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Review

Embryonal Fyn-associated substrate (EFS) and CASS4: The lesser-known CAS protein family members

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ABSTRACT

The CAS (Crk-associated substrate) adaptor protein family consists of four members: CASS1/BCAR1/p130Cas, CASS2/NEDD9/HEF1/Cas-L, CASS3/EFS/Sin and CASS4/HEPL. While CAS proteins lack enzymatic activity, they contain specific recognition and binding sites for assembly of larger signaling complexes that are essential for cell proliferation, survival, migration, and other processes. All family members are intermediates in integrin-dependent signaling pathways mediated at focal adhesions, and associate with FAK and SRC family kinases to activate downstream effectors regulating the actin cytoskeleton. Most studies of CAS proteins to date have been focused on the first two members, BCAR1 and NEDD9, with altered expression of these proteins now appreciated as influencing disease development and prognosis for cancer and other serious pathological conditions. For these family members, additional mechanisms of action have been defined in receptor tyrosine kinase (RTK) signaling, estrogen receptor signaling or cell cycle progression, involving discrete partner proteins such as SHC, NSP proteins, or AURKA. By contrast, EFS and CASS4 have been less studied, although structure–function analyses indicate they conserve many elements with the better-known family members. Intriguingly, a number of recent studies have implicated these proteins in immune system function, and the pathogenesis of developmental disorders, autoimmune disorders including Crohn's disease, Alzheimer's disease, cancer and other diseases. In this review, we summarize the current understanding of EFS and CASS4 protein function in the context of the larger CAS family group.

Abbreviations: 5-HT, 5-hydroxytryptamine, serotonin; A549, non-small cell lung cancer cell line; AD, Alzheimer's disease; ADPKD, autosomal dominant polycystic kidney disease; Aire, autoimmune regulator; AP-1, activator protein 1; APP, amyloid precursor protein; AREB6, ZEB1; ATF, activating transcription factor; *AURKA*, aurora A kinase; BCAR1, breast cancer anti-estrogen resistance 1; BE1, non-small cell lung cancer cell line; BRAF, v-Raf murine sarcoma viral oncogene homologue B; c-CRK, cellular CRK; c-RAF, cellular RAF; c-SRC, cellular SRC kinase; C/EBPα, CCAAT/enhancer-binding protein alpha; C20orf32, chromosome 20 open read frame 32; C3G, RAPGEF1, CRK SH3-binding GNRP; CAKb, PTK2B, cell adhesion kinase; CAS, Crk-associated substrate; Cas-L, NEDD9, Crk-associated substrate, lymphocyte type; CASS3, Crk-associated substrate 3; CASS4, Crk-associated substrate 4; *CBLN4*, cerebellin-4; CCAAT, DNA sequence; CD4/8, cluster of differentiation 4/8; CDCP1, CUB domain-containing protein 1; CGS, Canadian Consortium for Genetic Studies; CHOP-10, C/EBP homologous protein 10; CHS, *Chediak–Higashi syndrome*; CHS1, Chediak–Higashi syndrome protein 1; CIZ, Cas-interacting zinc finger protein; CRK, v-Crk avian sarcoma virus CT10 oncogene homologue; Crk-L, Crk-like protein; *CSTF1*, cleavage stimulation factor subunit 1; DAG, diacylglycerol; DCAS, Drosophila Crk-associated substrate; DECODE, DECipherment Of DNA Elements; *ECRG4*, esophageal cancer-related gene 4 protein, Augurin; EFS, embryonal Fyn-associated substrate; EFS1, embryonal Fyn-associated substrate 1; EFS2, embryonal Fyn-associated substrate 2; ERK, extracellular-signal-regulated kinase; FAK, focal adhesion kinase; *FLNC*, filamin-C; FRNK, FAK-related non-kinase; GAS, group A streptococci; GATA-3, transcription factor binding GATA DNA sequence; GEF, guanine nucleotide exchange factor; GEP, gene expression profile; GMS, Gene Modifier Study; GRChB38p2, Genome Reference Consortium Human Build 38 patch release 2; GWAS, genome-wide association study; H1299, non-small cell lung cancer cell line; HEF1, NEDD9, human enhancer of filamentation 1; HEFL, HEF like protein; HEFS, human EFS; HEPL, HEF1-EFS-p130Cas-like protein; HOP-62, lung adenocarcinoma cell line; IGAP, International Genomics of Alzheimer's Disease Project; IL-2, interleukin 2; IP3, inositol three phosphate; *KCNMA1*, potassium large conductance calcium-activated channel, subfamily M, alpha member 1; KGF, keratinocyte growth factor; KODA-PC, 9-keto-12-oxo-10-dodecenoic acid ester of 2-lyso-phosphocholine; LCR-F1, Locus Control Region-Factor 1; LNCaP, prostate cancer cell line; LTE, non-small cell lung cancer cell line; LYST, lysosomal trafficking regulator; MAX1, Myc-associated factor X; *MC3R*, melanocortin receptor 3; MHC I/II, major histocompatibility complexes I/II; MSI, microsatellite instability; MSS, microsatellite stable; mTEC, medullar thymus epithelial cells; Nck, non-catalytic region of tyrosine kinase adaptor protein; NEDD9, neural precursor cell expressed, developmentally down-regulated 9; NF-κβ, nuclear factor kappa-light-chain-enhancer of activated B cells; NF-κβ1, nuclear factor NF-kappa-B p105 subunit; NFAT, nuclear factor of activated T-cells; NFE2-L1, nuclear factor, erythroid 2-like1; NSCLC, non-small cell lung cancer; NSP, novel SH2 containing protein; Oct-6, octamer transcription factor 6; OR, odds ratio; PBMC, peripheral blood mononuclear cell; PC, prostate cancer; *PDLIM4*, PDZ and LIM domain 4; PIP2, phosphoinositide diphosphate; *PITX2*, pituitary homeobox 2; PLC-γ, phosphoinositide phospholipase C gamma; POU, Pit-Oct-Unc; POU3F1, POU domain, class 3, transcription factor 1, aka Oct-6; PTK2B, protein tyrosine kinase 2B; PTP-PEST, protein tyrosine phosphatase containing C-terminal PEST motif; PTP1B, protein tyrosine phosphatase 1B; PTPase, protein tyrosine phosphatase; Pyk2, PTK2B, protein tyrosine (Y) kinase; RAFTK, PTK2B, related adhesion focal tyrosine kinase; RAP1, Ras-proximate-1 or Ras-related protein 1; RAPGEF1, Rap guanine nucleotide exchange factor 1; RHD, rheumatoid heart disease; RPTPα, receptor–protein–tyrosine phosphatase alfa; RTK, receptor tyrosine kinase; SH2, Src homology 2 domain; SH3, Src homology 3 domain; SHC, Src homology 2 domain containing; Sin, Src interacting or signal integrating protein; SNP, Single nucleotide polymorphism; TCR, T-cell receptor; TEC, thymus epithelial cell; TNM, tumor, nodules, metastases scale; Trask, CDCP1, transmembrane and associated with src kinases; TSS, Twins & Sibs Study; UCSC, University of California Santa Cruz; UM, uveal melanoma; v-RAF, virus-induced rapidly accelerated fibrosarcoma; ZEB1, zinc finger E-box binding homeobox 1.

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