	
	1	1	0	1	1	0	0	1	0	0	0	is needed for the full activation of
	1	1	0	1	1	0	0	1	0	1	0	Dal 2 mastain
	1	1	0	1	1	0	0	1	1	0	0	Bcl-2 protein.
	1	1	0	1	1	0	0	1	1	1	0	Beta-catenin and GSK3-beta
	1	1	0	1	1	0	1	0	0	0	0	
	1	1	0	1	1	0	1	0	0	1	0	upregulates Bcl-2 expression
	1	1	0	1	1	0	1	0	1	0	0	11
7 0	1	1	0	1	1	0	1	0	1	1	0	level.
58	1	1	0	1	1	0	1	1	0	0	0	Bcl-2 activity is suppressed if any
	1	1	0	1	1	0	1	1	0	1	0	
	1	1	0	1	1	0	1	1	1	0	0	of its negative regulators is
	1	1	0	1	1	0	1	1	1	1	0	activated.
	1	1	0	1	1	1	0	0	0	0	0	activated.
	1	1	0	1	1	1	0	0	1	0	0	Hence, the activation condition for
	1	1	0	1	1	1	0	0	1	1	0	
	1	1	0	1	1	1	0	1	0	0	0	Bcl-2_M is
	1	1	0	1	1	1	0	1	0	1	0	AND OD MITEmatein M
	1	1	0	1	1	1	0	1	1	0	0	'AND(OR(MITFprotein_M,
	1	1	0	1	1	1	0	1	1	1	0	CREB_M), OR(Akt_M, ERK_M,
	1	1	0	1	1	1	1	0	0	0	0	
	1	1	0	1	1	1	1	0	0	1	0	RSK_M, b-catenin_M,
	1	1	0	1	1	1	1	0	1	0	0	CCIVAL MAN NOTIOD (152 M
	1	1	0	1	1	1	1	0	1	1	0	GSK3b_M), NOT(OR(p53_M,
	1	1	0	1	1	1	1	1	0	0	0	JNK_M, p38_M)))'.
	1	1	0	1	1	1	1	1	0	1	0	· ·
	1	1	0	1	1	1	1	1	1	0	0	
	1	1	0	1	1	1	1	1	1	1	0	
	1	1	1	0	0	0	0	0	0	0	0	
	1	1	1	0	0	0	0	0	0	1	0	
	1	1	1	0	0	0	0	0	1	0	0	
	1	1	1	0	0	0	0	0	1	1	0	
	1	1	1	0	0	0	0	1	0	0	0	
	1	1	1	0	0	0	0	1	0	1	0	
	1	1	1	0	0	0	0	1	1	0	0	
	1	1	1	0	0	0	0	1	1	1	0	
	1	1	1	0	0	0	1	0	0	0	0	
	1	1	1	0	0	0	1	0	0	1	0	
	1	1	1	0	0	0	1	0	1	0	0	
	1	1	1	0	0	0	1	0	1	1	0	
	1	1	1	0	0	0	1	1	0	0	0	

											1	
	1	1	1	0	0	0	1	1	0	1	0	
	1	1	1	0	0	0	1	1	1	0	0	
	1	1	1	0	0	0	1	1	1	1	0	
	1	1	1	0	0	1	0	0	0	0	0	
	1	1	1	0	0	1	0	0	0	1	0	
	-					1						
	1	1	1	0	0	1	0	0	1	0	0	
	1	1	1	0	0	1	0	0	1	1	0	
	1	1	1	0	0	1	0	1	0	0	0	
	1	1		U		1	U			Ü	· ·	
	1	1	1	0	0	1	0	1	0	1	0	
	1	1	1	0	0	1	0	1	1	0	0	
	1	1	1	0	0	1	0	1	1	1	0	
		-										
	1	1	1	0	0	1	1	0	0	0	0	
	1	1	1	0	0	1	1	0	0	1	0	
	1	1	1	0	0	1	1	0	1	0	0	
	1	1	1	0	0	1	1	0	1	1	0	
	1	1	1	0	0	1	1	1	0	0	0	
	1	1	1	0	0	1	1	1	0	1	0	CDED or MITE is required for the
						1						CREB or MITF is required for the
	1	1	1	0	0	1	1	1	1	0	0	
	1	1	1	0	0	1	1	1	1	1	0	transcriptional activation of Bcl-2
	1	1	1	0	1	0	0	0	0	0	0	
	1	-										gene.
	1	1	1	0	1	0	0	0	0	1	0	
	1	1	1	0	1	0	0	0	1	0	0	Phosphorylation of BAD (a Bcl-2
	1	1	1	0	1	0	0	0	1	1	0	Children of Bill (a Bei 2
	1	1				U						antagonist) by Akt, ERK, or RSK
	1	1	1	0	1	0	0	1	0	0	0	antagonist) by Akt, EKK, of KSK
	1	1	1	0	1	0	0	1	0	1	0	. 1 10 4 011 4 4 0
				0	1	0	0	,		0		is needed for the full activation of
	1	1	1	0	1	0	0	1	1	0	0	
	1	1	1	0	1	0	0	1	1	1	0	Bcl-2 protein.
	1	1	1	0	1	0	1	0	0	0	0	
	1		,	0	1	0		0	0	1	0	Beta-catenin and GSK3-beta
	1	1	1	0	1	0	1	0	0	1	· ·	
	1	1	1	0	1	0	1	0	1	0	0	upregulates Bcl-2 expression
	1	1	1	0	1	0	1	0	1	1	0	apregulates Bel 2 expression
												level.
	1	1	1	0	1	0	1	1	0	0	0	ievei.
58	1	1	1	0	1	0	1	1	0	1	0	D 10 41 14 1 116
	1	1	1	0	1	0	1	1	1	0	0	Bcl-2 activity is suppressed if any
	1	1	1	0	1	0	1	1	1	1	0	of its negative regulators is
	1	1	1	0	1	1	0	0	0	0	0	
	1	1	1	0	1	1	0	0	0	1	0	activated.
		-										activated.
	1	1	1	0	1	1	0	0	1	0	0	Hence, the activation condition for
	1	1	1	0	1	1	0	0	1	1	0	Tience, the activation condition for
	1	1	1	0	1	1	0	1	0	0	0	D 12 M:
						1					Ü	Bcl-2_M is
	1	1	1	0	1	1	0	1	0	1	0	
	1	1	1	0	1	1	0	1	1	0	0	'AND(OR(MITFprotein_M,
	1	1	1	0	1	1	0	1	1	1		_
						1						CREB_M), OR(Akt_M, ERK_M,
	1	1	1	0	1	1	1	0	0	0	0	,,
	1	1	1	0	1	1	1	0	0	1	0	RSK_M, b-catenin_M,
		1				,			1			TOTA_IVI, U-Catclini_IVI,
	1		1	0	1	1	1	0	-	0	0	GSK3b_M), NOT(OR(p53_M,
	1	1	1	0	1	1	1	0	1	1	0	OBIASU_IVI), INOT (OK(pss_IVI,
	1	1	1	0	1	1	1	1	0	0	0	INTERNATIONAL CONTRACTOR
												JNK_M, p38_M)))'.
	1	1	1	0	1	1	1	1	0	1	0	
	1	1	1	0	1	1	1	1	1	0	0	
	1	1	1	0	1	1	1	1	1	1	0	
	1	1	1	1	0	0	0	0	0	0	0	
	1	1	1	1	0	0	0	0	0	1	0	
	1	1	1	1	0	0	0	0	1	0	0	
	1	1	1	1	0	0	0	0	1	1	0	
	1	1	1	1	0	0	0	1	0	0	0	
	1	1	1	1	0	0	0	1	0	1	0	
											U	
	1	1	1	1	0	0	0	1	1	0	0	
	1	1	1	1	0	0	0	1	1	1	0	
	1	1	1	1	0	0	1	0	0	0	0	
	1	1	1	1	0	0	1	0	0	1	0	
	1	1	1	1	0	0	1	0	1	0	0	
	1	1	1	1	0	0	1	0	1	1	0	
	1	1	1	1	0	0	1	1	39	0	0	
					0							
	1	1	1	1	v	0	1	1	0	1	0	

	1	1	1	1	0 0	1 1	1	0	0	
	1	1	1	1	0 0 0	1 1 0	0	0	0	
	1	1	1	1	0 1	0 0	0	1	0	
	1	1	1	1	0 1	0 0	1	0	0	
	1	1	1	1	0 1	0 0	1	1	0	
	1	1	1	1	0 1 0 1	0 1 0 1	0	0	0	
	1	1	1	1	0 1	0 1	1	0	0	CDED on MITE is no swined for the
	1	1	1	1	0 1	0 1	1	1	0	CREB or MITF is required for the
	1	1	1	1	0 1 0 1	1 0	0	0	0	transcriptional activation of Bcl-2
	1	1	1	1	0 1	1 0	1	0	0	gene.
	1	1	1	1	0 1	1 0	1	1	0	Phosphorylation of BAD (a Bcl-2
	1	1	1	1	0 1 0 1	1 1	0	0	0	
	1	1	1	1	0 1	1 1	1	0	0	antagonist) by Akt, ERK, or RSK
	1	1	1	1	0 1	1 1	1	1	0	is needed for the full activation of
	1	1	1	1	1 0	0 0 0	0	0	0	Bcl-2 protein.
	1	1	1	1	1 0	0 0	1	0	0	Beta-catenin and GSK3-beta
	1	1	1	1	1 0	0 0	1	1	0	
	1	1	1	1	1 0	0 1 0 1	0	0	0	upregulates Bcl-2 expression
~ 0	1	1	1	1	1 0	0 1	1	0	0	level.
58	1	1	1	1	1 0	0 1	1	1	0	Bcl-2 activity is suppressed if any
	1	1	1	1		1 0	0	0	0	of its negative regulators is
	1	1	1	1	1 0	1 0	1	0	0	
	1	1	1	1	1 0	1 0	1	1	0	activated.
	1	1	1	1	1 0	1 1	0	0	0	Hence, the activation condition for
	1	1	1	1		1 1	0	0	0	Bcl-2_M is
	1	1	1	1	1 0	1 1	1	1	0	'AND(OR(MITFprotein_M,
	1	1	1	1	1 1	0 0	0	0	0	_
	1	1	1	1	1 1	0 0 0	0	0	0	CREB_M), OR(Akt_M, ERK_M,
	1	1	1	1	1 1	0 0	1	1	0	RSK_M, b-catenin_M,
	1	1	1	1	1 1	0 1	0	0	0	GSK3b_M), NOT(OR(p53_M,
	1	1	1	1	1 1	0 1 0 1	0	0	0	JNK_M, p38_M)))'.
	1	1	1	1	1 1	0 1	1	1	0	
	1	1	1	1	1 1	1 0	0	0	0	
	1	1	1	1	1 1	1 0	0	0	0	
	1	1	1	1	1 1	1 0	1	1	0	
	1	1	1	1	1 1	1 1	0	0	0	
	1	1	1	1	1 1	1 1 1 1	0	1	0	
	1	1	1	1		1 1	1	1	0	
			I	B-catenin_N	M CREB_M	MITFml	RNA_M		•	Binding of beta-catenin and CREB
				0	0	(•		
59				0	1	C				to the MITF gene promoter region
										stimulates MITF transcription,
				1	0	(hence forming an AND relation.
				1	1	1				

	MITFmRNA_M	ERK_M	MITFprotein_M	The phosphorylation of MITF at
	0	0	0	serine 73 by ERK results in
60	0	1	0	upregulation of the MITF
	1	0	0	melanogenic function.
	1	1	1	
	MITFprote	ein_M	Melanin	MITF promotes melanin synthesi
61	0		0	by upregulating expression of
	1		1	melanogenic enzymes.

Blue and red boxes denote positive and negative regulators, respectively.

Supplementary Table S3. *In silico* node control analysis for the identification of appropriate strategies to reduce UVB-induced skin pigmentation.

	Δ Mela	nin (%)	Δ Bcl-	2_K (%)	Δ Bcl-2_M (%)		
		bation		rbation		bation	
Perturbed node	(-)	(+)	(-)	(+)	(-)	(+)	
Akt_K	24.84	-57.02	-29.80	45.62	14.22	-70.77	
a-MSH_K	37.27	-1.14	2.46	-0.75	17.23	-41.21	
ASK1_K	-13.95	31.73	42.15	-100.00	-17.88	-11.96	
b-catenin_K	0.00	-4.34	0.00	0.46	0.00	-5.86	
COX-2_K	9.82	-27.99	-0.44	0.50	18.40	-44.35	
EGFR_K	13.49	-57.03	-31.75	45.62	3.44	-70.77	
ERK_K	-6.00	29.44	-2.67	-56.84	-6.40	-7.69	
ET-1_K	-60.72	371.98	2.45	36.92	-71.30	178.15	
GSK3b_K	-27.99	9.82	0.50	-0.44	-44.35	18.40	
IL-1_K	-78.43	316.83	8.13	26.75	-71.61	151.76	
JNK_K	0.00	0.00	0.00	-72.95	0.00	0.00	
MDM2_K	10.24	-14.47	-4.44	11.13	5.82	-29.37	
MEK_K	-6.00	30.85	-2.67	-46.15	-6.40	-5.97	
MKK4_K	0.00	0.00	0.00	-72.95	0.00	0.00	
MKK6_K	-13.95	31.73	28.74	-100.00	-17.88	-11.96	
NFAT_K	0.00	-4.34	0.00	0.46	0.00	-5.86	
p38_K	-13.95	30.43	28.74	-100.00	-17.88	-12.77	
p53_K	-14.49	62.81	11.12	-70.93	-29.38	-3.30	
PDK1_K	24.94	-57.01	-29.78	45.62	14.24	-70.76	
PGE2_K	9.82	0.81	-0.44	-0.40	18.40	-40.30	
PI3K_K	24.93	-57.03	-29.76	45.62	14.34	-70.78	
PTEN_K	-10.43	24.93	13.28	-29.76	-11.58	14.34	
RAF_K	-6.00	30.85	-2.67	-46.15	-6.40	-5.97	
RAS_K	-6.00	-1.00	-2.67	-23.78	-6.40	-15.48	
RSK_K	0.00	0.00	-5.35	6.17	0.00	0.00	
SCF_K	-36.46	34.92	1.31	0.08	-34.08	29.66	
SG_K	-6.00	-0.68	-2.67	-23.78	-6.40	-15.30	
AC_M	37.35	1.19	2.45	-0.31	17.25	-40.40	
Akt_M	-100.00	157.75	7.78	9.77	-100.00	189.53	
ASK1_M	77.58	-100.00	-1.04	7.78	120.00	-100.00	
b-catenin_M	-100.00	81.02	7.78	-2.07	-8.15	1.82	
cAMP_M	51.07	-100.00	3.99	7.78	28.74	-100.00	
c-kit_M	-36.46	34.92	1.31	0.08	-34.08	29.66	
CREB_M	-100.00	6.97	7.78	0.18	-86.62	1.09	
EP4_M	9.82	1.19	-0.44	-0.31	18.40	-40.40	
ERK_M	-100.00	118.89	7.78	-3.56	-58.53	0.54	

ETR_M	-60.72	372.69	2.45	37.08	-71.30	178.48
GSK3b_M	81.02	-100.00	-2.07	7.78	1.82	-13.75
JNK_M	0.00	0.00	0.00	0.00	0.00	-100.00
MC1R_M	37.35	0.81	2.45	-0.40	17.25	-40.30
MDM2_M	0.00	0.00	0.00	0.00	-22.55	15.48
MEK_M	-100.00	9.19	7.78	0.52	-58.53	5.21
MITFmRNA_M	-100.00	95.71	7.78	-1.02	-23.75	1.58
MITFprotein_M	-100.00	402.49	7.78	45.62	-23.75	-100.00
MKK4_M	0.00	0.00	0.00	0.00	0.00	-100.00
MKK6_M	77.62	-100.00	-1.10	7.78	91.15	-100.00
MSK_M	-10.72	6.97	0.23	0.18	-7.26	1.09
p38_M	77.70	-100.00	-1.29	7.78	91.35	-100.00
p53_M	0.00	0.00	0.00	0.00	15.48	-100.00
PDE_M	-35.54	51.07	2.45	3.99	-27.01	28.74
PDK1_M	-100.00	157.75	7.78	9.77	-100.00	189.53
PI3K_M	-100.00	157.19	7.78	9.84	-100.00	189.53
PKA_M	-42.82	51.38	2.83	4.00	-34.06	31.92
PKC_M	-60.73	372.69	2.45	37.08	-71.30	178.48
RAF_M	-100.00	9.11	7.78	0.54	-58.53	5.30
RAS_M	-52.83	372.69	1.77	37.08	-49.26	178.48
RSK_M	0.00	0.00	0.00	0.00	-15.61	17.09
SG_M	-36.46	372.69	1.31	37.08	-34.08	178.48

Node control analysis for the identification of appropriate strategies to reduce UVB-induced skin pigmentation. Each internal regulatory node was pinned to either '0' or '1' before Boolean model simulations were performed under UVB stimulation. The perturbation effect of the node control of each internal regulatory node was measured as described in the Materials and Methods. '-' and '+' denote inhibition and constitutive activation, respectively. In the model, activation of MITFprotein_M requires activation of both ERK_M and MITFmRNA_M, and activation of MITFmRNA_M requires activation of both CREB_M and b-catenin_M. Therefore, in the model simulation, inhibition of either ERK_M or MITFmRNA_M results in inactivation of MITFprotein_M, which leads to 100% Melanin reduction. Similarly, inhibition of either CREB_M or b-catenin_M results in inactivation of MITFmRNA_M, which causes inactivation of MITFprotein_M and consequently 100% Melanin reduction. In conclusion, activation of Melanin node requires activation of ERK_M, CREB_M, beta-catenin_M, MITFmRNA_M, and MITFprotein_M nodes, and therefore inhibition of any of these nodes results in 100% Melanin reduction in the model simulation.

Supplementary Table S4. *In silico* analysis of changes in UVB-induced melanin synthesis with respect to the inhibition of beta-catenin, Ras, PKA, or a combination of Ras and PKA.

Node #1 perturbation	Node #2 perturbation	Δ Melanin (%)
beta-catenin inhibition	-	-100.00
Ras inhibition	-	-52.83
PKA inhibition	-	-42.82
Ras inhibition	PKA inhibition	-24.05

Inhibition of beta-catenin, Ras, or PKA can reduce the activity of node 'melanin' in response to UVB irradiation. Among these three intervention strategies, the most effective strategy was beta-catenin inhibition. The simultaneous inhibition of Ras and PKA was less effective in suppressing the melanin synthesis compared to the individual inhibition of any of these nodes. See Fig. S4 for the biochemical validation of the simulation results.

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