Table 1. Representative key findings in Ras research

Year	Discovery	Reference
1964	Harvey murine sarcoma virus ("Ha-MuSV") is isolated by passage of Moloney mouse type-C virus in rats	1
1967	Kirsten murine sarcoma virus is isolated by passage of Kirsten mouse type-C virus in rats; later designated "Ki-MSV"	2
1973	HaSV murine sarcoma virus genome contains rat gene sequences	3
1979	Viral *ras* genes encode 21 kDa proteins, which are designated "p21 Src"	4
	Viral H-Ras and K-Ras proteins are GDP- and GTP-binding proteins	5, 6
	DNA from chemically transformed rodent cells can cause morphologic transformation (focus formation) when transfected into recipient NIH/3T3 cells	7
1980	Arf (ADP ribosylation factor) is identified as a "cytosolic macromolecule" required for cholera toxin-mediated activation of adenylate cyclase; shown later to be a GTP-binding protein and a member of the Ras superfamily	8
	HaSV (Ha-MuSV) p21 protein is located at the inner face of the plasma membrane	9
	Antiserum against viral Ha-MSV p21 detects a related endogenous 21 kDa protein that is conserved in mammalian cell lines and other vertebrates	10
1981	Human tumor cell lines contain transforming genes detectable upon transfection of DNA into NIH/3T3 cells	11, 12
	Overexpression of normal rat sequences homologous to the *Ha-MuSV* transforming gene transforms NIH/3T3 cells	13
	Viral *H-ras* and *K-ras* genes each have a normal cellular gene counterpart	14
	Viral *ras* genes can promote growth of normal erythroid precursors	15
1982	Viral H-Ras protein is synthesized initially as a soluble precursor	16
	Overexpression of normal human H-Ras causes growth transformation of NIH 3T3 fibroblasts	17
	Transforming genes detected in human cancer cell lines are identified as *HRAS* and *KRAS* sequences	18-20
	Molecular cloning of human *HRAS* and *KRAS* genes is accomplished by use of probes from the coding regions of *v-Ha-ras* and *v-Ki-ras*	21
	Nucleotide sequence of viral *H-ras* gene is determined	22
	Normal p21 Ras proteins bind GDP and GTP	23
	Transforming *HRAS* from the EJ/T24 bladder tumor cell line is activated by a single amino acid substitution at codon 12	24-26
	Membrane-associated H-Ras contains lipid, as shown by 3H-palmitic acid labeling	27
1983	Complete genomic organization and sequence of human *HRAS* is determined	28
	Mutationally-activated *NRAS* is identified in neuroblastoma cells	29
	HRAS, KRAS and *NRAS* map to different chromosomes (11, 12 and 1, respectively)	30
	Complete genomic organization and sequence information indicates that normal and tumor human *KRAS* both have splice variants of exons 4A and 4B, as well as a processed pseudogene; first suggestion that *RAS* gene products have a common modular structure with a "constant" and a "variable" region	31, 32
	Transforming *KRAS* genes isolated from lung and colon cancers can be activated by different point mutations at codon 12	33
	Activated H-Ras transformation of primary rodent fibroblasts requires concurrent activation of Myc oncogene or inactivation of Rb tumor suppressor, e.g., by polyoma large-T antigen/adenovirus E1A	34, 35
	S. cerevisiae RAS genes are molecularly cloned and sequenced	36
	First Ras-related protein, YPT1, is identified in *S. cerevisiae*; later recognized as the founding member of the Rab family (Rab1)	37
	Chemically induced mammary tumors in mice display activating *HRAS* mutations	38
1984	The C-terminus of H-Ras, and specifically cysteine 186, is required for Ras lipid binding, membrane association and transformation	39, 40
	Microinjection of recombinant H-Ras stimulates cell proliferation	41-43
	Mutant Ras has impaired intrinsic GTPase activity	43 -45
	H-Ras transforming activity is activated by 18 of 19 different amino acid substitutions at	46

	amino acid 12	
1985	Adenylate cyclase is identified as an effector of *S. cerevisiae* but not mammalian Ras	47, 48
	Normal Ras is required for cell proliferation	49
	Ras homologous (Rho) proteins identified fortuitously in *Aplysia*; human orthologs identified	50
	Transforming *NRAS* genes identified from patient acute myelogenous leukemia samples in a nude mouse tumorigenicity assay have activating mutations at codon 13	51
	Ras activation causes differentiation including neurite formation and cessation of growth in PC12 pheochromocytoma cells	52
1986	Any substitution at amino acid 61 of H-Ras impairs its intrinsic GTPase activity	53
	Normal Ras is required for transformation by receptor tyrosine kinase but not Raf oncoproteins	54
	Ras effector domain is defined as residues 32-42	55
1987	Identification of *S. cerevisiae* mutant dpr1 indicating that fatty acid acylation is not the first Ras processing step; foreshadows discovery of farnesyltransferase	56
	Tissue-specific transgene expression of activated H-Ras causes mouse mammary tumor development that is enhanced by concurrent Myc activation	57, 58
	Colon cancers have a high frequency of *KRAS* mutation	59
	Ras GTPase activating protein (GAP) activity is identified; mutant Ras is refractory to stimulation	60
1988	First H-Ras crystal structure determined, for residues 1-171, at 2.7A resolution; however, in response to a second independent determination of H-Ras crystal structure published in 1989, aspects of this first report were reinterpreted and were found to be in agreement with this second study	61-63
	Pancreatic cancers have a high frequency of *KRAS* mutations	64
	Ras proteins are carboxyl-methylated	65, 66
	A Ras mutant, S17N, is identified as a dominant negative protein that has preferential affinity for GDP and blocks the function of endogenous Ras; becomes key tool for Ras studies	67
	The SAR1 (Secretion-associated and Ras-related) gene is identified in a genomic library screen for suppressors of SEC12 in *S. cerevisiae*	68
	Purification and molecular cloning of p120 RasGAP	69, 70
1989	All Ras proteins are modified by a farnesyl isoprenoid lipid, which is essential for Ras membrane association	71-73
	H-Ras and N-Ras but not K-Ras are additionally modified by palmitoylation on cysteines upstream of the CAAX, which enhances membrane association and biological activity	72
1990	Ras undergoes a conformational change during GDP/GTP cycling	74, 75
	IRA1 and IRAS2 encode GAPs for yeast RAS proteins	76
	SCD25 established in *S. cerevisiae* as the first RasGEF	77
	Farnesyltransferase enzyme is identified and shown to be inhibited by tetrapeptides that mimic the C-terminal CAAX motif of Ras	78
	Normal Ras is transiently activated by extracellular stimuli or by tyrosine kinase oncoproteins	79-81
	NF1 tumor suppressor gene encodes a RasGAP	82-84
	Ras membrane association requires the CAAX motif and a second signal within the C-terminal hypervariable domain consisting of either a polybasic domain (K-Ras4B) or palmitoylation (H-Ras, N-Ras and K-Ras4A)	85
1991	Minimal Ras membrane targeting domain is defined: Ras CAAX motif or CAAL motif plus a hypervariable domain-derived second signal, is sufficient to target Ras or a cytosolic heterologous protein to membranes	86
1992	First mammalian Ras guanine nucleotide exchange factor (GEF) is identified	87
	Raf activates MEK1 and MEK2 (MAPKKs)	88-92
1993	Disruption of mutant *KRAS* by homologous recombination impairs colon tumor cell growth	93
	Grb2 is identified as a key link between EGFR and Sos, in a chain leading to activation of Ras	94

	Farnesyltransferase inhibitors block the growth of H-Ras-transformed cells in culture	95, 96
	Raf is identified as the first mammalian effector of Ras	97
	Ran is a regulator of nuclear transport	98-100
1994	Membrane targeted Raf-1 is constitutively activated, supporting a role for membrane translocation in Ras activation of effector function	101, 102
	Class I phosphatidylinositol 3-kinases are Ras effectors	103
1995	Selective Ras effector domain mutants demonstrate a role for non-Raf effectors in Ras transformation	104
	NRAS is dispensable for mouse development	105
	K-Ras4B, the Ras isoform most common in cancer, is resistant to FTIs in vitro	106
	Ras transformation is dependent on Rac1 and RhoA	107-109
	Structure of Raf-1 RBD in complex with Rap1A determined	110
	FTIs cause regression of mammary tumors in an *HRAS* transgenic mouse model	111
	Sensitivity to FTI-mediated growth inhibition of tumor cell lines in vitro does not correlate with their Ras mutation status, suggesting that Ras may not be the key FTI target	112
	Genetic studies in *Drosophila* and *C. elegans* identify the KSR (kinase suppressor of Ras) scaffold protein as a regulator of the Raf-MEK-ERK cascade	113-115
1996	First structure of RasGAP is solved for the p120 RasGAP catalytic domain	116
	Ras binding domain of Raf is utilized as an affinity pulldown assay to monitor Ras-GTP formation in cells, thus sparing the need to use mCi levels of ^{32}P to determine Ras activation	117, 118
1997	Senescence induced by ectopic activated H-Ras in primary fibroblasts is prevented by loss of p53 or p16	119
	K-Ras and N-Ras are alternatively prenylated by GGTase-I in the presence of FTIs, causing their resistance to FTI-mediated inhibition of processing	120-122
	2.5A structure of H-Ras complexed with the RasGAP catalytic domain of p120 RasGAP provides a structural basis for the mechanism of activating mutations at G12 and Q61	123
	KRAS but not *HRAS* or *NRAS* is essential for mouse development	124, 125
	NF-κB activation is required for Ras-mediated transformation because it suppresses oncogenic Ras-induced p53-independent apoptosis	126
1998	Nore1 (RASSF5) effector binds preferentially to Ras-GTP	127
	RasGRP family of RasGEFs identified as transforming proteins	128, 129
	Structure of the RA domain of RalGDS in complex with activated H-Ras shows interactions similar to those of the Raf-1 RBD, despite poor sequence homology of these two Ras-GTP interaction domains. However, the tetrameric “Ras-dimer” complex identified in this study was later shown to be a crystallographic artefact	130, 131
	First structure of a RasGEF, Sos1, solved in complex with H-Ras identifies a structural basis for Sos1-induced nucleotide release and Ras activation	132
1999	Sprouty is identified in a genetic screen as an inhibitor of *Drosophila* EGFR and Ras signaling	133
	N-Ras and H-Ras but not K-Ras traffick to the plasma membrane via the endomembrane, a process that requires a second signal in addition to the CAAX	134, 135
	Ras transforms primary human cells in cooperation with the catalytic subunit of telomerase (hTERT), SV40 large T Ag-mediated inactivation of Rb and p53 and with SV40 small t-mediated inactivation of PP2A	136
	Continuous expression of mutant NRAS is required for maintenance of melanomas	137
2000	*HRAS* is dispensable for mouse development, but its loss reduces susceptibility to DMBA/TPA carcinogen-induced oncogenesis; *KRAS* mutations occur instead	138
	Structure of activated H-Ras in complex with the p110 gamma catalytic subunit of PI3K shows both similarities and differences compared to other Ras-effector complexes	139
2001	Somatic activation of endogenous mutant *KRAS* induces lung tumor development	140
	The Ras effector RIN1 is also a GEF for Rab5	141
	WT *KRAS* can inhibit mutant *KRAS*-induced lung tumor formation in mice	142
2002	Nore1 (RASSF5) interacts with MST1 to promote Ras-induced apoptosis	143
	Ras can signal from endomembrane locations	144
	BRAF mutations found in melanoma and colon cancers in nonoverlapping occurrence	145

	with *RAS* mutations	
	The RacGEF Tiam1 is identified as a Ras effector and is required for *HRAS*-induced skin tumor formation in mice	146, 147
	The RalGEF effector pathway is important for Ras-mediated transformation of human cells	148
	shRNA-mediated suppression of mutant *KRAS* impairs tumorigenic growth of a pancreatic cancer cell line	149
	Yeast two-hybrid screen identifies putative small molecule inhibitors of the Ras/Raf interaction	150
2003	Structure of Ras/SOS complex suggests Ras-GTP-mediated positive feedback on Sos1 RasGEF activity	151
	Calcium activates Ras on Golgi via the RasGEF RasGRP1 and inactivates it on the plasma membrane via the RasGAP CAPRI	152
	Loss-of-function mutations in RASA1 (p120 RasGAP) are found widely in the autosomal dominant disorder capillary malformation-arteriovenous malformation (CM-AVM)	153
2004	IMP E3 ligase identified as a Ras effector that downregulates the KSR scaffold to modulate Raf activation of MEK	154
	RASAL is a calcium-sensing RasGAP	155
	Endogenous mutant *KRAS* expression induces proliferation rather than senescence	156
	PIK3CA mutations are common in human cancers	157
	Galectin-1 is a chaperone for H-Ras and has a farnesyl-binding pocket similar to the geranylgeranyl-binding pocket of RhoGDI for Cdc42	158
	H-Ras-induced IL-8 gene expression is required for stromal support of tumor angiogenesis and growth	159
	The Ras effector PLCε is required for *HRAS*-induced skin tumorigenesis	160
2005	Integration of mouse and human data identifies a gene expression signature of mutant *KRAS* in human lung cancer	161
	The Ras effector and RalGEF, RalGDS, is required for *HRAS*-induced skin tumorigenesis	162
	RAS transcription is regulated by the *let-7* family of microRNAs	163
	Palmitoylated H-Ras and N-Ras undergo an acylation-deacylation cycle that dictates their membrane distributions	164, 165
	Endogenous *KRAS* activation and p53 mutation cooperate to promote pancreatic cancer progression	166
	RalA and RalB serve distinct and complementary roles in pancreatic tumor growth	167
	Ras induces an EphA2 receptor tyrosine kinase negative feedback loop	168
	An RNAi library screen identifies the homeobox protein PITX1 as a suppressor of Ras and growth transformation due to upregulation of the RasGAP RASAL1	169
	Endogenous *KRAS* activation causes expression of senescence markers in vivo in premalignant lung and pancreatic tumors	170
	Germline activating *HRAS* mutations are found in patients with Costello syndrome	171
	Ras has differential effector requirements for tumor initiation versus progression	172
	Structure of H-Ras in complex with the RA domain of PLC epsilon is determined	173
2006	Protein kinase C phosphorylation of K-Ras4B causes mitochondrial localization and apoptosis	174
	Germline activating *KRAS* mutations are found in patients with cardio-facio-cutaneous (CFC) and Noonan syndromes	175-177
	Ubiquitination of H-Ras promotes its subcellular localization to endosomes	178
	Germline activating mutations in MEK1 and MEK2 are found in CFC	179
	Germline activating BRAF mutations are found in CFC	176, 179
	RalB activation of Sec5 and TBK1 is required for tumor cell survival	180
	Genome-wide sequencing establishes *KRAS* as the most frequently mutated oncogene in colon cancer	181
2007	Germline activating mutations in *SOS1* are found in Noonan syndrome	182, 183
	Chronic pancreatitis facilitates mutant *KRAS*-induced pancreatic tumorigenesis in mice	184
	Ras binding to p110alpha is required for *RAS*-induced tumorigenesis in mice	185

	PP2A phosphosphatase dephosphorylates RalA and inactivates its transforming activity	186
	Germline activating mutations in Raf-1 are found in Noonan and LEOPARD syndromes	187, 188
2008	Activated *KRAS* but not *NRAS* stimulates proliferation of colonic epithelium	189
	Genome-wide sequencing establishes *KRAS* as the most frequently mutated oncogene in pancreatic cancer	190
	Untransformed mammary cells resident in the lung can be induced to form tumors there upon delayed expression of ectopic mutant *KRAS* and *MYC*	191
	KRAS regulatory elements and role for KRAS4A in mouse model of lung cancer	192
	Concurrent pharmacologic inhibition of MEK and PI3K is required to block the growth of lung tumors induced by mutant K-Ras	193
2009	Synthetic lethal gene partners of mutant *KRAS* are identified in human tumors; neither mutation nor overexpression is required	194-196
	KRAS-/TP53-driven mouse model of pancreatic cancer displays same desmoplastic nature and poor vascularity of the human disease, and the same poor response to gemcitabine	197
	Lung and pancreatic tumor cell lines dependent on *KRAS* for viability have a well-differentiated epithelial phenotype	198
	A mitochondrial function of STAT3 is required for Ras-mediated transformation	199
	Genetic ablation of Raf-1 impairs mutant *HRAS*-driven skin carcinoma formation	200
	Chronic inflammation can alter the fate of differentiated pancreatic endocrine cells and sensitize them to mutant *KRAS*-initiated oncogenesis	201
2010	Ras cooperates with Aurora-A via RalA	202
	NRAS germline mutations identified in Noonan syndrome	203
	Raf inhibitors paradoxically activate ERK in *RAS*- but not *BRAF*-mutant tumor cells	204-206

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Table 2. Evolutionary conservation of Ras superfamily[a]

Species	Ras	Rho	Rab	Arf	Ran	Other	Total	Reference
Human	36	20	61/64	27/29	1	9	154	1-5
D. melanogaster	19	9	32	28	2	0	90	6
C. elegans	11	7	25	12	1	0	56	7
S. cerevisiae	4	6	11	7	2	0	30	6
A. thaliana	0	11	57	21	4	0	93	8
O. sativa	0	17	47	43	4	0	111	6

[a]Some compilations differ in number due to different sequence criteria for inclusion in a particular family.

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Table 3. Genetic syndromes with mutation of Ras signaling components

Syndrome	Protein[a]	Reference
Autoimmune lymphoproliferative (ALPS)	N-Ras GTPase (gof)*	1
Capillary malformation-arteriovenous malformation (CM-AVM)	p120 RasGAP (lof)	2
Cardio-facio-cutaneous (CFC)	K-Ras GTPase (gof)	3
	B-Raf serine/threonine kinase (gof)	3, 4
	MEK1 dual specificity kinase (gof)	4
	MEK2 dual specificity kinase (gof)	4
Costello (CS)	H-Ras GTPase (gof)	5
Hereditary gingival fibromatosis 1 (HGF)	Sos1 RasGEF (gof)	6
Legius (neurofibromatosis 1-like)	SPRED1 scaffold protein (lof)	7
LEOPARD (LS)	SHP2 phosphatase (lof)	8, 9
	c-Raf-1 serine/threonine kinase	10
Neurofibromatosis 1 (NF1)	Neurofibromin RasGAP (lof)	11-13
Noonan (NS)	SHP2 phosphatase (gof)	14
	Sos1 RasGEF (gof)	15, 16
	K-Ras GTPase (gof)	17
	N-Ras GTPase (gof)	18
	c-Raf-1 serine/threonine kinase (gof)	10, 19
Noonan-like syndrome with loose anagen hair	Shoc2 scaffold protein (gof)	20

*Gain-of-function (gof) ; loss-of-function (lof)

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