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Review

RASSF tumor suppressor gene family: Biological functions and regulation

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ABSTRACT

Genetic changes through allelic loss and nucleic acid or protein modifications are the main contributors to loss of function of tumor suppressor proteins. In particular, epigenetic silencing of genes by promoter hypermethylation is associated with increased tumor severity and poor survival. The RASSF (Ras association domain family) family of proteins consists of 10 members, many of which are tumor suppressor proteins that undergo loss of expression through promoter methylation in numerous types of cancers such as leukemia, melanoma, breast, prostate, neck, lung, brain, colorectal and kidney cancers. In addition to their tumor suppressor function, RASSF proteins act as scaffolding agents in microtubule stability, regulate mitotic cell division, modulate apoptosis, control cell migration and cell adhesion, and modulate NFκB activity and the duration of inflammation. The ubiquitous functions of these proteins highlight their importance in numerous physiological pathways. In this review, we will focus on the biological roles of the RASSF family members and their regulation.

1. Introduction

The RASSF family of proteins is comprised of ten members each with multiple splice variants, with the exception of RASSF9 and 10 [1,2]. These proteins were named due to the presence of a Ras association (RA) domain in their N-terminus or C-terminus. The RA domain potentially interacts with the Ras GTPase family of proteins [2] that control a number of cellular processes including membrane trafficking, apoptosis, and proliferation [1–5]. Direct association with K-Ras has been only observed for RASSF2, 4, 5A, 6 and 9 [6–8]. In addition, RASSF proteins have several other functional domains that modulate associations with other proteins (see Table 1 for the list of RASSF interacting partners). These include a Salvador-RASSF-Hippo (SARAH) domain involved in several protein–protein interactions and for homo- and heterodimerization of RASSF isoforms. RASSFs can associate via the SARAH domain with downstream kinases such as mammalian sterile 20-like kinases (MST1 and MST2 [mammalian Hippo] also known as or STK4 and STK3 respectively) and the mammalian orthologue of the tumor suppressor Salvador, SAV1 in order to promote apoptosis [9]. These various structural domains allow for associations with numerous molecules and determine RASSF proteins' involvement in several biological pathways in order to carry out tumor suppressor functions.

An ATM phosphorylation site is present on some RASSF proteins (RASSF1A and RASSF1C), and RASSF1A and RASSF1C also contain an N-terminal protein kinase C conserved region 1 (C1) domain that co-localizes with microtubules [1]. The C1 domain has also been demonstrated to allow for the association of RASSF1A with death receptor complexes, such as TNF-R1 and TRAIL [10]. The ATM phosphorylation site has been found to be phosphorylated in several RASSF proteins upon DNA damage/repair [11] (Reviewed in [12]).

2. The diverse nature and biological function of RASSF proteins

2.1. RASSF1A

In 2000 Dammann et al. cloned a gene that was mapped to the 3p21.3 region, whose genomic instability was frequently described in lung cancer. The gene was named RASSF1 as it contains Ras-association domain [13]. RASSF1 has eight transcripts (A–H),

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Table 1
Summary of currently known biological information of the RASSF family of proteins.

RASSF isoform	Chromosome/MW	Biological functions	Interacting proteins	Mice knockout
1A	3p21 39.2 kDa	Regulates: • MST kinase-dependent apoptosis [42,44,109] • Death-receptor dependent apoptosis [40,41,175] • Microtubule formation and stabilization [14,176] • Cell cycle [35,165,176] • Mitosis [25] • Stability of mitotic cyclins and the timing of mitotic progression by inhibiting APC-Cdc20 [27,28,31] • Cardiac hypertrophy [49]Modulates NFκB activity [46,50] Inhibits β-catenin accumulation [5] Involved in DNA repair [12] Stabilizes p53 [36] and p73 [11,45] Protects from inflammation-induced injury [46]	MST1 [42–44,50,168,177] MST2 [45,177] MOAP1 [40,41,175] 14–3-3 [109] RABP1 [25] Cdc20 [28] Aurora A/B [29,165,169] MAP1B, MAP1S [14] MDM2 [36] Ran [176] Rap1A [178] RASS1A, RASSF5A [81] p120 E4F [33] Chk1 [170] DDB1[172] H-Ras [179] ATM [11] Skp2 [166]	Yes [47,48]. Spontaneous tumorigenesis [47]; susceptible to DSS-induced colitis [46]
1C	3p21 31.2 kDa	Stimulates cell growth, may promote metastasis and survival of cancer cells [16] Promotes cell migration, attenuates apoptosis [17] Silencing resulted in a decrease in osteosarcoma and lung cancer cell proliferation [16,18] Inhibits β-catenin degradation [5] Activates SAPK/JNK signaling pathway [54] Down-regulated by CAS/CS1L [180]	MST1 [43,177] MST2 [177] IGFBP5 [18] TFPI-2 [56] βTrCP [5] DAXX [54,55]	No
2	20p13 37.8 kDa	Inhibits cell growth, arrests cell cycle [58,62] Involved in actin cytoskeleton organization [148] Induces apoptosis [58,62,145] Suppresses transcriptional activity of NFκB [181] Inhibits MST2 activity [93]	K-Ras [62] PAR4 [64] MST1 [66,177] MST2 [177]	Yes [67] growth retardation, systematic haematopoietic anomalies, defects in osteoclast and osteoblast differentiation
3	12q14.1 28.6 kDa	Regulates apoptosis and cell cycle via p53 stabilization, possibly involved in DNA repair [69,72]	MOAP1, Mdm2 [72] MST1, MST2 [72,177]	Not available
4	10q11.21 36.7 kDa	Required for apoptosis and growth inhibition [8] Inhibits MST2 activity [93] Modulates the MAP kinase signal downstream of the Ras signal [77]	K-Ras [8] ST1, MST2 [177] MST1 [75]	Not available
5A (Nore1A)	1q32 47.1 kDa	Suppresses tumour growth via apoptosis induction or cell cycle delay [7,82] Regulates microtubule formation [182] Induces degradation of HIPK1 oncoprotein [183] Required for the TNFα mediated apoptosis and full activation of MST1 [80]	Ras, Carma1 [182,184] MST1 [43,177] MST2 [177] tubulin, Aurora A [182] Mdm2 [183] Itch [185]	Yes [80] resistant to TNFα-induced apoptosis, fail to activate Mst1 in vivo
5C (Nore1B, RAPL)	1q32 30.4 kDa	Regulates lymphocyte adhesion, T cell migration, T cell receptor regulation [84,86,186] Controls the directional migration of vascular endothelial cells [6]	Ras, Carma1 [184] Rap1, Rap2, MST1 [6,84,86,186]	Yes [86] impaired lymphocyte trafficking and lymphoid organ abnormalities
6	4q13 43.4 kDa	Regulates apoptosis [87,93,94] Regulates cell cycle [94] Suppresses NFκB pathway [87,187] Stabilizes p53 [94] Potentially plays a role in the inflammatory response to respiratory syncytial virus-induced bronchiolitis [87,88] Possible obesity regulator [149]	MST2 [93] K-Ras, MOAP-1 [87] MST1, MST2 [177] MDM2 [94]	Not available
7	11p15 39.9 kDa	Regulates cell growth and mitosis [102,103] Has anti apoptotic activity [104]	N-Ras [104] MST1, MST2 [177] CHMP1B, DISC1 [3]	Not available
8	12p12 48.3 kDa	Inhibits cell growth, regulates Wnt and NFκB pathways, regulates cell–cell adhesion [4]	14-3-3γ, FRMD4A, PSMD4 [3]	Not available
9	12q21.31 50.0 kDa	Possible role in endosome recycling [110] Essential for epidermal homeostasis [112]	Peptidylglycine α-amidating monooxygenase [111] N-, K- and R-Ras [188] (contradicts to [177])	Yes [112] alopecia, shorter life expectancy and growth retardation
10	11p15 56.9 kDa	Suppress tumor cell growth [189,190] Induces apoptosis, inhibits Wnt/β-catenin pathway [116]	None described	Not available

The table summarizes current knowledge of the RASSFs with their chromosomal location, protein molecular weights (MW), biological functions, association partners and genetic knockouts.

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