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Structure and function of IQ-domain GTPase-activating protein 1 and its association with tumor progression (Review)

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Abstract. IQ-domain GTPase-activating proteins (IQGAPs) are evolutionary conserved multidomain proteins that are found in numerous organisms, from yeast to mammals. To date, three IQGAP proteins have been identified in humans, of which IQGAP1 is the best characterized. As a scaffold protein, IQGAP1 contains multiple protein-interacting domains, which modulate binding to target proteins. Recent mounting studies demonstrated a role for IQGAP1 in tumor progression, supported by the altered expression and subcellular distribution of IQGAP1 in tumors. The contribution of IQGAP1 to tumor progression appears to involve a complex interplay of cell functions by integrating diverse signal transduction pathways and coordinating activities, such as cell adhesion, migration, invasion, proliferation and angiogenesis.

Contents

1. Introduction

IQ-domain GTPase-activating proteins (IQGAPs) belong to a recently identified protein family, which is an evolutionary conserved multistructural domain protein family, playing an important role in adjusting cell adhesion, migration, signaling, division and other biological processes (1-3). IQGAPs, bearing extensive sequences similar to those of the Ras GTPase-activating proteins (GAPs), have 4 isoleucine/glutamine-containing domains (IQ), which interact with multiple proteins. In mammals, the IQGAP protein family comprises three homologues: IQGAP1, IQGAP2 and IQGAP3, among which IQGAP1 is the most ubiquitously expressed and widely investigated (4).

IQGAP1 contains one calponin-homology domain, one poly-proline protein-protein domain (WW), four IQ domains, one Ras GTPase-activating protein-related structure domain and one C-terminal Ras GAP-related structure domain. The traditional GTPase-activating protein is a GTPase regulatory effector, which can improve GTPase activity and promote the conversion of the GDP-binding state from active to inactive. However, IQGAP1, unlike a traditional GAP, can inhibit the endogenous GTPase activity and stabilize the GTP-bound state of Rho GTPases Rac1 and Cdc42 (1).

As a scaffolding protein, IQGAP1 is able to bind several proteins to regulate cell functions. IQGAP1 binds to Rac1, Cdc42 and F-actin to regulate the assembly of the actin cytoskeleton (5,6) and combines with microtubule-associated protein CLIP170, adenomatous polyposis coli (APC) and S100B to regulate cell polarization and determine the direction of cell movement (7-9). Furthermore, IQGAP1 may bind B-Raf, ERK1/2 and MEK1/2 to activate the mitogen-activated protein kinase (MAPK) signaling pathway to mediate cell proliferation and differentiation (10,11) and combine with calmodulin, β-catenin and E-cadherin to regulate intercellular adhesion and migration (12-15). Certain proteins that combine with IQGAP1 play important roles in tumor biology, such as oncogenic β-catenin and Src, tumor-inhibiting factor E-cadherin, Rho GTPase Cdc42 and Rac1, as well as members of the MAPK cascade, indicating that IQGAP1 may be involved in the generation and development of tumors (16,17). In addition, IQGAP1 may interact with neural Wiskott-Aldrich syndrome protein (N-WASP), epidermal growth factor (EGF) receptor, receptor tyrosine kinases, Sec3/Sec8 and several other functional proteins (18-21). Therefore, IQGAP1 may be considered as a molecular scaffold, connecting and integrating several components of the cytoskeleton, and may combine with cell signal transduction molecules, jointly constituting the complex signal transduction cellular network.

2. Research progress of IQGAP1 in tumors

Expression of IQGAP1 in tumor tissues. Several studies demonstrated that the expression of IQGAP1 in a number of tumor tissue samples and tumor cell lines is distinctly upregulated. Research on clinical tumor specimens demonstrated

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that IQGAP1 exhibits a high expression in colorectal, gastric and breast cancer, astrocytoma, squamous cell carcinoma of the head and neck and several other types of cancer, with its expression level being closely associated with tumor grade and metastatic potential (22-27).

Immunohistochemical investigations demonstrated that, in addition to increased expression, there is also altered localization of IQGAP1 in tumor tissues and certain cancer cell lines. Compared to central tumor regions and normal tissues, highly metastatic colorectal and ovarian cancers displayed intense IQGAP1 staining, particularly at the periphery of the tumor (24,28-31). IQGAP1 staining is usually located in the cell membrane ruffles, particularly along the junctions of neighbouring cells or at the invasion front of aggressive tumors. The change in localization of IQGAP1 from the cytoplasm to the membrane exhibits a certain correlation with the pathological grading of the tumor. According to the statistical analysis, the altered staining pattern from cytoplasmic to membranous and the high expression of IQGAP1 exhibited a significant correlation with poor prognosis (28-32). When IQGAP1 is highly localized in the cell membrane, it may decrease adherent junction stability and render tumor cells easily dissociable. Of note, the overexpression of IQGAP1 may be crucial for several tumors in order to achieve rapid growth, high invasive potential and angiogenesis (31).

IQGAP1 and intercellular adhesion. Epithelial-derived cancer cells must undergo a transformation process from epithelial to mesenchymal to obtain the phenotype of mobility and invasiveness (33). The loss of adhesion function reduces intercellular adhesion and loosens the adhesion with the basal membrane, contributing to cell transformation. High IQGAP1 expression and translocation to the area of adhesion between the cells may affect the stability of the adherens junction (1,34). IQGAP1 also binds to certain catenins and regulates their function. It was demonstrated that IQGAP1 may competitively bind to β-catenin, causing α-catenin to dissociate from the cell-cell junctions. In this way, IQGAP1 weakens cell-cell adhesion (13). Therefore, there is a dynamic equilibrium between the E-cadherin-β-catenin-α-catenin and E-cadherin-β-catenin-IQGAP1 complexes and the proportion of these two complexes determines the strength of adhesion (1). The former complex stabilizes cell-cell adhesion and the latter may promote cell migration. IQGAP1 also opposes the enzymatic activity of GTP. When IQGAP1 combines with Cdc42 and Rac1 and maintains their state of activation, it does not directly interact with β-catenin or disassociate α-catenin from the adhesion complexes, thereby sustaining the stability of actin filaments and leading to strong adhesions (1,34).

IQGAP1 and cell migration and invasion. Coordinated restructuring of microtubules and microfilaments is required for cell polarization and migration. IQGAP1 was shown to play a key role in organizing microtubule networks and the actin cytoskeleton. IQGAP1 may combine with actin to promote microfilament crosslinking, and may also directly combine with plus-end APC proteins to tether the microtubule plus-ends of the actin network. In addition, IQGAP1 may activate the cytoskeletal regulatory factors N-WASP and Dia1 to promote Arp2/3-dependent actin assembly (18,35-37). Furthermore, IQGAP1 may interact with microtubule tip protein CLIP-170 and modulate the transient capture of microtubules at the cortical regions, inducing formation of polarized microtubule arrays and cell polarization (7). In addition to enhancing cell migration caused by rearrangements in the cytoskeleton, IQGAP1 stimulates cell invasion by promoting the degradation of extracellular matrix, which is essential for the metastasis of tumor cells (38). IQGAP1 may combine with, regulate and control the exocyst-Sec3/8 complexes, causing anchoring of membrane type-1 matrix metalloproteinase to invadopodia, a process also modulated by activated Cdc42 and RhoA (21). In addition, IQGAP1 may combine with hyaluronan receptor CD44 to induce recombination of the cytoskeleton to stimulate cell invasion through cell-matrix signaling events, such as ERK-2 signaling (39,40).

IQGAP1 and cell proliferation. Emerging evidence suggests that altering IQGAP1 expression levels may affect the rate of cell proliferation. The overexpression and silencing of IQGAP1 may induce and abrogate cell proliferation, respectively. Jadeski *et al* (26) reported that the overexpression IQGAP1 increased the proliferation of MCF-7 breast epithelial cells and the reduction of endogenous IQGAP1 by RNA interference impeded anchorage-independent and serum-dependent growth of MCF-7 cells. Wang *et al* (41) demonstrated that IQGAP1 modulates cell proliferation, through its phosphorylation and binding to Cdc42, although different domains exhibited varied functions. The C-terminal region of IQGAP1 was shown to reduce cell size, whereas the N-terminus increased cell size by interacting with the mammalian traget of rapamycin, which is required for IQGAP1-mediated cell proliferation. Chen *et al* (42) reported that the growth of hepatocellular carcinoma cells was inhibited by the knockdown or mutation of the IQGAP1 gene and high IQGAP1 expression *in vitro* stimulated cell proliferation through Akt phosphorylation.

IQGAP1 and angiogenesis. Angiogenesis is crucial for the growth and survival of tumors. The results from animal studies indicated that MCF-7 human breast cancer cells overexpressing IQGAP1 formed invasive tumors in nude mice, whereas tumors derived from MCF-7 cells with stable knockdown of IQGAP1 were smaller and less invasive (26). According to previous studies on the angiogenesis model, the expression of IQGAP1 is markedly increased in new vessels. In addition, interference with IQGAP1 may restrain vascular endothelial factor (VEGF)-induced angiogenesis (17,20). IQGAP1 may also regulate angiogenesis by binding to VEGF receptor (VEGFR)2, which is crucial for the recombination and migration of endothelial cells (20,43). Furthermore, IQGAP1 may directly combine with proto-oncogene c-Src, promoting VEGFR2-mediated proliferation of blood vessel endothelial cells through the B-Raf signaling pathway (17). The above-mentioned studies demonstrated that IQGAP1 is involved in endothelial cell angiogenesis and represents a potential therapeutic target for anti-angiogenesis treatments.

IQGAP1 and tumor-related signaling pathways

MAPK signaling pathway. The MAPK signaling pathway is involved in multiple biological processes, such as cell proliferation, differentiation and migration and it is aberrantly

regulated during tumor development (44,45). IQGAP1 may combine with various components of the MAPK signaling pathway and plays an important role in the regulation of cellular processes when stimulated by certain growth factors (10,11). Under stimulation by EGF, the interaction between IQGAP1 and different components of the MAPK pathway may be altered. EGF promotes the association between IQGAP1 and MEK-1, while decreasing the interaction between IQGAP1 and MEK-2 (46). It was previously suggested that MEK-1 enhances cell proliferation, whereas MEK-2 enhances differentiation and IQGAP1 may be more likely to activate the MEK-1 signaling pathway (11,47). Furthermore, the combination of IQGAP1 and MEK is crucial for the regulation of ERK-2 activation by EGF. Previous data demonstrated that IQGAP1 is required for B-Raf activation by VEGF. The association of B-Raf and IQGAP1 resulted in higher kinase activity and the knock-out of IQGAP1 alleviated the B-Raf activation stimulated by VEGF (10). However, whether it is the interaction between IQGAP1 and B-Raf that increases the sensitivity of B-Raf to EGF or IQGAP1 binds more readily to activated B-Raf has not been fully elucidated.

IQGAP1 may bind to ERK-2 through its WW functional domain and adjust the activity of ERK-2. In cells lacking endogenous IQGAP1, ERK-2 cannot be activated and the high expression of IQGAP1 may reduce the activity of ERK-2. Therefore, only the proper expression of IQGAP1 can ensure maximum activation of ERK-2 (46). It was demonstrated that the cell proliferation stimulated by IQGAP1 is inhibited through the downregulation of the MAPK signaling pathway in MCF-7 breast cancer cells (26). Moreover, IQGAP1 silencing inhibits the ERK-mediated phosphorylation of transcription factor Elk-1, leading to the suppression of migration of tumor cells (39,46). The above-mentioned findings demonstrated that IQGAP1 plays a vital role in MAPK signal transduction, regulating cell proliferation and differentiation and contributing to tumorigenesis.

β-catenin-mediated signal transduction. β-catenin, an oncogenic protein, is a crucial component of E-cadherin adherens junction complexes and an important molecule of the Wnt pathway, participating in cell proliferation and adhesion (48-52). Under normal conditions, β-catenin and E-cadherin form complexes at cell-cell junctions (53). When Wnt signaling is activated, the overexpression of IQGAP1 may protect soluble β-catenin against degradation by casein kinase I and glycogen synthase kinase 3β, promote β-catenin nuclear localization and transcription factor activation accordingly, inducing the expression of multiple oncogenes and cell cycle proteins (54-56). Thus, it is clear that IQGAP1 is a crucial regulatory protein of β-catenin.

IQGAP1 and Ca^{2+}/calmodulin-mediated signal transduction. The Ca^{2+}/calmodulin-mediated signal transduction system may interact with other signal transduction systems through IQGAP1 and the concentration of Ca^{2+} may also affect the IQGAP1-calmodulin-mediated cell-cell adhesion. When the Ca^{2+} concentration is low, IQGAP1 binds to Rac1 and Cdc42, promoting multimerization of actin and stabilizing cell-cell adhesion; when its concentration is higher, Ca^{2+} binds to calmodulin and hinders the combination of Cdc42 and IQGAP1, leading to weakened cell-cell adhesion mediated by E-cadherin (13). In addition, the overexpression of IQGAP1 in SW480 colon carcinoma cells was found to promote β-catenin-mediated transcriptional co-activation and this stimulation was also shown to be regulated by calmodulin (54).

3. Conclusion

In conclusion, accumulating evidence indicates that overexpression and altered localization of IQGAP1 are commonly detected in certain types of cancer cells and tissues and exhibit a correlation with poor prognosis. This scaffolding protein, comprising multiple structural domains, may interact with different protein molecules, integrating diverse signaling pathways, and is involved in cell biological activities, including proliferation, migration and apoptosis. Moreover, some of the IQGAP1 binding partners are involved in tumorigenesis and tumor progression. The studies mentioned above indicated that IQGAP1 sits at the crossroad of different cell biological processes and may contribute to cancer progression. However, the mechanisms underlying the triggering of the abnormal expression of IQGAP1, whether IQGAP1 is an oncoprotein directly involved in tumor development and the stage of tumor cell transformation and invasion during which IQGAP1 is upregulated, have not been fully elucidated. Therefore, further investigations are required to dissect the function and mechanism of IQGAP1 in tumor development and progression.

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