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Review

IQ Motif Containing GTPase Activating Proteins (IQGAPs), A-Kinase Anchoring Proteins (AKAPs) and Kinase Suppressor of Ras Proteins (KSRs) in Scaffolding Oncogenic Pathways and Their Therapeutic Potential

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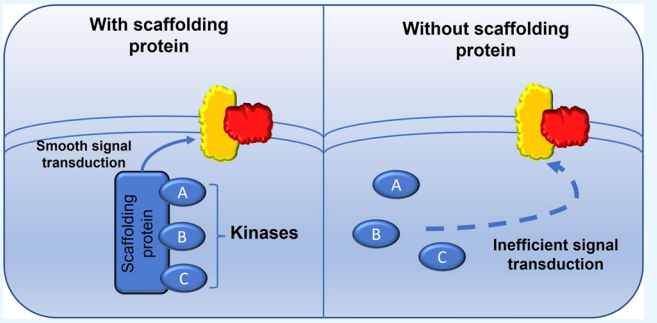
ABSTRACT: Scaffolding proteins colocalize interacting partners on their surface and facilitate complex formation. They have multiple domains and motifs, which provide binding sites for various molecules. This property of scaffolding proteins helps in the orderly transduction of signals. Abnormal signal transduction is frequently observed in cancers, which can also be attributed to the altered functionality of scaffolding proteins. IQ motif containing GTPase activating proteins (IQGAPs), kinase suppressor of Ras (KSR), and A-kinase anchoring proteins (AKAPs) tether oncogenic pathways RAS/RAF/MEK/ERK, PI3K/AKT, Hippo, Wnt, and CDC42/RAC to them. Scaffolding proteins are attractive drug targets as they are the controlling hub for multiple pathways and regulate crosstalk between them. The first part of this review describes the human scaffolding proteins known to play a role in oncogenesis, pathways altered by them, and the impact on oncogenic processes. The second part provides information on the therapeutic potential of scaffolding proteins and future possibilities. The information on the explored and unexplored areas of the therapeutic potential of scaffolding proteins will be equally helpful for biologists and chemists.



INTRODUCTION

The spatiotemporal positioning of molecules inside a cell is vital for coordinating the numerous cell type-specific functions.[1] Within the seeming chaos of the cell, the local order of signaling molecules ensures the integrity of information processing. Scaffolding proteins provide a space for assembling the functionally interacting proteins to form a complex.[2] They position domains of interacting molecules in such a way as to allow the modifications in an orderly manner.[3] Although maximum scaffolding proteins use a tethering mechanism to enhance the interplay among the interacting partners, some use their scaffold domains to regulate the signaling molecule allosterically.[4] The first scaffolding protein, Ste5, was discovered in 1994;[5] since then, the notion of protein scaffolds as control centers for integrating and distributing subcellular information has progressed significantly. Interacting molecules have a specific time of expression in a specific compartment, which results in a very organized management of the whole cascade.[6] Scaffold proteins put forward a flexible way of regulating selectivity in pathways and establishing a cross-talk between different pathways leading to tissue-specific behavior of signaling molecules.[7]

Scaffolding proteins as a controlling center for the molecular cross-talk have attracted research as a therapeutic target for cancers.[8] Currently, most therapeutic targets are downstream molecules and show limited success due to resistance development attributed to activation of the compensatory pathway.[9] However, targeting the scaffolding proteins has dual advantages: First, we can block interlinking pathways which can control tumor growth more rapidly. Second, it can reduce the chances of resistance development in patients.

The scope of this review is to summarize the scaffolding proteins known to coordinate molecular signaling in tumorigenesis, interacting proteins, pathways regulated by the scaffolding protein, and the cellular processes controlled by the signaling. In another section, we have provided information on known activators or inhibitors targeting the binding of proteins to the scaffolding proteins. Lastly, we have discussed

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the gaps in the research and the possibility of developing inhibitors and activators.

PROTEIN SCAFFOLDS: ASSEMBLERS OF VARIED PATHWAYS

Scaffolding proteins are present in organisms from invertebrates to vertebrates, which signifies their evolutionary conservation. While discussing the characteristics of scaffolding proteins, some crucial points are common to these proteins:[10]

1. Structurally they have multiple domains and motifs interacting with many signaling molecules.
2. These proteins mandatorily interact with at least two catalytic or enzymatic molecules.
3. Some of them are known to anchor various molecules in a phosphorylation-dependent manner.
4. These scaffolding proteins and the interacting partners must be involved in the same signaling complex.

All these characteristics allow them to act as a controlling hub for various molecular pathways.

SCAFFOLD PROTEINS IN HUMANS

About 10% of total proteins are involved in signal transduction, including scaffolding and signaling molecules.[11] Around 83 different human scaffolding proteins have proper validation according to the information provided in ScaPD (a scaffolding protein database).[12] Such a small number of molecules ensure the proper orderly signal transduction and crosstalk between various pathways in normal cellular operations. Further, a detailed list of predicted scaffolding proteins and signaling pathways can be obtained from the dedicated database ScaPD.[12] Some of the most common scaffolding proteins in humans tethering the major signaling pathways include IQGAPs,[13] KSR),[14] AKAPs,[15] Pellino,[16] HOMER,[17] NLRP,[18] DLG1,[19] and spinophilin.[20] IQGAPs, KSR, and AKAP are primarily involved in controlling MAPK, AKT, PKA, and JNK, which are the most critical pathways in tumorigenesis. HOMER, NLRP, DLG1, and spinophilin are responsible for tethering the immune pathway signaling. As per the scope of our review, we will be discussing IQGAPs, KSR, and AKAP in detail, as they are mostly responsible for tethering oncogenic signals.

IQGAPs. Since the discovery of IQGAP1 (IQ motif containing GTPase activating protein 1) in 1994,[21] it has captured researchers' attention because of its extensive role in regulating various human physiological activities. To date, three IQGAP family members, IQGAP1, IQGAP2, and IQGAP3, are known. They have been discovered in amoeba, yeast, *Caenorhabditis elegans*, *Xenopus laevis*, and mammals.[22] In continuation with this segment, Table 1 provides detailed domain-wise interactions of IQGAPs. In the following section, we will discuss these members in detail.

IQGAP1. IQGAP1 is evolutionarily conserved from amoeba to mammals. In *Schizosaccharomyces pombe*, there is only one member of the IQGAP family named Rng2.[23] Similarly, *Saccharomyces cerevisiae* has one member, namely, Iqg1. Amoeba, which is a lower eukaryote, has DdIQGAP1. Rng2, Iqg1, and DdIQGAP1 share structural homology with IQGAP1.[24]

IQGAP1 is ubiquitously expressed in humans. Within the cell, it is localized to nucleus, plasma membrane, and cytoskeletal structures.[25] Human IQGAP1 has four domains: CH (calponin homology), WW, IQ motif, and RG.[26] More than 130 molecules have been reported to interact with IQGAP1 since 2015.[27−30] Due to its large size and multiple domains, IQGAP1 can control numerous pathways. Major tumorigenesis-related pathways controlled by IQGAP1 include ERK, CDC42/RAC, Hippo, WNT, PI3K, TGFβ, and cAMP/PKA,[31] as depicted in Figure 1. Details of each pathway and associated oncogenic processes have been explained below.

Table 1. Domain-wise Interactions of IQGAPs

Domain	Interactors
	IQGAP1
CH	actin, CaM, CXCR2
WW	ERK1/2, RAPTOR
IQ	IQGAP1, myosin light chain, KRAS, RAP1, S100, MEK1/2, BRAF, HER1/2, EGFR
RG	E-cadherin, β-catenin, CLIP 170, DIA1, TGFβR2, APC
GRD	CDC42, RAC1, DVL, LGR4
full length	cytoskeleton-associated proteins, adhesion-associated proteins, Ca^{2+}-binding proteins, receptor tyrosine kinase, receptor serine/threonine kinase
	IQGAP2
IQ	CaM (2nd and 3rd IQ motif)
GRD	CDC42 (ex domains)
full length	β-catenin, ezrin, LGR5, F actin, NRON, RAC 1, RhoG
	IQGAP3
WW	ERK1/2
IQ	CaM
full length	Cdc42, DGKζ, F-actin, H-Ras, LGR4, myosin ELC, Rac1

ERK/MAPK Pathway and Oncogenic Processes. The ERK pathway plays an essential role in transducing external signals from any mitogen or growth factor into signaling events promoting cell growth and proliferation. MAPK signaling transmits extracellular signals received by receptors via a signaling cascade composed of a series of kinases, namely, RAS−RAF−MEK−ERK, and IQGAP1, being the scaffold for multiple components of the MAPK pathway, ensures the stoichiometric activation of these molecules.

To elaborate the process, IQGAP1 provides binding sites to RAF, MEK, and ERK through different domains[32,33] (Figure 2). In response to the external signal leading to autophosphorylation of the receptor, RAS which is bound to the IQ region gets activated by switching from the GDP to GTP bound form.[34] Activated RAS facilitates RAF activation, which is bound to the IQ domain.[35] Further, activated RAF phosphorylates MEK,[33] which is anchored to the WW domain.[36] Lastly, in this chain, activated MEK activates ERK.

IQGAP1 is an oncogene. The loss of IQGAP1 lowers the activation of these kinases, resulting in less active MAPK signaling.[37] In breast cancer, overexpression of IQGAP1 enhances the proliferative and invasive properties of cells via ERK activation.[38]

TGFβ Pathway and Oncogenic Processes. This pathway regulates many physiological processes, including cell proliferation, migration, and differentiation. In hepatocellular carcinoma (HCC), stromal IQGAP1 binds to TGFβ receptor II (TβRII) and targets the E3 ubiquitin ligase SMAD ubiquitination regulatory factor 1 (SMURF1) for TβRII ubiquitination.[39] TβRII degradation inhibits the differentiation of the quiescent pericytes to myofibroblasts in the tumor microenvironment. In HCC, TGFβ1 upregulates SULF1/2 and thereby increases IQGAP1, which results in the enhanced

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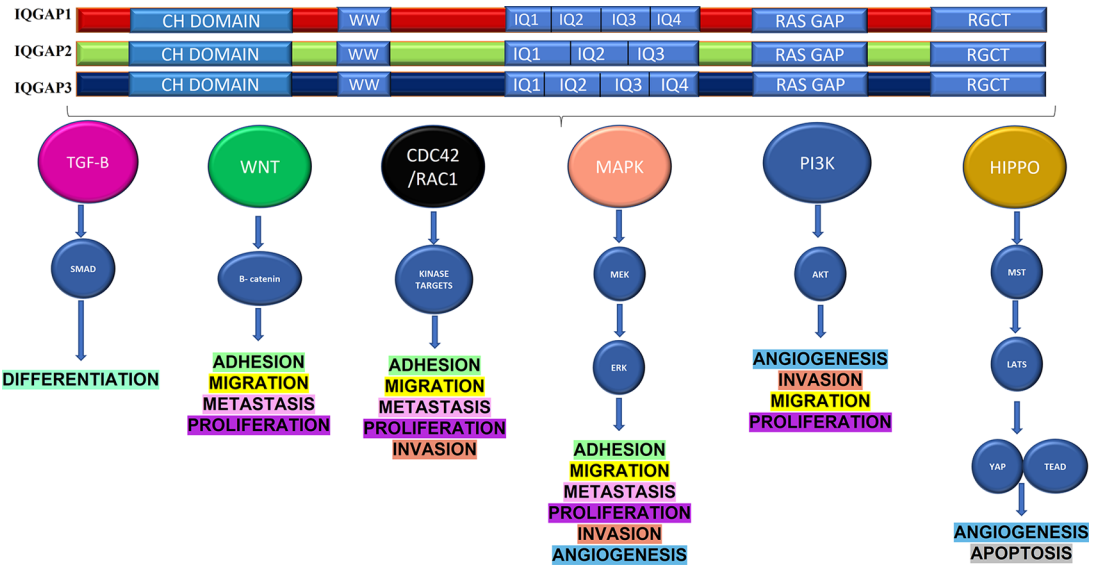

Figure 1. IQGAP binding molecules and regulated pathways. This figure depicts the overall role of IQGAPs in regulating different pathways and hence the hallmarks of cancers.

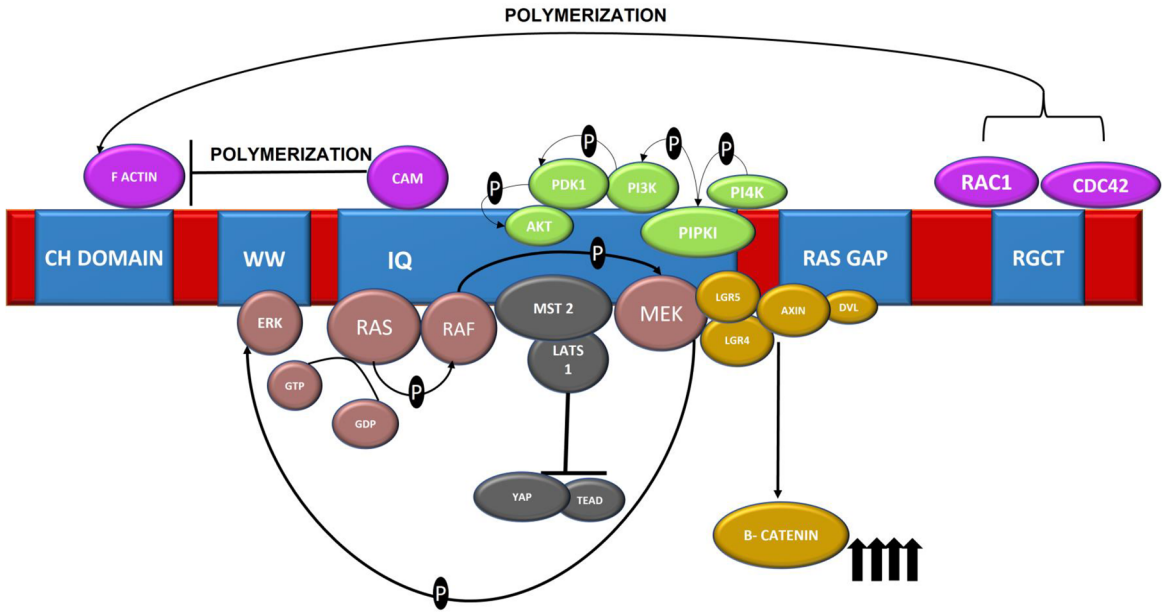

Figure 2. IQGAP domains in scaffolding different pathways. Brown circles show MAPK pathway, yellow circles show Wnt* pathway, green circles show AKT pathway, purple circles show CDC42/RAC pathway, and gray circles show Hippo pathway. *Exact domains are yet to be deciphered for the components of this pathway.

carcinogenic properties of cells. In contrast, IQGAP2 shows a negative correlation with SULF2.[40]

CDC42/RAC Pathway and Oncogenic Processes. This pathway is well-known for linking the stimuli for transduction of signals promoting cytoskeletal rearrangement. The Rho family of small GTPases or G proteins, RAC1 and CDC42, was first discovered as IQGAP1 binding partners.[25] Through its GRD domain, IQGAP1 binds to and stabilizes GTP-bound active RAC1 and CDC42. IQGAP1 binds to F-actin via its CHD domain to promote actin cross-linking, which is augmented by active CDC42 binding and decreased by Ca^{2+}/calmodulin binding.[41] Post-translational modifications (PTMs) of IQGAP1 influence its interaction with CDC42. Phosphorylation of IQGAP1 at Ser1443 promotes its binding to CDC42, while ubiquitination of IQGAP1 decreases its binding.[42,43]

IQGAP1 regulates cell migration, invasion, adhesion, and metastasis throughout cancer formation via controlling cytoskeleton structure.[44] IQGAP1 frequently colocalizes with Rho GTPases at the leading edge of cancer cells' invasive front.[45] In breast cancer, IQGAPs are known to interact with CDC42/RAC and promote the invasive characteristics of the cells.[46] In pancreatic cancer, IL6 activates the JAK−STAT3 pathway, where STAT3 is bound to IQGAP1 and mediates the activation of CDC42 cell invasion.[47]

Wnt Signaling and Oncogenic Processes. Wnt signaling is essential for tissue homeostasis, development, and destiny determination, and it is frequently dysregulated during carcinogenesis. Wnt receptors LGR4 and LGR5 and APC

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protein are the primary regulators of the Wnt signaling Dishevelled (Dvl) pathway that mediates the pathway into the cytoplasm via β-catenin, the eventual intracellular mediator of Wnt signaling.[48] IQGAP1 is responsible for raising the levels of nuclear-localized β-catenin by binding with the LGR4 and LGR5 of Wnt signaling. LGR4 and LGR5 interaction with IQGAP1 at adherent junctions disrupts the β-catenin complex and eventually reduces cell−cell adhesion.[49] Hence, it facilitates the metastatic movement of cells. In colorectal cancer, IQGAP1 interacts with Wnt signaling molecules, thereby increasing β-catenin-induced events. Further, the cell−cell adhesion is reduced in colorectal cancer by the PAK6−IQGAP1−E-cadherin complex at the junction.[50]

PI3K−AKT Signaling and Oncogenic Processes. PI3K−Akt signaling pathways control cell survival, proliferation, differentiation, metabolism, motility, and stemness. This pathway is frequently altered in cancers. IQGAP1 acts as a scaffold for the PI4P, PI(4,5)P2, and PI(3,4,5)P3-generating enzymes (PI4-KIII, PIPKI, and PI3K).[51] These kinases together lead to the generation of the PI(3,4,5)P3 lipid messenger 4, which recruits PDK1 and AKT onto the IQ3 motif of IQGAP1.[52] This cascade activates AKT to start the downstream signaling.

In nasopharyngeal cancer, metastasis associated protein 1 regulates the expression of IQGAP1 and leads to PI3K/AKT mediated enhancement of cell proliferation and motility.[53] In thyroid cancer, the AKT/PI3K pathway is frequently altered, with overexpression of IQGAP1. This pathway enhances cell proliferation, invasiveness, and resistance to apoptosis.[54] In hepatocellular carcinoma, IQGAP1 is known to induce aberrant activation of AKT by recruiting AKT and mTOR, which enhances cell proliferation. AKT can also get activated upon RAC1 and IQGAP1 binding in hepatocellular carcinoma.[55] Their interaction activates the Src/FAK pathway, which increases cell migration, invasion, and anoikis resistance. In the triple-negative breast cancer cell lines, IQGAP1 overexpression stimulated DNA synthesis even in the absence of RhoA by interacting with BRaf/AKT. This enhances cell proliferation.[56]

Hippo Pathway and Oncogenic Processes. The Hippo pathway regulates organ development and is an evolutionarily conserved pathway. Cancers frequently exhibit dysregulation of the Hippo system. Through its IQ domain, IQGAP1 suppresses the activity of important components of the Hippo pathway, MST2 and LATS1. It serves as a scaffold for the complex MST2−LATS1.[57] The IQ domain of IQGAP1 also binds directly to the TEAD-binding domain of YAP1, a Hippo pathway effector, hence competing with TEAD for YAP1 binding.[58] As a result, IQGAP1 suppresses YAP1−TEAD transcription. However, when IQGAP1 is overexpressed or knocked out, the YAP−TEAD interaction rises. IQGAP1 overexpression also disrupts the YAP1−p73 complex,[59] preventing YAP1-associated pro-apoptotic signaling in liver cancer. It is unclear if IQGAP1 enhances YAP1 nuclear localization.[60] IQGAP1 does not enhance YAP1 nuclear importation in mouse embryonic fibroblasts, but it does so in a mouse model with hyperactive Wnt and MET (mesenchymal to epithelial transition) receptor kinase signaling.[61]

IQGAP2. IQGAP2 is the second member of the IQGAP family. Like IQGAP1, IQGAP2 is also conserved from invertebrates to vertebrates. In the case of amoebas, it is termed DDGAP2; in other organisms, it is called IQGAP2.[22] This protein harbors four domains, CH, WW, IQ, and RG. Though structurally it shares around 62% similarities with IQGAP1, functionally, it acts antagonistically.[30,62] The GRD region binds to CDC42 and facilitates the dimerization of IQGAP2; however, the purpose behind the complex formation is still not completely understood.[30] IQ motifs of IQGAP2 interact with CaM in the presence of calcium, which ensures cytoskeletal stability and hence reduces the migratory capacities of cells. Other interactors of full-length IQGAP2 include β-catenin, ezrin, and LGR5, but the exact domains need to be deciphered.[27]

Unlike IQGAP1, IQGAP2 has been reported as a tumor suppressor. IQGAP2 overexpression leads to decrease in phosphorylated ERK and AKT-473, eventually leading to the reduction of oncogenic activities in breast cancer.[37] A similar report about hepatocellular carcinoma showed that IQGAP1 and IQGAP2 function antagonistically.[63] In gastric cancer, IQGAP2 inhibits invasion and migration by elevating the phosphatase activities of SHIP2. IQGAP2, SHIP2, and Rho GTPases form scaffolding complexes to regulate cytoskeleton dynamics, affecting migration and invasion.[64]

IQGAP3. IQGAP3, the third member of the IQGAP family, has structural (80−85% at amino acid level) and functional similarities with IQGAP1.[65] Like IQGAP1 and IQGAP2, IQGAP3 is known as DDGAP3 in amoeba and IQGAP3 in other organisms.[22] IQGAP3 contains all the domains of the IQGAP family. It binds to ERK via its WW domain and enhances the proliferation and migration of cells in gastric, bladder, and ovarian cancer and hepatocellular carcinoma.[66] All the IQ motifs of IQGAP3 are known to interact with CaM in the presence of calcium.[67]

Unlike IQGAP2, IQGAP3 has been reported as an oncogene in multiple types of cancers. IQGAP3 levels increase on activation of ERK via CDC42 signaling, enhancing the metastatic and tumorigenic capacities of the ovarian cells.[68] In lung and breast cancer, the development of radioresistance is connected with the interaction of IQGAP3 with RAD17, which eventually leads to the recruitment of the MRN complex upon DNA damage. This eventually leads to increased ATM and ATR expression, which starts the DNA damage repair.[69] IQGAP3 also enhances the epithelial−mesenchymal transition (EMT) by directly binding to hnRNPC (heterogeneous nuclear ribonucleoprotein C) as IQGAP3 gets stabilized by this interaction. The association between protein kinase C (PKC) δ and PKC α is competitively inhibited by IQGAP3 when it interacts with PKC δ, eventually leading to PKC α phosphorylation by E2F1, which promotes cell proliferation in hepatocellular carcinoma. IQGAP3 promotes colorectal cancer invasion and progression by regulating phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 beta (PIK3C2B) expression.[70] Down-regulation of IQGAP3 increases the expression of the p53 and reduction of matrix metalloproteinase (MMP) 9, Snail, Twist, CDC42, p-ERK1/2, kinesin family member (KIF) 2C, KIF4A, and proliferating cell nuclear antigen (PCNA), which signifies its role in the progression of breast cancer.[71]

AKAP. AKAPs are a family of around 50 scaffolding proteins that anchor mainly protein kinase A (PKA), other protein kinases, protein phosphatases, and phosphodiesterase within specific intracellular sites.[15] Hence, they restrict the associated enzyme activity locally. AKAPs do not have significant sequence similarities. Hence, their classification is based on the conserved sequence required for PKA anchoring.[72] PKA holoenzyme is a tetrameric complex composed of a dimer of

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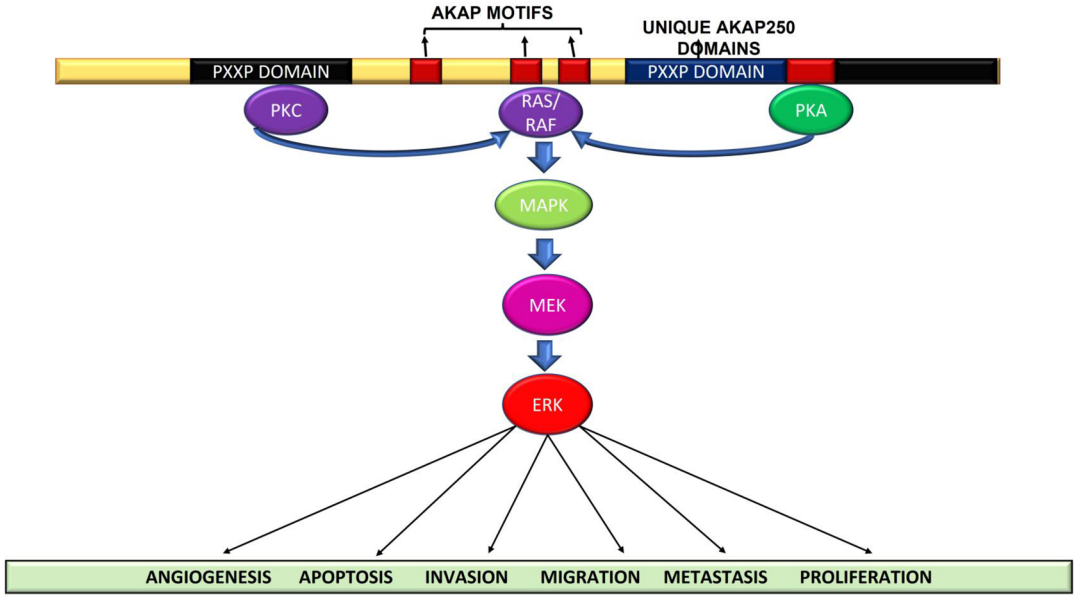

Figure 3. AKAP scaffold protein regulated pathway: involvement of AKAPs in activation of RAS/RAF pathway and its effect on oncogenic processes.

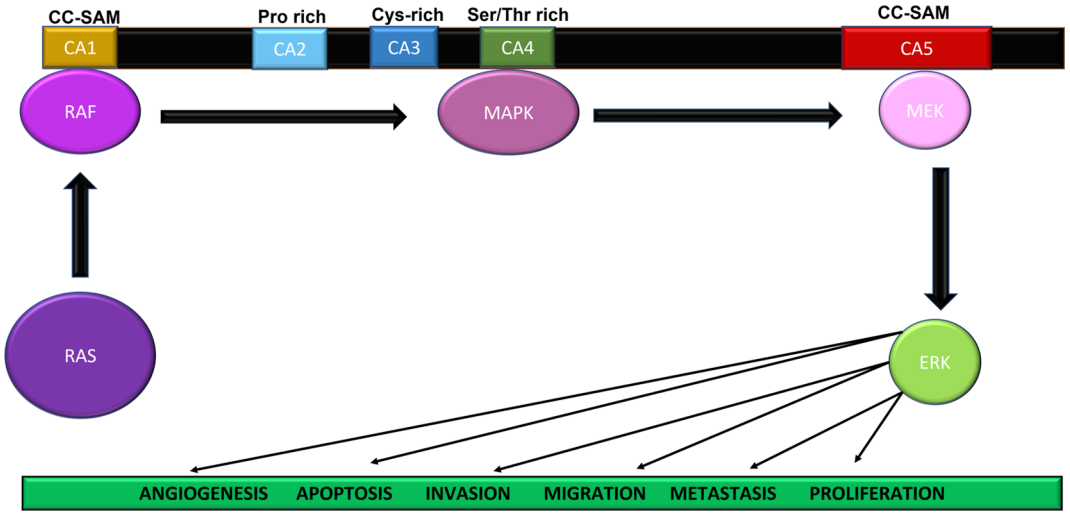

Figure 4. KSR harboring RAS/RAF pathway: involvement of KSR in activation of RAS/RAF pathway and its effect on oncogenic properties of cells.

type I or II regulatory subunits and two catalytic subunits (Cα, Cβ, or Cγ). AKAPs are further classified based on their binding with the RI or RII regulatory subunit of PKA as AKAP RI or AKAP RII.[73] In some cases, AKAPs can bind to both the subunits and are termed dual-specific AKAPs.

AKAP Mediated Pathways and Oncogenic Processes. Due to hypermethylation of its promoter, the down-regulation of AKAP12 is observed in several tumors, including radiation-induced osteoblastoma and breast, ovary, and prostate cancer.[74] In the absence of AKAP12 anchoring, activated Src induces PKC to stimulate the RAF−MEK−ERK kinase cascade, increasing cell proliferation and invasion[75] (Figure 3). The AKAP12-containing locus is prone to deletion in breast, ovary, and prostate cancers. AKAP4, another member of the AKAP family, acts as a cancer tissue antigen (CTA) that triggers immunosuppression in multiple myeloma patients.[76] In a recent study on non-small-cell lung cancer (NSCLC), knock-down of AKAP4 inhibited the EMT via activation of cAMP/PKA signaling.[77] Genetic variants of AKAP9 (M463I and AKAP-lbc) are associated with familial breast cancer.[78] SNP A2073G in D-AKAP2 results in amino acid substitution I646V, which is present in the PKA-binding domain. This results in the alteration of subcellular localization of PKA type 1, leading to abnormal signal transduction.[74]

KSR. Kinase suppressor of Ras (KSR) protein was first discovered in *Drosophila* and *C. elegans*.[79] This KSR protein is conserved from invertebrates to mammals. The *Drosophila* genome has one member in this family, while the rest have two members, namely, KSR1 and KSR2.[80] These two proteins are highly homologous and have five conserved areas from CA1 to CA5. KSR1 and KSR2 differ by the presence of an extra region between CA2 and CA3 in KSR2. CA1 and CA2 regions of KSR1/2 are cysteine- and proline-rich, respectively.[81] BRafs bind to the CA1 region, whereas MEK1/2 binds to the CA5 region of KSR1[82] (Figure 4). Amino acids 25−170 within the CA1 domain include a coiled-coil and sterile-motif (SAM

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Table 2. Most Updated Information on Cancer Therapies Available with Their Targets

name	target	in use/clinical trial	ref
letrozole, anastrozole, and exemestane	aromatase inhibitor, reduce estrogen levels and production	clinical trial	108
tamoxifen and toremifene	selective estrogen receptor modulators, bind to ER and form complex with co-repressor hence halting its production	in use and in clinical trial, due to development of resistance	109,110
fulvestrant	selective estrogen receptor degraders. bind to ER, prevent its nuclear translocation and lead to its subsequent degradation	clinical trial as a combinatorial drug	111
gefitinib and erlotinib	RTK targeting, compete with ATP for the kinase domain of EGFR	gefitinib first generation TKI, used in NSCLC, erlotinib and palbociclib combination therapy in clinical trial	112,113
afatinib and dacomitinib	improved affinity for the EGFR kinase domain	afatinib, first-line treatment of Asian patients with advanced NSCLC, dacomitinib second generation TKIs	114
osimertinib	covalently bind to cysteine residue on EGFR	clinical trial	115
trastuzumab and pertuzumab	target HER2 dimerization and prevent its activation	trastuzumab and the cytotoxic reagent emtansine used to treat HER2+ breast and lung cancers	116
MCLA-128	target HER2 and HER3	clinical trial	117
GBR1302	HER2 and CD3 bispecific antibody, which directs cytotoxic T cells to HER2+ breast cancer cells	clinical trial	118
lapatinib and neratinib	against HER2 phosphorylation	clinical trial	119,120
tucatinib	inhibits HER2/HER3-mediated MAPK and PI3K/AKT signaling	approved by the FDA in combination with trastuzumab and capecitabine	121
idelalisib	isoform-selective PI3K inhibitors	first FDA-approved PI3K-isoform specific inhibitor; in use for chronic lymphocytic leukemia	122
alpelisib	PI3Kα-specific inhibitor	approved for the treatment of ER+/HER2− PIK3CA mutant and metastatic breast cancer in combination with fulvestrant	123
taselisib	PI3K-specific inhibitor	phase II clinical trial	124
dabrafenib, encorafenib, and vemurafenib	B-Raf inhibitors	available for the treatment of melanoma and NSCLC harboring the BRAF V600E/K mutations	125
PLX704 and PLX8394	type-II Raf inhibitors	paradox breaker, clinical trial	99
sorafenib and LY3009120	first generation type-II RAF inhibitors	sorafenib approved for hepatocellular carcinoma; LY3009120 clinical trial	126
AZ628, TAK632, and LXH254	pan-RAF inhibitors	clinical trial	127
linsitinib	IGFR inhibitor	clinical trial	128
ARS-1620	KRAS G12C specific inhibitor	clinical trial	128
everolimus	mTOR inhibitor	clinical trial	129
binimetinib, trametinib, and cobimetinib	MEK1/2 inhibitors	in use for treatment of melanoma and NSCLC harboring the BRAF V600E/K mutations	125
RO5126766 and LY3214996	MEK inhibitors	second generation MEK inhibitors, clinical trial	130
ulixertinib	ERK inhibitors	clinical trial	131
abemaciclib, ribociclib, and palbociclib	CDK4/6 inhibitor	FDA approved	132
topotecan and etoposide	topoisomerase inhibitors	clinical trial	133
cyclophosphamide and cisplatin	DNA alkylating agents	clinical trial	133
olaparib, niraparib, talazoparib, and rucaparib	PARP inhibitors	in use for the treatment of HR-deficient breast and ovarian cancers	134

region), which encourages membrane adhesion of KSR1 and ERK activation. Although KSR binding to RAF/ERK/MEK is reported, its direct binding to RAS is not reported.[81]

KSR Mediated Pathways and Oncogenic Processes. Cancers with KSR1 perturbation are RAS dependent. Epithelial-stromal interaction 1 (EPSTI1) is required to trigger the transition from E- to N-cadherin. KSR1-mediated activation of ERK increases EPSTI1 protein levels, which promotes EMT-like phenotype in colorectal cancer.[83] In pancreatic cancer, a contradictory effect of KSR1 on ERK activation has been observed in different studies.[84] In one study, the knockout of KSR1 did not affect phospho-ERK levels. However, tumor growth was modestly affected. In another report, a 14-fold increase in KSR1 led to MEK-mediated activation of ERK, but a 20-fold increase inhibited ERK activation.[85]

SCAFFOLD PROTEINS AS THERAPEUTIC TARGETS

There is a growing demand for kinase-directed medications that allosterically block kinase activity or disrupt protein−protein interactions. Currently, inhibitors specific for many of the key components of the RAS/RAF/MEK/ERK and RAS/PI3K/PTEN/mTOR pathways have been developed. Among these drugs, some have already been in use, like osimertinib, which irreversibly binds to the C797 residue in the ATP-binding pocket of epidermal growth factor receptor (EGFR).[86] That has improved progression-free survival (PFS) in patients with the acquired T790M mutation. Some are in a clinical trial like neratinib (HER2 inhibitor)[87] and fulvestrant.[88] Targeting receptor tyrosine kinases (RTKs) has proven clinically effective, for instance, sorafenib for hepatocellular carcinoma[89] or tamoxifen for breast cancer, but they cannot cure the disease completely because of resistance development. For instance, in

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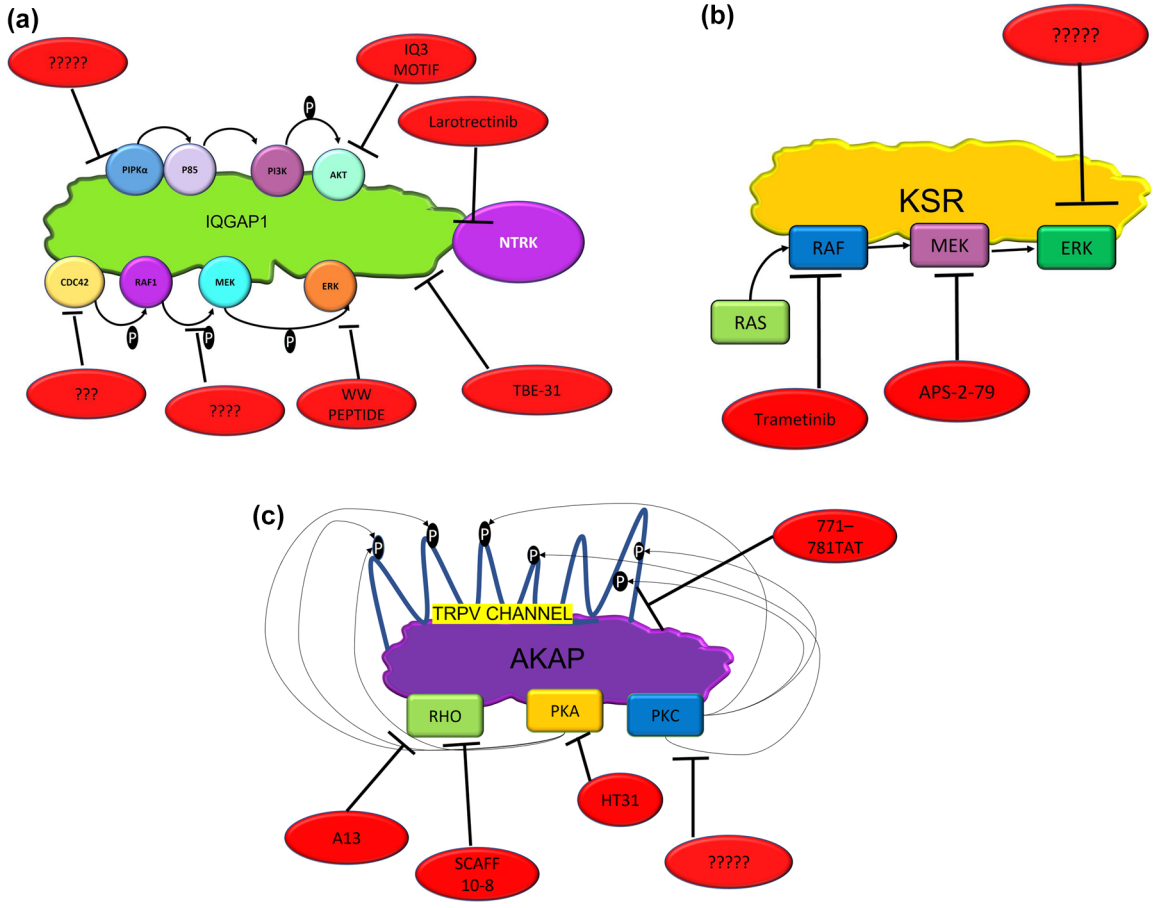

Figure 5. Therapeutic significance of scaffolding proteins. In the schematic representation, the red circles depict the known drugs that target (a) IQGAP1, (b) KSR, or (c) AKAP directly. The red circles with question marks are the scopes for future drug targeting.

triple-negative breast cancer cell line MDA-MB-231, when there is a higher expression of phosphorylated ERK, there is a reduction of phosphorylated AKT. Table 2 shows the complete information on available drugs with their targets against cancers.[90]

This section discusses scaffolding protein-based anticancer therapies being used and the possibilities for future exploration for the development of drugs.

IQGAPs. *Classical Therapies.* IQGAPs are known to tether many pathways, including the PI3K/AKT/mTOR signal transduction pathway and the RAS/MAPK pathway. These pathways are highly interconnected and frequently activated or mutated in cancer. Targeted inhibition of mTORC1 with the injection of rapamycin analogs, also known as rapalogs,[91] can result in MAPK reactivation and resistance to single mTORC1 inhibition. Imatinib for chronic myelogenous leukemia (CML), tamoxifen for ER-positive breast cancer, and trastuzumab for HER2-positive breast cancer are a few of the many drugs discovered.[92] Nevertheless, their efficacy is reduced because of inherent limitations such as drug toxicity and acquisition of de novo or acquired mechanisms of resistance. Even in targeted hormone therapy, patients tend to get resistant to it. For instance, in breast cancer estrogen targeting therapies, eventually, either the patient loses the estrogen receptors or there might be rewiring of signaling pathways leading to engagement of different RTKs such as EGFR, HER2, and fibroblast growth factor receptor (FGFR). Hence, it causes resistance in patients.

IQGAPs as a Drug Target. Although IQGAP1 is a major hub for regulating multiple molecular pathways, very few drugs are known to control its activity indirectly (Figure 5a). Larotrectinib is a neurotrophic tyrosine receptor kinase (NTRK)−IQGAP1 fusion protein inhibitor that significantly reduces the progression of pleomorphic liposarcoma in the uterus.[93] Tbe-31 inhibits migration by targeting the polarity maintaining proteins and might target IQGAP1.[94] A few groups present designed specific peptides derived from IQGAP1's domains and used them against IQGAP1. WW and IQ3 domains of IQGAP1 reportedly bind to the ERK and PIK3 proteins, respectively; hence, peptides derived from these domains block the activation of ERK and AKT.[95] This has reduced the oncogenic capacities of cells.

Further, these IQGAPs, the controlling hubs for the signaling cascade, can be targeted in varied ways to stop or attenuate the oncogenic properties. Drugs targeting the dimerization of IQGAP1 and IQGAP1−IQGAP2 binding, may affect multiple downstream signaling pathways. Inhibition of IQGAP1 binding with actin will affect the cytoskeletal arrangement of cells and therefore multiple cellular processes. IQGAP1 and PIPKα interaction inhibition is still unexplored but is an important target for controlling AKT pathway.

KSR. *Classical Therapies.* Since RAFs are primarily affected by oncogenic changes that abnormally activate RAS/RAF/MEK/ERK signaling, BRAF or upstream molecules are considered good drug candidates. Small molecule inhibitors of BRAF(V600E) PLX4720, vemurafenib (PLX4032), and

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regorafenib (SCH66336) and MEK inhibitor cobimetinib are some of the effective drugs that can reduce tumor growth and metastatic lesions[96] (Figure 5b). Though these drugs are promising, patients develop resistance within 4−6 months of administration. The overexpression or upregulation of RTKs such as platelet-derived growth factor receptor (PDGFR) β and EGFR are the first types of alterations that lead to RAF inhibitor resistance.[97] RAS activation triggers this resistance, activating CRAF−MEK−ERK signaling and bypassing BRAF.[98] Resistance also develops when there is a high level of active RAS present; this induces heterodimerization between BRAF and CRAF hence activates the cascade. This is termed as the paradoxical effect of RAF inhibitors.[99]

KSR as a Drug Target. Unlike IQGAP1, KSRs do not control multiple pathways but bind multiple molecules from the RAS/RAF/MEK/ERK signaling pathway. ERK activation can be mediated directly by KSR or via AKAP anchored PKA. Targeting multiple KSR binding sites at a time can provide better control of ERK activation and avoid chances of cross-talk.

In RAS-driven PANC-1 (pancreatic cancer) and A549 (non-small-cell lung cancer) derived tumor xenografts in nude mice, phosphorothioate antisense oligonucleotides against KSR1 significantly reduced the tumor size and prevented metastases.[100] APS-2-79 is a small molecule that inhibits the KSR2 and MEK1 complex by binding to the KSR binding pocket.[101] Trametinib is another drug that is responsible for weakening the interaction between MEK1 and RAF by binding to the binding pocket of the MEK1 and KSR2 complex.[102]

Besides these drug targets, the researcher can think of targeting the KSR and AKAP cross-talk in the future. This cross-talk leads to both direct and indirect activation of ERK, which synergistically upregulates the expression levels of ERK and hence the proliferative and invasive capacity of cells. A study about the reason for failure of RAS inhibitors in cancer showed that KSR can activate MAPK in a RAS independent manner, which also signifies the therapeutic potential of KSR and development of resistance against RAS inhibitors.[103]

AKAP. *Classical Therapies.* The AKAP protein kinase enzyme family controls and regulates almost all cellular processes, including metabolism, division, proliferation, transcription, motility, and survival. So, initially, it was thought to be a promising drug target against cancer. The dephosphorylation of PKA substrates by phosphatases, the breakdown of cAMP by phosphodiesterase, and the inhibition of PKA by protein kinase inhibitor (PKI, a soluble peptide in the cell) are some strategies to inhibit PKA signaling (Figure 5c). Rp-cAMP, KT-5720, and H89 are small molecule inhibitors facilitating PKA inhibition via PKI.[104] Nonpeptide inhibitors include cAMP analogs, H8 and its derivatives, and KT5720. When combined, the disadvantages of nonpeptide PKA inhibitors include the necessity for high concentrations (like Rp-cAMP and H89) or nonspecific effects.[104] Therefore, more potent and specific PKA inhibitors are necessary for its inhibition. Cross-talk between the cAMP PKA−KSR RAF/MEK/ERK pathway leads to the development of resistance in the patients.

AKAP as Drug Target. AKAP is another family of scaffolding proteins known to harbor PKA through its regulating domains. The 24-residue peptide Ht31 acts against AKAP and inhibits PKA signaling.[105] The 771−781TAT peptide interacts with transient receptor potential vanilloid (TRPV) 4 ion channels and AKAP79, reducing the pain induced by chronic inflammation.[106] Compound A13 and Scaff10-8 inhibit the interaction between RhoA and AKAP-lbc, inhibiting PKA signaling. A13 and Scaff10-8 reduce the GEF (guanine exchange factor) activity of AKAP; hence RhoA GTPase activity is affected.[107]

CONCLUSION AND FUTURE ASPECTS

Scaffolding proteins are responsible for channeling molecular pathways in a controlled manner. Due to their interaction with several molecules, they bridge the gap between separate pathways. Scaffolding proteins also play a role in compartmentalized signaling. Targeting these molecules will help us inhibit more than one pathway at a time, reducing the chance of feedback loops or resistance. The role of these scaffolding molecules in the field of cancer is indispensable, as these proteins are known to tether almost all the major cancer pathways, including MAPK, PI3K, TGFβ, and Hippo. Although researchers are working in this direction, scaffolding proteins have not been explored to their full therapeutic potential. IQGAP1 holds particular promise out of all scaffolding proteins as it controls multiple signaling pathways and their cross-talk.

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Notes

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ABBREVIATIONS

IQGAP	IQ motif containing GTPase-activating protein
AKAP	A-kinase anchoring protein
KSR	Kinase suppressor of Ras
DLG1	Discs large homolog 1
NLRP	NOD-like receptor protein
RAS	rat sarcoma virus
RAF	rapidly accelerated fibrosarcoma
MEK	mitogen-activated ERK kinase
ERK	extracellular signal-regulated kinase
PI3K	phosphatidylinositol 3-kinase
AKT	protein kinase B
MST	macrophage stimulating protein
LATS	large tumor suppressor kinase

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LGR4 leucine rich repeat containing G-protein-coupled receptor 4
LGR5 leucine rich repeat containing G-protein-coupled receptor 5
CDC42 cell division cycle 42
RAC1 Ras-related C3 botulinum toxin substrate 1
TGFβ transforming growth factor-beta
SULF2 sulfatase 2
SHIP SH-2 containing inositol 5′-polyphosphatase
CaM calmodulin

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