

Oncogenic KRAS Mutations in Apoptosis and Autophagy Regulation

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Contributor: Anabela Ferreira, Flávia Pereira, Celso Reis, Maria José Oliveira, Maria João Sousa, Ana Preto

KRAS, one of the RAS protein family members, plays an important role in autophagy and apoptosis, through the regulation of several downstream effectors. In cancer cells, *KRAS* mutations confer the constitutive activation of this oncogene, stimulating cell proliferation, inducing autophagy, suppressing apoptosis, altering cell metabolism, changing cell motility and invasion and modulating the tumor microenvironment.

Keywords: KRAS mutations ; cell death resistance ; apoptosis ; autophagy

1. Introduction

RAS proteins are a family of small monomeric guanosine triphosphatases (GTPases) that function as transducers of extracellular stimuli to intracellular signaling. RAS proteins regulate important cellular functions, including apoptosis, autophagy, cell proliferation, differentiation, gene expression, migration, invasion and tumor microenvironment (TME) ^{[1][2][3][4][5]}.

The *RAS* family includes *Harvey (H-)RAS*, *Kirsten (K-)RAS* and *Neuroblastoma (N-) RAS* genes, which are the most frequent oncogenes and one of the most prevalent drivers of cancer. These three *RAS* genes encode four homologous proteins: HRAS, NRAS, KRAS4A and KRAS4B, whose structures and sequences are highly conserved. RAS isoforms share 85–90% sequence homology in the G-domain and diverge mainly at the C-terminal ^{[6][7][8]}. The G-domain contains G motifs, which bind directly to GDP or GTP, such as switch I and II and the P-loop. The C-terminal disparities are caused by post-translational modifications (PTMs) that specifically occur in a string of residues termed the hypervariable region (HVR), which is responsible for appropriate membrane localization, interaction and cellular trafficking of the proteins. Therefore, such C-terminal disparities result in different subcellular localization, that can be linked to variations in the diversity or amplitude of signaling ^{[8][9]}. In fact, KRAS has a polybasic region required for plasma membrane localization, whereas HRAS and NRAS are palmitoylated; therefore, they are more likely to localize into lipid rafts ^{[9][10]}. KRAS4A and KRAS4B are protein products generated through alternative gene splicing of the fourth exon of the *KRAS* gene, which determines the presence or absence of exon 4A. The alternative fourth exon encodes the HVRs responsible for membrane targeting. Thus, KRAS4A is palmitoylated, whereas KRAS4B is not, because it lacks a site of palmitoylation ^[11]. Additionally, KRAS4A is expressed at low levels, whereas KRAS4B (hereafter referred to as KRAS) is ubiquitously expressed and accounts for 90–99% of all *KRAS* mRNA forms ^{[12][13]}.

Despite their high homology, the functions of RAS proteins also differ significantly and do not display redundant roles. This is particularly surprising since the regions of the proteins that interact with downstream effectors are identical to the three RAS isoforms. Therefore, their specific roles may be explained by various other factors, such as cellular context, differential interaction with effectors, compartmentalized signaling and PTMs ^[14].

Regarding oncogenic *RAS* mutations, they are found in approximately 30% of all human cancers and contribute to important aspects of the malignant phenotype, such as invasion, programmed cell death, deregulation of tumor-cell growth and the induction of new blood-vessels' formation ^{[3][15][16]}. From all human cancers, *RAS* mutations are more frequently found in about 60–90% of pancreatic cancer cases, followed by approximately 30–50% of colorectal cancer (CRC) cases, and between a range of 20% and 30% of lung cancer cases ^{[12][17]}.

2. The Oncogene KRAS

As a member of the human *RAS* family, the *KRAS* oncogene encodes a 21 kDa small GTPase, which functions as an on/off switch protein that alternates between an active GTP-bound and an inactive GDP-bound state, by cleaving the terminal phosphate of the nucleotide. The on/off state of KRAS is regulated by GTPase activating proteins (GAPs) and

guanine nucleotide exchange factors (GEFs) (**Figure 1**). GAPs have a GTPase activity responsible for the inactivation of KRAS, through the hydrolysis of GTP. In turn, GEFs facilitate the activation of KRAS, forcing the release of bound GDP and allowing its replacement by GTP. In mammalian cells, KRAS is normally found in its inactive state—GDP-bound [4][18][19].

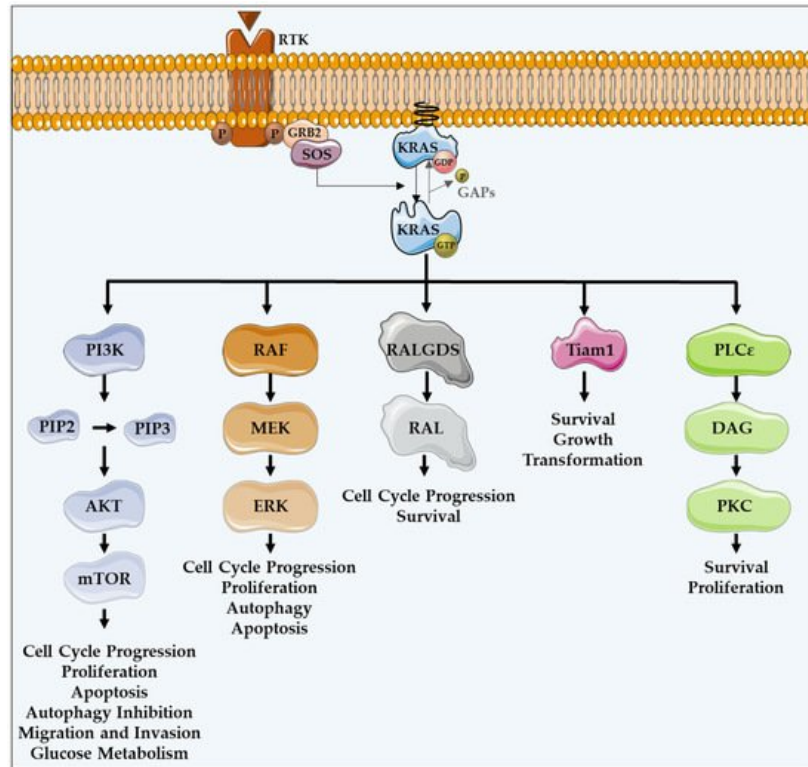


Figure 1. KRAS major effectors and cellular functions. KRAS proteins are activated upon activation of an RTK-like EGFR. KRAS is a GTPase that functions as an on/off switch that alternates between an active GTP-bound and an inactive GDP-bound state, regulated by GAPs and GEFs, such as Sos1. This oncogene regulates several effector pathways, including the MAPK and PI3K/AKT pathways. GTP-bound KRAS leads to the activation of RAF proteins, resulting in the initiation of MAPK signaling. Subsequently, MEK is activated and, in turn, phosphorylates and activates ERK. Downstream of this, ERK can regulate numerous transcription factors, promoting cell cycle progression and influencing proliferation and apoptosis. Besides MAPK pathway, KRAS can interact with PI3K, whose activation leads to the phosphorylation of PIP2, resulting in PIP3. This second messenger is able to activate a large number of proteins containing a pleckstrin homology domain, including PDK1 and AKT, whose main downstream effector is mTOR. These proteins regulate cell cycle progression, cell survival, glucose metabolism, cell growth and proliferation. In addition to MAPK and PI3K/AKT pathways, KRAS can activate RALGDS, whose downstream effector is RAL GTPases, promoting cell cycle progression and survival. Furthermore, KRAS interacts with Tiam1, a Rho family GTPase, which is implicated in the development of RAS-driven tumors, growth transformation and promotion of cell survival. KRAS also binds to PLCε 44, a phospho-lipase C isoform responsible for KRAS mediated production of DAG, resulting in calcium release and activation of the PKC signaling cascade, involved in survival, proliferation, and calcium mobilization.

KRAS proteins are activated following the activation of different receptor tyrosine kinases (RTK), such as the epidermal growth factor receptor (EGFR) [12][16]. Upon ligand binding in the extracellular portion, RTKs dimerize, resulting in conformational changes that lead to the autophosphorylation of their intracellular carboxyl-terminal domain. Such phosphorylation stimulates the binding of proteins containing SH2 domains, also known as docking adaptor proteins, to the phosphorylated tyrosine residues, turning RTKs able to recruit GEFs. Grb2 is an example of an adaptor molecule that binds directly to RTKs, or through other adaptor proteins present on growth factor receptors, such as IRS. Grb2 associates to Sos1, which is a GEF, activating the KRAS-RAF-MEK-ERK-MAPK pathway [20][21]. GEFs interact and activate KRAS, promoting the dissociation of GDP and the binding of GTP [22][23][24]. KRAS, in a GTP-bound active state, transduces intracellular signals through other GTPases and kinases, thus linking the presence of extracellular growth factors to intracellular signaling cascades. There are several intracellular signaling cascades activated by KRAS (**Figure 1**) [25].

Once they are active, KRAS proteins transduce signals across the plasma membrane [12][16], stimulating several effectors by the recruitment and activation of proteins involved in the propagation of signaling from growth factors and other receptors [18][26].

The protein serine/threonine kinase rapidly-accelerated fibrosarcoma (RAF) was the first RAS effector to be characterized and is still the best known. Upon binding to KRAS-GTP, RAF proteins are relocated to the plasma membrane and activated, leading to the initiation of the mitogen-associated protein kinase (MAPK) cascade. This kinase phosphorylates and activates MAPK/ERK kinase (MEK), which subsequently phosphorylates and activates extracellular signal-regulated kinase (ERK). Downstream of this, ERK can regulate numerous transcription factors and cellular functions, such as cell cycle progression, proliferation, autophagy and apoptosis (**Figure 1**) ^{[16][27]}.

In addition to the MAPK pathway, KRAS can interact with phosphatidylinositol 3-kinase (PI3K), whose activation leads to the phosphorylation of phosphatidylinositol-4,5-diphosphate (PIP2), resulting in the phosphatidylinositol-3,4,5-triphosphate (PIP3) production. This second messenger is able to recruit and activate a large number of proteins containing a pleckstrin homology domain, including phosphatidylinositol dependent kinase 1 (PDK1) and AKT, whose main downstream effector is a mammalian target of rapamycin (mTOR). Such proteins transmit signals regulating cell cycle progression, proliferation, apoptosis, autophagy, migration, invasion and glucose metabolism (**Figure 1**) ^{[12][16][26][28]}.

Another important KRAS effector is RAL guanine nucleotide dissociation stimulator (RALGDS), which activates RAS-like (RAL) GTPases and has pro-survival functions and promotes the cell cycle progression. Additionally, KRAS interacts with T-lymphoma invasion and metastasis protein 1 (Tiam1), a Rho family GTPase, which is implicated in the development of RAS-driven tumors, growth transformation, promotion of cell survival, activation of the c-Jun amino-terminal kinase (JNK) mitogen-activated protein kinase and the activation of the NF- κ B transcription factor ^[29]. RAS also binds to PLC ϵ 44, a phospholipase C isoform responsible for the RAS-mediated production of the membrane lipid diacylglycerol (DAG), which results in calcium release and activation of the PKC signaling cascade involved in survival, proliferation, and calcium mobilization (**Figure 1**) ^{[12][16][29][30]}.

The combined action of these signaling pathways regulated by this oncogene can lead to several features of malignant transformation, if cells express *KRAS*-activated mutants ^[16].

3. KRAS Mutations and Cancer

Of the three RAS isoforms, *KRAS* has the highest mutation rate (86%) and leads to a poor prognosis. Oncogenic *KRAS* mutations are a hallmark of cancer, being a very frequent event in many cancers, including pancreatic cancers (90%), CRCs (30–50%) and lung cancers, especially non-small-cell lung cancer (NSCLC) (15–20%). Such mutations are also present in endometrial cancer, biliary tract malignancies, cervical cancer, liver cancer, bladder cancer, breast cancer and myeloid leukemia ^{[31][32][33]}.

KRAS mutations, featured by single base missense mutations, lead to alterations in the homeostatic balance of GTP and GDP binding, resulting in its constitutively GTP-bound active state, through the reduction in GTP hydrolysis or the increase in the rate of GTP loading. Thus, mutated *KRAS* is able to constitutively activate oncogenic pathways and cellular signal transduction ^{[7][34][35][36]}. Point substitutions in codons 12 and 13 are the most common oncogenic *KRAS* mutations, representing 90% of them. In addition, mutations occur less frequently in codons 61, 63, 117, 119 and 146 ^{[32][37]}. In detail, the hotspot *KRAS*-mutated codons 12 and 13 correspond to a glycine, and are positioned in the P-loop of *KRAS* protein, which is essential in maintaining its active form. In these codons, the replacement of glycine by other amino acids, except proline, prevents the arginine finger of GAPs from promoting hydrolysis of GTP ^{[14][21][34][38]} ^[39]. Thus, the *KRAS* hotspot mutations result in insensitivity to GAPs increasing time in the GTP bound state ^{[21][22][40][41]} ^{[42][43][44][45]}. In other words, these *KRAS* mutations prevent GAPs from promoting GTP hydrolysis, resulting in the constitutive activation of the *KRAS* protein and the downstream pathways ^{[24][41][45][46]}. Different amino acid substitutions activate different *KRAS* downstream signaling pathways and display different clonogenic growth potential and responses to targeted therapies. This happens because different mutations influence the way the interaction between *KRAS* and its effectors occurs ^{[21][45]}. Codon 12 mutations increase aggressiveness by the differential regulation of *KRAS* downstream pathways that leads to the inhibition of apoptosis, the enhanced loss of contact inhibition, and the increased predisposition to anchorage-independent growth. Codon 13 mutations lead to reduced transforming capacity compared to codon 12 mutations ^[43]. Alternatively, codon 61 substitutions activate *KRAS* through a similar mechanism, indicating the essential nature of codon 61 in *KRAS* deactivation ^[21]. This constitutively active *KRAS* protein contributes to cell proliferation, suppression of apoptosis, altered cell metabolism and changes in the tumor microenvironment, which leads to tumorigenesis, tumor maintenance, invasion and metastasis ^{[2][24][46][47]}.

Generally, tumors harboring *KRAS* mutations present higher resistance to chemotherapy and EGFR-inhibitors-targeted therapy, including cetuximab and panitumumab, leading to a worse overall survival, especially in CRC ^{[37][48]}.

In addition, the direct inhibition of KRAS has not presented successful results and efforts have been made to focus on targeting their downstream signaling proteins ^[49]. This is why it is so important to find the Achilles heel of mutated KRAS. KRAS is implicated in the regulation of crucial cellular processes that can prevent tumorigenesis, including apoptosis and autophagy ^{[1][12]}. However, there are still several unanswered questions regarding the role of KRAS mutations in autophagy and apoptosis regulation, and their regulation loop.

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