RAF1 (v-raf-1 murine leukemia viral oncogene homolog 1)

Max Cayo, David Yu Greenblatt, Muthusamy Kunnimalaiyaan, Herbert Chen

Endocrine Cancer Disease Group, University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, H4/750 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792, USA

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Identity

Hugo: RAF1
Other names: CRAF; Raf-1; c-Raf
Location: 3p25

DNA/RNA

Note: History and Nomenclature:
c-Raf-1 was the first successfully cloned functional human homolog of the v-Raf gene, and thus the gene product of c-Raf-1 has historically been referred to in the literature simply as Raf-1. Subsequently, B-Raf and A-Raf-1 paralogues (BRAF, located in Xq13 and ARAF, located in Xp11) were discovered. A suitable nomenclature is as follows: A-RAF, B-RAF, and C-RAF for the functional human proteins and A-RAF, B-RAF, and C-RAF for the corresponding genes; a-raf, b-raf, and c-raf for the murine proteins and A-Raf, B-Raf, and C-Raf for the corresponding genes. Raf-1 (or RAF-1) is generally taken to mean C-RAF-1 but could apply to A-RAF-1 equally. Here, RAF-1 will be taken to mean C-RAF-1 (RAF-1 = C-RAF-1, etc.).

Description

C-RAF (RAF-1, C-RAF-1) encompasses 80,570 bp of DNA; 17 Exons.

Transcription

RAF-1 transcribed mRNA contains 3212-3216 nucleotides.

Protein

Description

The RAF proteins share three conserved domains: two (CR1 and CR2) in the N terminus and a third (CR3-encoding for the serine/threonine kinase domain) in the C terminus. The RAF proteins exhibit complex regulation involving numerous phosphorylation sites throughout the proteins. Despite constitutional similarity, the Raf isoforms have been shown to carry out non-redundant functions, implying that they are distinct.

RAF-1 (C-RAF-1): 72-74 kDa.
Note: A-RAF: about 68 kDa.
Note: B-RAF (which undergoes alternate splicing): ranges from 75 to 100 kDa.

Expression

C-RAF (RAF-1) and A-RAF mRNA is expressed ubiquitously. A-RAF mRNA is highly expressed in urogenital organs. B-RAF is expressed in a wide range of tissues, but most substantially in neuronal tissues.

Localisation

Cytosolic.

Function

RAF proteins are part of the conserved MAPK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase) signaling cascade between the cell surface and the nucleus. RAF is regulated by the upstream RAS family of small G proteins. RAS is predominantly located on the inner leaflet of the plasma membrane and is functionally activated by GTP-binding. Binding of various extracellular ligands such as growth factors and hormones activates RAS and subsequently RAF proteins. RAS binds directly to the N-terminal regulatory domain or RAF (the RAS binding domain (RBD)). RAS interacts secondarily with the cysteine-rich domain (CRD) on CR1 of RAF. RAS-RAF binding can be affected by 14-3-3 proteins and other scaffold/adaptor proteins kinase suppressor of
RAS (KSR), the multidomain protein connector-enhancer of KSR (CNK), and the leucine-rich-repeat protein suppressor of RAS mutations-8 (SUR8), which cause formation of various homo- and heterodimers and subsequently affect signal transduction. RAF activation leads to activation of the protein kinases MEK1 and MEK2 and subsequently the MAPK proteins ERK1 and ERK2. The downstream effects of MEK1/2-ERK1/2 activation are varied, complex, and depend on the cellular context. Resultant effects include activation of transcription factors involved in tumorigenesis, cell growth, survival, differentiation, metabolism, and cytoskeletal rearrangements. RAF-1 (C-RAF-1), A-RAF, and B-RAF are all capable of activating the MEK1/2-ERK1/2 signaling pathway.

RAF-1 is capable of activating the NF-kB transcription factor through an unknown mechanism that does not seem to involve direct phosphorylation of NF-kB and is independent of MEK1/2-ERK1/2 signaling. RAF-1 is known to directly affect cell survival through phosphorylation of BAG1 (BCL2-associated athanogene-1), an anti-apoptotic protein that binds to BCL2, a second anti-apoptotic factor, also the prototype for a family of mammalian genes involved in mitochondrial outer membrane permeability (MOMP), thus restoring its function. BCL2 also targets RAF-1 to the mitochondrial membrane, where it is able to more readily phosphorylate substrates. The RAF-1/BAG1/BCL2 interaction allows RAF-1 to phosphorylate the pro-apoptotic protein BAD at the mitochondrial membrane, promoting cell survival. Other known substrates of RAF-1 include the phosphatase CDC25C, the apoptosis signal-regulating kinase-1 (ASK1), and the tumor-suppressor protein retinoblastoma (Rb).

RAF-1 is tightly regulated by the AKT/PKB pathway through phosphorylation at S259.

**Mutations**

**Somatic**

It has been widely established that RAF-1 over activity, typically via ras-activating mutations, is central to tumorigenesis and cell proliferation in numerous cancers (about 30% of all human cancers). However, it has come to the fore that oncogenesis may be due to ras/RAF-1 dysregulation (either increased or decreased expression) rather than increases in ras/RAF-1 activity exclusively.

**Implicated in**

**Medullary Thyroid Cancer (MTC)**

**Disease**

A neuroendocrine tumor derived from parafollicular C cells of the thyroid gland, MTC is the third most common form of thyroid cancer, accounting for 3-5% of all cases. MTC cells secrete hormones and tumor markers such as calcitonin, chromogranin A (CgA), and carciinoembryonic antigen (CEA). Symptoms are related to either direct invasion or metastasis (neck mass, dyspnea, dysphagia, voice changes, pain) or tumor secretion of bioactive amines and peptides (diarrhea, flushing).

**Prognosis**

Currently, surgery is the only potentially curative therapy for patients with MTC. The recommended operation is total thyroidectomy with lymph node dissection. However, 50% of patients treated with surgery suffer persistent or recurrent disease.

**Oncogenesis**

20% of patients with medullary thyroid cancer have an autosomal dominant inherited form of the disease, which is the result of well-characterized point mutations in the RET proto-oncogene. RAF-1 is conserved but not expressed at baseline in MTC. Preclinical studies have shown that activation of RAF-1 in MTC (TT) cells by means of RAF-1 gene transfection or RAF-1 activating small molecules (ZM336372) results in tumor cell growth inhibition in vitro and in vivo.

**Carcinoid Tumors**

**Disease**

Carcinoids are tumors that arise from the diffuse neuroendocrine cell system of the gut, lungs, and other organs. The incidence is 1-5 per 100,000 individuals. Carcinoids frequently metastasize to the liver and are the second most common source of isolated liver metastases. Carcinoids secrete various bioactive hormones such as 5-HT (5-hydroxy tryptophan, also known as serotonin) and chromogranin A.

**Prognosis**

Patients with hepatic metastases suffer debilitating symptoms such as abdominal pain, flushing, bronchoconstriction, and diarrhea. Palliative treatment for these hormone-induced symptoms includes somatostatin analogs (such as octeotride). Conventional anticancer treatments such as chemotherapy and external beam radiation are largely ineffective for carcinoid tumors.

**Oncogenesis**

RAF-1 activation is detrimental to tumorigenesis in carcinoid cells. Marked reduction in neuroendocrine phenotypic markers such as human achaete-scute complex like-1 (ASCL-1) and bioactive hormones 5-HT, chromogranin A, and synaptophysin has been noted upon RAF-1 activation using an estrogen-inducible RAF-1 construct in human GI (BON) and pulmonary carcinoid cell lines (NCI-H727).

Treatment of GI carcinoid cells with RAF-1 activator ZM336372 led to a decrease in bioactive hormone levels, a suppression of cellular proliferation,
increase in cell cycle inhibitors p21 and p18, as well as a decrease in the neuroendocrine phenotypic marker ASCL-1. ZM336372 treatments also led to progressive phosphorylation (activation) of MEK1/2, ERK1/2, and RAF-1.

**Small Cell Lung Cancer (SCLC)**

**Disease**

SCLC tends to present with metastatic and regional spread. Carcinoids rarely metastasize, arise from major bronchi, and express neuron-specific enolase, chromogranin, and synaptophysin. Neuroendocrine carcinoids or atypical carcinoids have a more aggressive course.

**Oncogenesis**

Human small-cell lung cancer (SCLC) cell lines rarely harbor ras-activating mutations. In one cell line of SCLC, DMS53, it was shown that by RAF-1 induction using an estrogen-inducible RAF-1 construct SCLC cells underwent differentiation and G1-specific growth arrest in conjunction with MEK/ERK1/2 pathway activation.

**Non-Small Cell Lung Cancer (NSCLC)**

**Disease**

Adenocarcinoma is the most common type of NSCLC accounting for about 40% of cases. Lesions are generally located peripherally and develop systemic metastases despite small primary tumors. 25% of NSCLC are squamous cell carcinomas which often remain localized.

**Oncogenesis**

RAF-1 is over-expressed due to oncogenic ras mutations in about 35% of NSCLC. The majority of NSCLC exhibits EGFR overexpression leading to upregulation of RAF-1 activity. NSCLC has been shown to be mediated by a TGF-α/EGFR-mediated autocrine loop activated by signaling involving RAF-1 and PI3K-Akt.

**Pheochromocytoma**

**Disease**

Pheochromocytomas are neuroectodermal in origin and arise from the chromaffin cells of the adrenal medulla. 10% of tumors are bilateral. Typical symptoms such as hypertension, headaches, diaphoresis, palpitations, diarrhea, and skin rashes, are related to tumor production of catecholamines, especially in patients with metastases. Pheochromocytoma is potentially fatal, but relatively uncommon (2-8 cases per million people annually). Curative therapy is surgery, usually accomplished by laparoscopic adrenalectomy.

**Oncogenesis**

Activation of MEK1/2-ERK1/2 is necessary for differentiation of pheochromocytoma (PC12) cells and leads to decreased cell proliferation. RAF-1 activation in pheochromocytoma cells using ZM336372 led to cellular differentiation, growth arrest, and a decrease in the neuroendocrine marker chromogranin A.

**Non-Neuroendocrine Cancers with ras-activating Mutations**

**Oncogenesis**

About 30% of all human cancers express ras-activating mutations. More than 85% of pancreatic adenocarcinomas and 50% of colonic adenocarcinomas harbor K-ras mutations. K-ras is an upstream effector of RAF-1 in the RAF-1/MEK/ERK1/2 signaling pathway. Ras mutations have also been linked to tumorigenesis of cholangiocarcinoma, adenocarcinoma of the lung, squamous cell cancer, gastric adenocarcinoma, small bowel adenocarcinoma, and malignant melanoma.

**Colorectal Cancer**

**Oncogenesis**

RAF-1 is over-activated due to oncogenic ras mutations in about 50% of colon cancers. These mutations are associated with poor prognosis, and are necessary for maintenance of the malignant phenotype. RAF-1 inhibition in response to interaction with RAF kinase inhibitor protein (RKIP) (up-regulated in conjunction with the nuclear factor kappa B signaling pathway) has been linked with overall and disease-free survival in patients with colorectal cancers. RKIP has been identified as potentially useful for identifying early-stage CRC patients at risk for relapse.

**Pancreatic Carcinoma**

**Oncogenesis**

RAF-1 is overactivated due to oncogenic ras mutations in about 90% of pancreatic carcinomas (Panc-1 and Mia-PaCa2). It has been shown that malignancy of these cells is reduced using k-ras RNAi. Pharmacological inhibition of the RAF/MEK/ERK pathway in pancreatic cancer cell lines (via MEK inhibition) results in reduction in cellular proliferation and an increase in cell cycle arrest.

**Hepatocellular Carcinoma (HCC)**

**Oncogenesis**

RAF-1 is over-activated in about 50% of biopsies while the RAF-1 protein is over-expressed in nearly 100% of all HCC’s. Angiogenesis and other functions essential to tumorigenesis in HCC have been reported to depend on the RAF/MEK/ERK signaling pathway. RAF-1 inhibitor Sorafenib has been reported (in-vitro and in-vivo) to inhibit RAF-1 activity, leading to decreased MEK/ERK activity, reduced cellular proliferation, and apoptosis in several HCC cell lines including HepG2 and PLC/PRF/S.
**Prostate Cancer**

Oncogenesis

RAF kinase inhibitor protein (RKIP) coding mRNAs have been observed to activate interferon-inducible 2',5'-oligoadenylate synthetases (OAS). OAS activity is characteristically increased (via these mRNAs) in prostate cancer cell lines PC3, LNCaP and DU145. RKIP expression is detectable in primary prostate cancer sections but not in metastases. This suggests RKIP's characterization as an anti-metastasis gene using the RAF/MEK/ERK signaling pathway is appropriate.

RAF-1 inhibition using systemically delivered novel cationic cardiolipin liposomes (NeoPhectin-AT) containing a small interfering RNA (siRNA) against RAF-1 causes tumor growth inhibition in a xenograft model of human prostate cancer.

RAF/MEK/ERK signaling pathway activation via a biologically active peptide called a prosaptide (TX14A) stimulates cell proliferation/survival, migration, and invasion in human prostate cancer cells. NSC 95397 and NSC 672121, cdc25 inhibitors, were shown to activate the RAF/MEK/ERK pathway in prostate cancer cells. RAF-1 activation in LNCaP prostate cancer cells using an estrogen-inducible construct led to growth inhibition.

**Breast Cancer**

Oncogenesis

Growth hormone releasing hormone (GHRH) has been shown to regulate breast cancer cell proliferation and differentiation. In MDA-231 breast cancer cells, exogenous GHRH stimulated dose-dependent proliferation. RAF-1 inhibition using the agent PD98059 caused prevention of MAPK phosphorylation by GHRH as well as reduced cellular proliferation. Proliferative effects of steroid hormone estradiol on MCF-7 breast cancer cells have been linked with increased expression of RAF-1, possibly due to direct activation of RAF-1 by estradiol. RAF kinase inhibitor protein (RKIP) is associated with metastasis suppression. RKIP expression is lost in lymph node metastases. This suggests RKIP is a metastasis inhibitor gene and that RAF-1 expression enables metastasis.

The PTK inhibitor AG 879 inhibits proliferation of human breast cancer cells through inhibition of MAP kinase activation through inhibition of expression of the RAF-1 gene. RAF-1 down-regulation is associated with paclitaxel drug resistance in human breast cancer cell line MCF-7/Adr.

**Renal Cell Carcinoma**

Oncogenesis

RAF-1 is overactivated in conjunction with loss of function of the VHL (von Hippel-Lindau) tumor-suppressor gene.

**Glioma**

Oncogenesis

RAF-1 inhibitor AAL881 inhibited growth of glioma cell xenografts.

**Cervical Cancer**

Oncogenesis

Low RAF-1 kinase activity is significantly associated with paclitaxel sensitivity in cervical cancers.

**Ovarian Cancer**

Oncogenesis

RAF-1 dysregulation is associated with poor prognosis and possibly carcinogenesis. RAF-1 inhibition using RNAi reduces cellular proliferatin and inhibits ovarian tumor cell growth in vitro and in vivo. Similar results were observed using antisense oligonucleotide (ASO) therapy (ISIS 5132 and ISIS 13650). RAF-1 inhibition by the Akt pathway sensitizes human ovarian cancer cells to the drug paclitaxel.

**Gastric Cancer**

Oncogenesis

RAF-1 gene amplification was detected in 4% of bladder cancer samples. Deletions at the RAF-1 locus were detected in 2.2% of these samples. Both amplifications and deletions were heavily correlated with high tumor grade (P < 0.00001), advanced stage (P < 0.0001), and poor survival (P < 0.05).

**Bladder Cancer**

Oncogenesis

RAF-1 gene amplification was detected in 1% of bladder cancer samples. Deletions at the RAF-1 locus were detected in 2.2% of these samples. Both amplifications and deletions were heavily correlated with high tumor grade (P < 0.00001), advanced stage (P < 0.0001), and poor survival (P < 0.05).

**Lymphoma**

Oncogenesis

RAF-1 is typically over-expressed in thymic lymphomas from TCR transgenic mice.

**References**


RAF1 (v-raf-1 murine leukemia viral oncogene homolog 1)  

Cayo M et al.


This article should be referenced as such: