

Review

The Ras-association domain family (RASSF) members and their role in human tumourigenesis

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Received 16 April 2007; received in revised form 26 June 2007; accepted 26 June 2007

Available online 4 July 2007

Abstract

Ras proteins play a direct causal role in human cancer with activating mutations in Ras occurring in ~30% of tumours. Ras effectors also contribute to cancer, as mutations occur in Ras effectors, notably B-Raf and PI3-K, and drugs blocking elements of these pathways are in clinical development. In 2000, a new Ras effector was identified, Ras-association domain family 1 (*RASSF1*), and expression of the *RASSF1A* isoform of this gene is silenced in tumours by methylation of its promoter. Since methylation is reversible and demethylating agents are currently being used in clinical trials, detection of *RASSF1A* silencing by promoter hypermethylation has potential clinical uses in cancer diagnosis, prognosis and treatment. *RASSF1A* belongs to a new family of Ras effectors, of which there are currently 8 members (*RASSF1*–8). *RASSF1*–6 each contain a variable N-terminal segment followed by a Ras-association (RA) domain of the Ral-GDS/AF6 type, and a specialised coiled-coil structure known as a SARAH domain extending to the C-terminus. *RASSF7*–8 contain an N-terminal RA domain and a variable C-terminus. Members of the *RASSF* family are thought to function as tumour suppressors by regulating the cell cycle and apoptosis. This review will summarise our current knowledge of each member of the *RASSF* family and in particular what role they play in tumourigenesis, with a special focus on *RASSF1A*, whose promoter methylation is one of the most frequent alterations found in human tumours.

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Keywords: *RASSF*; Tumour suppressor; Methylation; Cell cycle; Apoptosis; Microtubule

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Abbreviations: AP-1, activation protein 1; APC, anaphase-promoting complex; ATM, ataxia telangiectasia mutant; C1, protein kinase C conserved region; CIMP, CpG island methylator phenotype; CRC, colorectal cancer; DAG, diacylglycerol; HCC, hepatocellular carcinoma; Hpo, hippo; EBV, human herpes virus; EGF, epidermal growth factor; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus virus; JNK, c-Jun-NH2-kinase; LATS1, Lats/Warts serine/threonine kinase; LOH, loss of heterozygosity; MAP-1, modulator of apoptosis-1; MAPK, mitogen-activated protein kinase; MEF, mouse embryonic fibroblast; MEK, MAPK/ERK kinase; MSP, methylation-specific PCR; MST1, mammalian sterile 20-like kinase-1; NORE1, novel Ras effector 1; NSCLC, non-small cell lung cancer; PI3-K, phosphatidylinositol 3-kinase; PMCA4b, plasma membrane calmodulin-dependent calcium ATPase 4b; RA, RalGDS/AF6 Ras association; RAPL, regulator of adhesion and polarization enriched in lymphocytes; *RASSF*, Ras-association domain family; RBP1, *RASSF1A*-binding protein 1; RTK, receptor tyrosine kinase; RSV, respiratory syncytial virus; SAPK/JNK, stress-activated protein kinase/c-Jun N-terminal kinase; SARAH, Sav/*RASSF*/Hpo; Sav, Salvador; SCLC, small cell lung cancer; SV40, simian virus 40; TCR, T-cell receptor; TNF α , tumour necrosis factor alpha; TRAIL, TNF α -related apoptosis-inducing ligand; TSG, tumour suppressor gene

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1. RASSF1

1.1. Introduction to Ras and its effectors

The Ras GTPases are a superfamily of molecular switches that regulate a diverse range of functions, including cell proliferation, differentiation, motility and apoptosis in response to extracellular signals. The Ras proteins exist in two states: a GTP-bound active state and a GDP-bound inactive state. In its GTP-bound state, Ras is able to interact with its downstream effectors, and mediate some component of Ras' cellular actions

through complex signal transduction cascades (Fig. 1). Ras effectors are proteins that specifically bind the GTP-bound form of Ras via the Ras protein effector domain. Two of the best-studied Ras effectors are Raf, a serine-threonine kinase that controls the MEK-ERK pathway that activates cellular proliferation [1], and phosphatidylinositol 3-kinase (PI3-K), whose activity is required for activation of the protein kinase B, Akt, which inhibits apoptosis induced by members of the Bcl-family (such as BAD) [2]; see Fig. 1. Raf and PI3-K interact with Ras through their Ras-binding domains (termed RBD and PI3K_rbd, respectively). There is another group of Ras effectors

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