

Oncogenic Ras

<p>Ras , 20 . Ras guanine nucleotide (GDP GTP) GDP GTP 가 , GTP GDP 가 GTPase 가 . Ras regulator molecular switch , epithelial cell . Ras downstream effector . Ras . Ras Ras isoform , Ras .</p>	<p>Ras 가 20-25kDa small GTP-binding group Ras-relat ed superfamily (Barbacid, 1987). superfamily 60 . Ras, Rho, Rab, Arf, Ran, Rad/GEM subfamily . H-ras, K-ras N-ras ras gene (Bos, 1997). Genome size 3kb(H-ras), 7kb(N-ras), 35kb(K-ras) chromosome . K-ras gene alternative splicing K-RasA K-RasB K-RasB가 . ras gene Ras 21kDa , H-Ras, K-RasA, N-Ras 189 . Fig. 1 Ras . 189 가 , K-RasB 가 188 가 . , 164 165</p>
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C-terminal(hypervariable region) 가 , Ras isoform (Bos, 1989; Rodenhuis, 1992; Manges et al., 1992). K-ras adenocarcinoma, pancreatic cancer, cholangiocarcinomas, colorectal malignancy, lung adenocarcinoma . H-ras 가 cutaneous squamous cell carcinoma squamous head and neck tumor , N-ras acute leukemia myelodysplastic syndrome . Ras oncogenic mutant GTP . NIH3T3 cell proto-oncogene 0.3% GTP Ras가 oncogenic Ras NIH3T3 cell 29% 가 GTP (Scheele et al., 1995). Ras 27가 GTPase GDP/GTP Ras 12 , 13 , 59 , 61 , 63 가 GTPase Ras GTPase p120GAP NF1 GAP activity . 16 , 17 , 116 , 117 , 119 , 144 , 146 guanine nucleotide (Lowy, 1993).

Ras H-Ras 가 , N-Ras 3 (168 , 184 , 188) , K-RasA 2 (131 , 187) , K-RasB 5 (131 , 181 , 183 , 185 , 186) (Barbacid, 1987).

Ras H-ras skin skeletal muscle , K-ras gut thymus , N-ras testis thymus ras gene 가

Ras 가 Ras 12 , 13 , 59 , 61 , 63 가 GTPase Ras GTPase p120GAP NF1 GAP activity . 16 , 17 , 116 , 117 , 119 , 144 , 146 guanine nucleotide (Lowy, 1993).

Ras 30% 가 가 , Ras isoform 가 (Table 1) 가

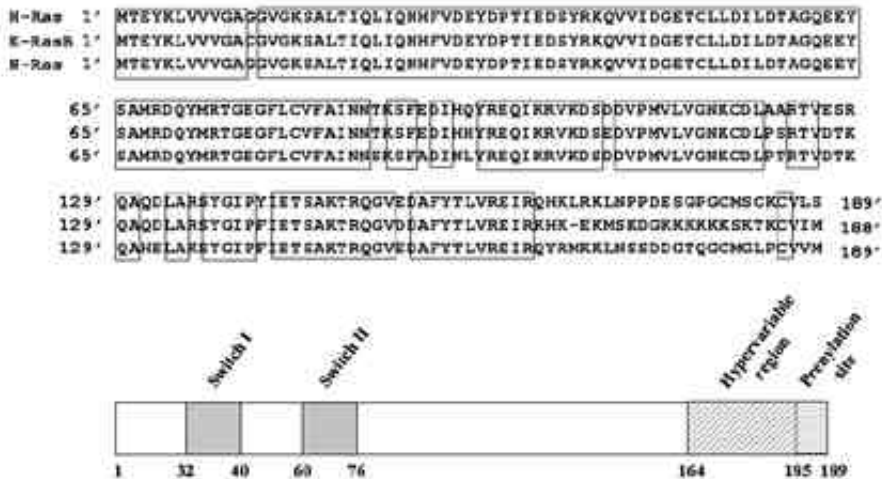


Fig. 1. Ras primary

ras gene 가 tion . ras gene 가
 . H-ras proto-oncogene modification Ras (Prior
 NIH3T3 GTP Ras (Prior
 parental cell 가 0.3% and Hancock, 2001). C-terminal
 Ras-GTP CAAX(C: Cysteine, A: Aliphatic
 mg 1.3~21.3 fmol amino acid, X: any amino acid motif
 가 (Scheele et al., 1995). ras , modification
 가 Ras-GTP 가 (Fig. 2). FTase
 retrovirus가 ras gene non- cysteine residue prenylation, RCE
 mutated Ras AAX proteolytic cleavage,
 , transgenic mice N-ras CMT prenylated cysteine
 codon 가 methyl (Choy et al.,
 (Mangues et al., 1992). 50% 1999; Chiu et al 2002). prenyla
 human tumor ras transcript level tion 가 .
 2~10 . in vitro Ras isoform CAAX motif
 100 가 . CVIM (K-rasB), CIIM (K-rasA), CVVM
 ras , oncogenic ras가 threshold (N-ras), CVLS (H-ras). Ras
 (Hua et al., 1997). CAAX motif cysteine farne
 sylation
 Ras
 Ras
 Post-translational modification . H-Ras N-Ras prenylation
 hypervariable region cysteine
 (181 185 cysteine) palmitoylation
 Ras . palmitoylation Ras
 free ribosome .
 post-translational modifica- prenytion membrane localization

Table 1. Ras

Tumor	Incidence (%)	Ras isoform
Lung adenocarcinoma	28	K-
Colon adenocarcinoma	44	K-
adenoma	50	K-
Pancreas adenocarcinoma	84	K-
Thyroid Follicular carcinoma	53	H,K,N-
Undifferentiated carcinoma	60	H,K,N-
Melanoma	14	N-
Acute myeloid leukemia	25	N-
Bladder carcinoma	17	H-
Kidney carcinoma	13	H-

K-RasB H-Ras N-Ras domain lysine 8 polybasic
 palmitoylation domain prenylation
 prenylation CAAX motif 10 positive charge lysine side chain

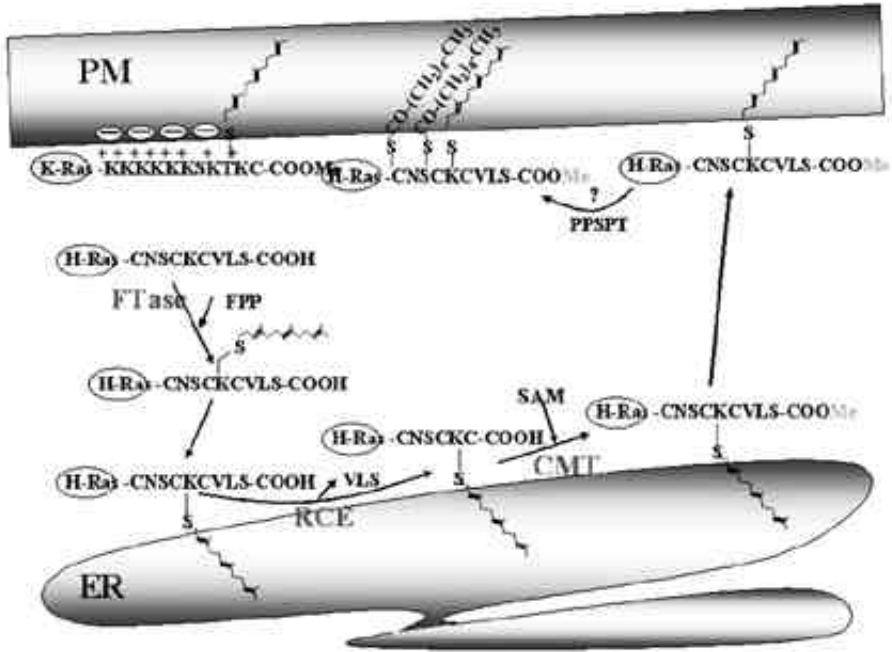


Fig. 2. Ras Post-translational modification

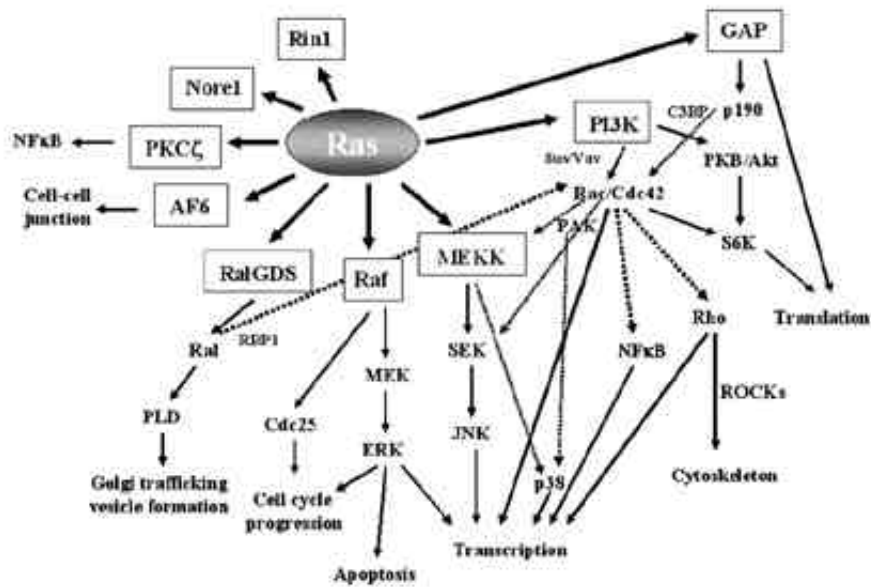


Fig. 3. Ras effectors and downstream pathways.

negative charge 가 tumor 가 K-Ras, H-Ras, N-Ras (Hancock et al., 1990). K-RasB farne sylation geranylgeranylation myeloid lymphoid disorder (Bos, 1989; Rodenhuis, 1992).

polybasic domain geranylgeranylation (James et al., 1995). 2) H-Ras protein kinase C activator Ras post-translation modifi- TPA c-fos cation (Carbone et al., 1991).

FTase inhibitor 3) p120-GAP N-Ras H-Ras (Bell, 2004), Schering-Plough, NF1-GAP N-Ras SCH66336(Ionafarnib, Ras H-Ras 4 가 (Bollag et al., 1991).

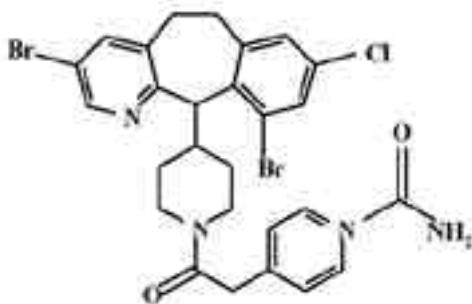
processing 가, K-Ras N-Ras 4) Ras-GEF smgGDS H-Ras Ras 가, K-Ras Ras-GRF (cdc25Mm) in vivo N-Ras K-RasB 가 H-Ras (Jones et al., 1998).

3 ras gene 5) Thyroid K-Ras H-Ras form, mammalian Ras iso- . K-Ras thyroid transcription factor- Malumbres and Pellicer, 1(TTF-1), H-Ras TTF-1 1998). target gene

1) ras gnene human (Francis-Lang et al., 1992).

6) transforming poten- H-Ras rat-2 tial . NIH3T3 fibroblast 10 N-ras human hematopoietic cell line FDC-P1 . K-, H-Ras mutant N-Ras mutant IL-3/granulocyte macrophage colony-stimulating factor-depend- TF-1 ent human myeloid cell line growth factor autonomy (Maher et al., 1995).

7) N-Ras-specific antisense in vitro IL-3, GM-CSF, M-CSF



(+)-4-[2-[4-(8-chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(R)-yl)-1-piperidinyl]-2-oxo-ethyl]-1-piperidinecarboxamide

Fig. 4. Ftase inhibitor SCH66336

hematopoietic cell granulocyte/macrophage-colony formation . , N-Ras가 hematopoietic cell granulocyte/macrophage-colony formation (Skorski et al., 1992). , K-ras human lung fibroblasts (MCR-5 cells) proliferation (Chen et al., 1996).

8) IL-6-dependent myeloma cell line ANBL6 N-Ras IL-6가 apoptosis . K-Ras (Billadeau et al., 1997).

9) H-Ras K-Ras b1 integrin glycosylation collagen I lamin cell adhesion , colon epithelial cell basolateral polarity differentiation embryonic adhesion carcinoembryonic antigen (CEA) 가 (Yan et al., 1997).

10) ras gene knockout mice response . N-ras H-ras knockout mice K-ras mouse embryo (Umanoff et al., 1995; Koera et al., 1997; Johnson et al., 1997).

11) H-Ras N-Ras in vivo Raf1 Erk Raf1 , H-Ras Erk Raf1 (Hamilton et al., 1998).

isoform 가 Ras upstream downstream

Ras Ras

. Ras growth factor, cytokine, (Walker and Olson, 2005). - tyrosine kinase receptor, cytokine receptor, G protein-coupled receptor- 가 Ras . Tyrosine kinase receptor tyrosine SH2 domain . Grb2, Shc, PI3-kinase, phospholipase C-g, p120-GAP SH-PTP2 tyrosine phosphatase(Syp) . Grb2 Shc Sos Ras G protein Gbg subunit Ras pathway PI3-kinase inhibitor wortmannin . EGF tyrosine kinase receptor Ras wortmannin (Lopez-Illasaca et al., 1996). Ras 가 G protein-coupled receptor PI3-kinase tyrosine kinase receptor 가 protein kinase C Ras/Raf1/MAP kinase Ras (El-Shemerly et al., 1997). NIH3T3 Raf1 Ras , COS Ras . Raf1 H-Ras N-Ras PKC N-Ras가 . Ras Ras GDP GTP Ras GEF . GTP/GDP Ras GDP GTP . RasGEF RasGRF(Cdc25Mn) Saccharomyces cerevisiae Ras exchange factor cdc25 가 . RasGEF SOS, RasGRF, RasGRF2, Ras

GRP, C3G, Vav, smgGDS . Vav
 C3G Ras GTPase GEF 가 . Ras pri-
 c-myc,
 Ras GTP 가 N-myc, E1A, polyoma large T
 GTPase , Ras-GTP가 . ras 가
 가 GAP 가 . Ras
 6 GAP
 p120GAP, neurofibromatosis type I
 protein (NF1), GAP1m, GAP1IP4BP, Rb, p16,
 IQGAP1, SynGAP GAP p21, p53
 Ras Ras
 , 12, 13, 61 codon
 , p120GAP NF1 Ras
 downstream
 Ras-GTP target Ras
 effector , Ras isoform 가
 effector Raf, RaIGDS family, 가
 PI3Kinase, MEKK1, Rin 1, AF-6, PKC α ,
 Nore1, GAP downstream
 stream Fig. 3 Ras
 (Marshall, 1995). Ras effec-
 tor Ras effector
 loop (a.a32-40), flanking residue (a.a41-59),
 switch II (a.a 60-72) . GTP
 switch I II
 effector
 Ras 21, 31,
 41, 45, 46, 48, 49, 53, flanking residue
 activator region
 constitutive effector region .

Malignant phenotype
 multistep .
 multiple
 . Established primary
 Ras

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