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Multifaceted Roles of Carbon Anhydrase IX in Cancer Cell Proliferation, Survival, Metastasis and Therapy Resistance and Indication of Promising Novel Therapies by its Inhibitors

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Abstract

Cancer cells of solid tumors suffer from decrease in blood supply and hypoxia. To compensate deterioration in the intra-tumorous environment, hypoxia inducible factors, HIF-1α, HIF-2α and HIF-3α, are induced and numerous target genes are activated by these HIFs. Of these, CA9 is highly important because of its involvement in oncogenesis of solid tumors and malignant lymphomas. The essential function of CA9 in cancer is regulation of intracellular phi and extracellular pHe by mitigating the decreased pH due to excessed glycolysis in cancer cell. In this review article, first, CA9's multifaceted roles in cancer cell proliferation, survival and metastasis and therapy resistance were summarized in association with effects of CA9 inhibitors. Second, after clarifying the CA9 activation via HIF-1α in the KRAS/RAF/MEK/ERK and PI3E/AKT/mTOR signaling pathways, molecular targeted therapies by means of CA9 inhibitors against therapy resistant triple negative breast cancer (TNBC), pancreatic ductal adenocarcinoma (PDAC), intraductal papillary mucinous neoplasms of the pancreas (IPMN) and adult T-cell leukemia/lymphoma (ATL) were shown to be promising novel therapies.

Keywords: CA9 • HIF • KRAS • PI3K/AKT/mTOR • TNBC • PDAC • IPMN • ATL

Introduction

Cancer cells of solid tumors suffer from decrease in blood supply and hypoxia [1,2] and require adequate blood perfusion to obtain nutrients and oxygen for proliferation and survival. To compensate deterioration in the intra-tumorous environment, hypoxia inducible factors (HIFs), HIF-1α, HIF-2α and HIF-3α, are induced [3,4]. Under normoxia, HIF-1α is subjected to ubiquitin-proteasomal degradation by von hippel-lindau tumor suppressor protein (pVHL) [5,6] or tumor suppressor protein p53 [7,8], whereas factor inhibiting HIF (FIH) inhibits HIF's recruitment of co-activator CBP/p300 [9,10], leading to inhibition of its functions. However, under hypoxia, expression of HIF-1α is activated and HIF-1α is accumulated in cytoplasm. Then, HIF-1α is translocated to nucleus via the nuclear trans localization signals [11] and forms a heterodimer with a constitutively expressed HIF-1β (known as aryl hydrocarbon receptor nuclear translocator [ARNT]) [12,13]. The HIF-1α/HIF-1β complex directly binds to hypoxia response elements (HREs) of target genes [14] with recruitment of CREB-binding protein (CBP)/p300 transcriptional co-activator [11] and activates numerous target genes involved in energy metabolism (glucose transporters [GLUTs] 1/2/3, hexokinases 1/2, phosphofructokinase L, aldolase A, pyruvate kinase M, phosphorglycerate kinase 1, enolase 1 and lactate dehydrogenase A), metabolic adaptation/pH regulation (carbonic anhydrase IX [CA9] and CA12), cell proliferation and survival (insulin-like growth factor 2 [IGF2], IGF binding proteins 1/2/3, transforming growth factors [TGFs] α/β, epidermal growth factor [EGF] and c-myc), angiogenesis (vascular endothelial growth factor [VEGF], VEGF receptor-1, leptin, LDL-receptor-related protein 1 and adrenomedullin), erythropoiesis (erythropoietin, transferrin, transferrin receptor and ceruloplasmin) and vasomotor control (nitric oxide synthase, adrenomedullin, α1B-adrenergic receptor and endothelia-1) [1,15-17].

Of these target genes, CA9 is highly important because the involvement of CA9 in oncogenesis [18,19] and therapy resistance [20-23] has been indicated and CA9 has been recognized to be an important target for cancer therapies [24-26]. CAs are metalloenzymes that containing a zinc, catalyze the reversible hydration of carbon dioxide to bicarbonate and proton: $CO_2 + H_2O \leftrightarrow HCO_3^- + H^+$. CAs are evolutionally grouped into six classes, α, β, γ, δ, ζ and η [27]. The human CAs belong to the α-class and consist of catalytically active 12 isoforms (CAs I–IV, CAs VA–VB, CAs VI–VII, CA IX and CAs XII–XIV) [28] while other 3 isoforms CA VIII, X and XI lack the metal ion within the active site. The essential function of CA9 in cancer is regulation of intracellular pHi and extracellular pHe by mitigating the decreased pH due to excessed glycolysis in cancer cells [19,28], leading to cancer progression [24-26,29]. In addition, molecular targeted therapies (MTTs) against CA9 by means of CA9 inhibitors are suggested to be effective against broad solid tumors and malignant lymphomas [2,24,26,30-33].

In this review, we show the current status about CA9 research on its multifaceted roles in cancer cell proliferation, survival, metastasis and therapy resistance and we indicate that molecular targeted therapies by means of CA9 inhibitors against therapy resistant triple negative breast cancer (TNBC), pancreatic ductal adenocarcinoma (PDAC), intraductal papillary mucinous neoplasms of the pancreas (IPMN) and adult T-cell leukemia/lymphoma (ATL) are promising novel therapies.

Overview of the regulation and functions of CA9

Under hypoxia in solid tumors, CA9 is induced by HIFs, in particular HIF-1α. In the promoter regions of *CA9*, there are several *cis*-acting elements [34,35]. Of these, HRE is the most potent activating element of *CA9* transcription by binding of the HIF-1α/HIF-1β complex with recruitment of CBP/p300 [5,35,36]. In addition, there are other enhancer elements of binding sites for specificity protein (SP)-1 and SP-3 [35,37] and activator protein-1 (AP-1) [34,37] in (Figure 1). Activation of HIF-1α is also induced by various mechanisms [1,2,38]. Proteasomal degradation of HIF-1α and HIF-2α is inhibited by inactivation of pVHL [5,6] and p53 [7,8], leading to accumulation of the HIF-1α and HIF-2α protein, while inactivation of the factor inhibiting HIF (FIH) that inhibits recruitment of coactivator CBP/p300

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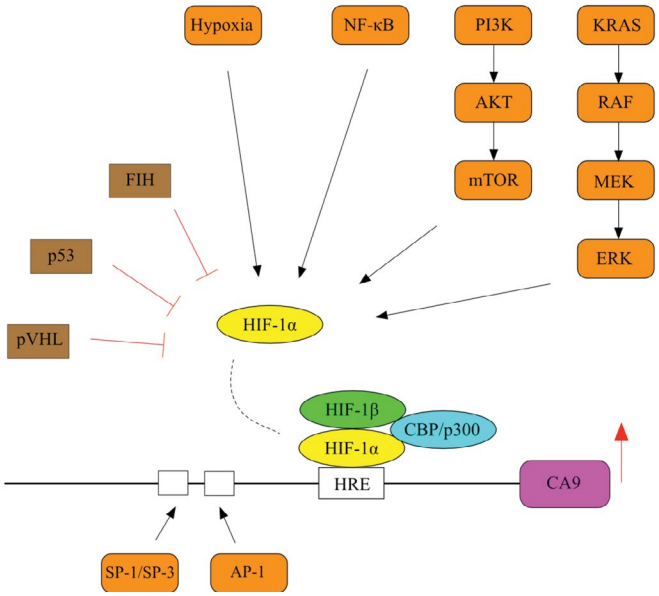

Figure 1. Overview of CA9 regulation: Under normoxia, functions of HIF-1α are inhibited by pVHL, p53 or FIH, while activation of HIF-1α induced under hypoxia or by various factors such as the NF-κB, PI3K/AKT/mTOR and KRA/RAF/MER/ERK signaling effectors. Then, HIF-1α in cytoplasm is translocated to nucleus and forms a heterodimer with a constitutively expressed HIF-1β. The HIF-1α/HIF-1β complex directly binds to hypoxia HRE of CA9 with recruitment of CBP/p300, leading to activated transcription of CA9 mRNA. In addition, SP-1, SP-3 and AP-1 enhances transcription of CA9 mRNA. Abbreviations: CA9, carbon anhydrase IX; FIH, factor inhibiting HIF; HIF, hypoxia inducible factor; HRE, hypoxia response element; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase; pVHL, von Hippel-Lindau tumor suppressor protein.

[9,10] recovers the recruitment, resulting in activation of HIF-1α and HIF-2α. Transcription of the HIF-α mRNA is activated by components of the nuclear factor kappa B (NF-κB) signaling pathway such as 50-RelA [39-41], IKKβ [42] or TRAF6 [43]. In addition, translation of the HIF-1α mRNA is activated by the phosphatidylinositol 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) signaling pathway [17,44] including loss of inhibitory phosphatase and tensin homolog (PTEN) [45] and the KRAS/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathway [17,46-48]. Activation of CBP/p300 by ERK also activates the function of HIF-1α [49]. In solid tumors under hypoxia, CA9 regulates intracellular (pHi) and extracellular (pHe) acidosis in the tumor microenvironment and promotes cancer progression by inducing cell proliferation [18,19], cell survival by apoptosis inhibition [50,51], cell migration, invasion and metastasis [26,29,52], therapy resistance [21,53,54] and tumorigenicity [55] as in (Figure 2).

Cell proliferation

Activated expression of a membrane-localized CA9 induces alkalization of intracellular pHi and acidification of extracellular pHe [19,28]. Compensation of the pHi and pHe by CA9 drives cancer cell proliferation, survival and migration [18,19]. In fact, CA9 expression is recognized as a biomarker of poor prognosis in solid tumors [25,56]. There are numerous reports on the CA9 expression that is correlated with severity of malignancy and poor prognosis in solid tumors and lymphomas such as breast cancer [21-23,54,57,58], PDAC [59-61], renal cell carcinoma (RCC) [62,63], non-small cell lung cancer (NSCLC) [64,65], colorectal cancer (CRC) [66], hepatocellular carcinoma (HCC) [67], prostate cancer [20], cervical cancer [68], brain tumor [69], thymic cancer [70], classical Hodgkin lymphoma [71,72], B-cell lymphoma [2,73,74], T-cell lymphoma [75] and ATL [55].

Cell survival by apoptosis inhibition

In many cancers, apoptosis is suppressed and this condition is favorable for cancer cell survival [50,51]. Apoptotic signaling pathways essentially consist of the extrinsic death receptor-dependent pathway and the intrinsic mitochondrial apoptosis pathway [76-78]. The extrinsic death receptor-dependent pathway is activated by binding of ligands such as tumor necrosis factor (TNF), Fas ligand (FasL) or TNF-related apoptosis-inducing ligand (TRAIL) to their corresponding death receptors, i.e., type 1 TNF receptor (TNFR1), Fas (also known as CD95 or Apo-1), TRAIL receptor 1 (TRAILR1 or DR4) or TRAIL receptor 2 (TRAILR2 or DR5) [79]. The activated ligand-bound death receptors (TNFα-TNFR1, FASL-FAS, TRAIL-TRAILR1 or TRAIL-TRAILR2) that contain intracellular death domain (DD) [80] recruit and interact with adaptor proteins Fas-associated death domain (FADD) and TNF receptor-associated death domain (TRADD) via DD [79].

In addition to DD, these adaptor proteins FADD and TRADD have also death effector domain (DED) [81] and interact with the initiators pro-caspase-8 and pro-caspase-10 that contain DED. The death receptors, FADD/TADD and pro-caspase-8/-10 thus form death-inducing signaling complex (DISC) [82], which promote auto-activation of pro-caspase-8 and procaspase-10, resulting in caspase-8 and caspase-10 that in turn activate the effectors caspase-3, -6 and -7 [83], leading to apoptosis. The intrinsic mitochondrial apoptosis pathway [84,85] is activated by various external stresses (irradiation, chemotherapy or others) and internal stimuli (irreparable genetic damage, hypoxia, cytosolic Ca^{2+} elevation or oxidative stress) [78,85] and numerous proteins of the B-cell lymphoma 2 protein (Bcl-2) family are activated. Proteins of the Bcl-2 family contain one to four different Bcl-2 homology domains (BH1, BH2, BH3 and BH4) and anti-apoptotic proteins have all the four BH domains (Bcl-2, Bcl-xL, A1, Mcl-1 and Bcl-w), while pro-apoptotic proteins contain either multidomains BH1, BH2 and BH3 (Bax, Bak and Bok) or only BH3 (Bid, Bad, Bim, Bmf, Bik, Hir/DP5, Blk, Nip3, BNip3/Nix, Puma and Noxa) [78,86].

When the intrinsic mitochondrial apoptosis pathway is stimulated, activation of pro-apoptotic proteins is induced and the activated pro-apoptotic proteins suppress anti-apoptotic proteins, resulting in disruption of mitochondrial membrane outer membrane permeabilization (MOMP) [87] that promotes release of cytochrome c from the mitochondrial inter membrane space into cytosol. Then, cytochrome c interacts with apoptosis protease-activating factor 1 (Apaf- 1) and forms a complex known as apoptosome [88]. The apoptosome recruits initiator pro-caspase-9 and promotes its autoactivation into caspase-9 that in turn activates executors caspase-3, -6 and -7 and finally apoptosis of cell is induced [85].

In addition, tumor suppressor p53 is involved in both the extrinsic and intrinsic apoptosis pathways [78,89,90], whereas there are several inhibitors of apoptosis proteins (IAPs) that contain one to three baculoviral IAP repeat (BIR) domains and are defined as BIR-domain-containing proteins (BIRPs) [91,92]. In solid tumors, apoptosis is suppressed by various mechanisms such as increased expression of anti-apoptotic proteins, decreased expression of pro-apoptotic proteins, increased expression of IAPs, decreased expression of caspases, impaired death receptor signaling pathway or defect/mutation in p53 [77,78,93]. However, CA9 inhibitors abrogate apoptosis inhibition of cancer cells. For instance, the CA9 inhibitor sulphonamide induces decreased intracellular pHi, increased intracellular free radical (ROS), reduced mitochondrial membrane potential that increases the production of free radicals, increased expression of PARP (an indicator of DNA damage), cell cycle arrest, increased expression of the mRNA of caspase-3, -8 and -9,

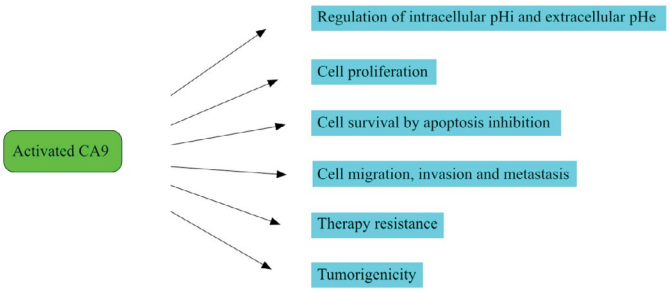

Figure 2. Multifaceted roles of CA9 in cancer progression of solid tumors: CA9 regulates intracellular pHi and extracellular pHe and promotes cancer progression by inducing cell proliferation, cell survival by apoptosis inhibition, cell migration/invasion/metastasis, therapy resistance, and tumorigenicity.

increased expression of pro-apoptotic proteins Bax and others, triggering of the apoptotic morphology and reduced viability and proliferation of cells [94]. Taken together, CA9 inhibitor reverses the apoptosis inhibition in cancer cells and induces reduction of cell proliferation. The similar results were obtained by other studies [68,95,96].

Cell migration, invasion and metastasis

CA9 plays also an important role in cancer cell migration and invasion in association with integrins and metalloproteases (MMPs) [26,29,97]. Various parts of CA9, including the proteoglycan-(PG)-like domain, intracellular domain and catalytic domains, are involved in the processes of cell adhesion and invasion of cancer cells [29,97]. CA9 is associated with the collagen and laminin receptors integrin β1, integrin α2, integrin α3, integrin α5 and integrin α6 [97]. These integrins promote focal adhesions that are early steps of cell mobility and migration toward metastasis. In addition, a matrix protease MMP14 in association with CA9 participates in matrix degradation and invadopodia formation [97,98], leading to cell invasion and metastasis. Proton (H^+) excretion by CA9 and consequent extracellular acidification (pHe) are prerequisite for the MMP14 activity [29,97].

A pH regulatory protein Na^+/H^+ exchanger 1 (NHE1) also contributes to the pHe acidification to promote the MMP14-related matrix degradation [99,100]. CA9 inhibitors SLC-0111 and AA-06-05 impair cancer cell migration and invasion in the *in vitro* experiments using a breast cancer cell line (MDA-MB-231) and a lung cancer cell line (A549) [101]. The same results have been obtained by other studies by means of CA9 inhibitors sulfonamide (CAI17) [102] or VD11-4-2 [103] in the *in vitro* systems with breast cancer cell lines 4T1, 66cl4, 67NR, MDA-MB-231 [102] or MCF-7, MDA-MB-231 [103]. Suppression of cell invasion and metastasis by CA9 inhibition is also confirmed by the *in vivo* animal models [98,102,104]. Accordingly, CA9 depletion by shRNAs also induces inhibition of cancer cell migration and invasion [52,102,105].

Therapy resistance by phenotypic plasticity (CSC and EMT)

There are various mechanisms of therapy resistance [67,106,107]. Primary resistance is derived from existence of the clones that have already resistant mutations before treatment of MTT [108,109], while acquired resistant is induced by different mechanisms such as secondary mutations of the target molecule [110,111], activation of downstream signaling pathways [112,113], or activation of bypass signaling pathways [114,115]. Intra-tumoral heterogeneity (ITH) [116,117] due to coexistence of cancer stem cell (CSC) [118,119] or clones harboring resistant mutations [120,121], which are accelerated by epigenetic changes [122,123], is another cause of therapy resistance. Accordingly, importance of phenotypic plasticity in resistance has been also recognized [124,125]. Phenotypic plasticity is induced by dedifferentiation (reversion from differentiated cell to stem cell) or transdifferentiation (direct shift from one differentiated cell type to another) [126].

Therapy resistance by dedifferentiation (reversion to CSCs) [124,127] is observed in TNBC [128,129], acute myeloid leukemia [130] and neuroblastoma [131].

CSCs possess stem cell features, i.e., self-renewal and differentiation potential [132] and stemness is induced by various signaling pathways and transcription factors such as Wnt signaling, Notch signaling, Hb signaling, PI3K/AKT/mTOR signaling, NF-κB signaling, JAK/STAT signaling, SOX2, NANOG and HIF [126,127,129]. Fortunately, there are several reports [21-23,58] that therapy resistance by CSCs in TNBC were abrogated by small CA9 inhibitors (CAI017, U104, RC44 or acetazolamide) or CA9-specific siRNAs. These studies show potential of CA9 inhibitors against therapy resistant TNBC. However, exact mechanisms of these anti-CA9 treatments should be further clarified. Therapy resistance by transdifferentiation is exemplified by epithelical-mesenchymal transition (EMT) [125,133,134] and EMT is found in NSCLC [135-137], prostate cancer [138], hepatocellular carcinoma [139] or gastric cancer [140]. Transcription factors such as Zeb1, Twist1, Snail1 and Slug are involved in EMT [126,129,133]. Fiaschi [20] proved the inhibition of EMT and invasiveness of prostate cancer cell lines by means of genetic silencing of CA9 or pharmacological inhibition of CA9 with sulfonamides-sulfamides inhibitors. These results are indicative of future therapeutic possibility of anti-CA9 treatment against NSCLC, HCC or gastric cancer.

In addition, trial reports on the CA9 inhibitors that enhance the sensitivity of combination therapy with conventional cytotoxic chemotherapy [21,141] or radiation therapy [22] also demonstrate a future therapeutic strategy of CA9 inhibitors.

The KRAS/RAF/MEK/ERK signaling pathway and bypass signaling

KRAS mutation is broadly observed in various cancers such as PDAC (67.61%), CRC (35.77%), NSCLC (20.42%) or others [142] and it causes activation of the downstream signaling effectors, leading to cancer progression. Concerning gene mutations of PDAC, KRAS mutation is observed in 93%, while other mutations of p53 (72%), *CDKN2A* (30%) and *SMAD4* (32%) are also found [143]. Of these, KRAS mutation is the most important [61,144,145] because it is required for initiation and maintenance of PDAC [144,146]. The KRAS signaling pathways are further ramified into the RAF/MEK/ERK [147-150], the PI3K/AKT/mTOR [151,152], the RALGDS/RAL [153,154] and other signaling pathways (TIAM1/RAC, PLCε and others) [142,155]. The RAF/MEK/ERK pathway is involved in oncogenesis of PDAC via CA9 activation [61], while the PI3K/AKT/mTOR pathway also activates CA9 via HIF [17,44], but the RALGDS/RAL pathway may not be associated with CA9 activation [153,154]. Interaction of the PI3K/AKT/mTOR with CA9 will be later discussed.

In addition to the KRAS/RAF/MEK1,2/ERK1,2 signaling pathway, there are several ERK signaling pathways that are not mediated by KRAS, i.e., the MEK4/JNK, the MEK5/ERK5 and the MEK6/p38 [156,157]. However, the KRAS/RAF/MEK1,2/ERK1,2 signaling pathway plays the central role in activation of CA9 via HIF-1α by mediating eukaryotic initiation factors (eIFs) [158,159]. In fact, the downstream effectors ERK1 and ERK2 stimulate translation of HIF-1α mRNA by activating several eIFs [17,46-48], resulting in CA9 activation.

In the KRAS-mutant tumors, exemplified by PDAC [61,144,145], the KRAS/RAF/MEK/ERK signaling effectors are thought to promote oncogenic progression. Thus, numerous inhibitors against the KRAS mutants and its downstream effectors have been developed [141,150,155,160,161]. However, therapeutic results by the inhibitors against KRAS [162,163], RAF [164] or MEK [165,166] for PDAC have not been satisfactory [61,162,163]. Certainly therapy resistant mutation of KRAS such as G12C is a cause of these unmet results [142,167], but activation of bypass signaling is a more serious problem in targeting the KRAS/RAF/MEK/ERK signaling pathway [145,161]. Of various bypass signaling pathways, the PI3K/AKT/mTOR pathway is important. Thus combination therapy of the KRAS/RAF/MEK/ERK and PI3K/AKT/mTOR inhibitors was pursued [168,169]. However, an early clinical trial of dual-pathway inhibition revealed moderate efficacy and toxicity significantly more severe than single inhibition regimen [170], resulting in stagnation of the dual-inhibition strategy.

In contrast, CA9 inhibition with SLC-0111 [59-61] or FC12-531A [59,60] induces reduction of PDAC cell growth in several models, including the *in vitro* cell line models [59-61], the *in vivo* animal models, the human cell-line derived xenograft models and the human patient-derived xenograft (PDX) models [61]. This PDAC cell killing is enhanced by HIF-1α inhibition [59,60], indicating that CA9 activation is mediated by HIF-1α activation. In addition, HIF-1α stabilization is induced by translation activation of HIF-1α mRNA in the KRAS/MEK/ERK-activated PDAC cell lines [61], while transcription activation of HIF-1α mRNA may not play a major role in CA9 activation in the KRAS mutant PDAC cells [61]. Certainly single administration of CA9 inhibitor is effective against PDAC cell growth inhibition, but combination therapy with HIF-1α inhibitor [59,60] or conventional cytotoxic chemotherapy using gemcitabine [61] shows more potent efficacy than the CA9 inhibitor single regimen. Efficacy and safety of CA9 inhibitor SLC-0111 has been scrutinized under clinical trials [59]. Since CA9 is activated by both the KRAS/RAF/MEK/ERK and PI3K/AKT/mTOR signaling pathways, this CA9 inhibition strategy is expected to be effective also against bypass activation of the PI3K/AKT/mTOR signaling in KRAS mutant PDAC.

Furthermore, KRAS mutation is also frequently found in IPMN [171-174]. The frequency of KRAS mutation in IPMN ranges from 38% [175] through 50% [176] or 61% [177] to 81% [178]. Among other gene mutations in IPMN [176,179], RAF mutation (2.7%) [180], PI3K mutation (11%) [181], AKT mutation (8.3%) [182] and PTEN loss (36%) [182] are relevant to CA9 activation, because the KRAS and RAF mutations induce activation of the KRAS/RAF/MEK/ERK signaling pathway while the PI3K mutation, AKT mutation and PTEN loss are associated with activation of the PI3K/AKT/mTOR signaling pathway, both leading to CA9 activation via HIFs. In this regard, just as in PDAC, CA9 inhibitors may pave a path to novel molecular targeted therapies against IPMN.

The PI3K/AKT/mTOR signaling pathway and tumorigenicity

Since CA9 inhibitor effectively reduces cell growth of KRAS mutant PDAC, CA9 inhibitor strategy is expected to be also applicable to the solid tumors and lymphomas that are activated by the PI3K/AKT/mTOR signaling pathway via HIFs and CA9. Phosphorylation of phosphoinositides (PtdIns) is a first step in activation of the PI3K/AKT/mTOR signaling pathway [183-185]. PtdIns(4,5)P2 binds to the pleckstrin homology (PH) domain of the agonist-activated PI3K in the membrane. Then, PI3K phosphorylates PtdIns(4,5)P2 and generates PtdIns(3,4,5)P3. In turn, PtdIns(3,4,5) is produced into PtdIns(3,4)P2 by Src-homology 2 containing inositol polyphosphate 5-phosphatase 1 (SHIP1). Then, the AKT-activating PtdIns(3,4)P2 is converted into inactive PtdIns(3)P by inositol polyphosphate-4-phosphatase (INPP4) [186]. PTEN reverses PI3K function by dephosphorylating PtdIns(3,4,5)P3 into PtdIns(4,5)P2 [183,185,186-188].

When PI3K is activated by its agonists, AKT in cytoplasm is recruited to the membrane and is bound via its PH domain to PtdIns(3,4,5)P3 and PtdIns(4,5)P2 that are produced by agonist-stimulated PI3K and SHIP1, respectively. This binding of AKT to PtdIns(3,4,5)P3 and PtdIns(4,5)P2 induces conformational change of AKT for consequent phosphorylation of Thr308 and Ser473 [189,190]. Then, Thr308 is phosphorylated by phosphoinositide-dependent kinase 1 (PDK1) [191,192], whereas Ser473 is phosphorylated by mTORC2 [193]. These phosphorylations activate AKT and activated AKT is then translocated through cytoplasm into nucleus and phosphorylates various substrates including mTORC1 [183,194]. mTORC1 then activates HIF-1α under normoxia [44,195,196] by stimulating translation of HIF-1α mRNA [17]. Translation of eukaryotic mRNA consists of four phases, i.e., initiation, elongation, termination and ribosome recycling [158,159].

Initiation is the rate-limiting phase [197] and starts from formation of pre-initiation 43S complex consisting of 40S ribosome subunit, termary complex (of eIF2, GTP and Met-tRNAi), eIF1, eIF1A, eIF3 and eIF5 [158]. This pre-initiation 43S complex attaches to unwounded mRNA activated by the eIF4F complex (consisting of eIF4E [a mRNA-cap binding component], eIF4G [a scaffolding protein] and eIF4A [an ATP- dependent RNA helicase]) [198] with assistance of eIF4B and poly(A)-binding protein (PABP) [199]. Then 48S initiation complex is formed and recognition of the initiation codon starts [158,159]. On the one hand, mTORC1 stimulates phosphorylation of 4E-binding proteins (4E-BPs), which is grouped into 4E-BP1, 4E-BP2 and 4E-BP3. Phosphorylation of 4E-BP1 induces its release from eIF4E, leading to association of eIF4E with eIF4G. This then induces assembly and activation of the mRNA-cap binding eIF4F complex (eIF4E, eIF4G and eIF4A) [158,159,198]. The activated eIF4F complex stimulates translation of mRNA. On the other hand, mTORC1 activates ribosomal S6 kinases (S6Ks). The relevant substrates of S6Ks in translation regulation are ribosomal protein S6 (rpS6), eIF4B, eukaryotic elongation factor 2 kinase (eEF2K) and programmed cell death 4 protein (PDCD4) [159], which finally stimulate translation of mRNA.

Taken together, the PI3K/AKT/mTOR signaling effectors activate translation of HIF-1α mRNA. Then, stimulated HIF-1α activates transcription of CA9 via HRE. The PI3K/AKT/mTOR signaling pathway, HIF-1α and CA9 are involved in oncogenesis of ATL [200,201], which is caused by human T-cell leukemia virus type 1 (HTLV-1) [202,203]. On the one hand, proliferation of ATL cells is suppressed by numerous inhibitors against the PI3K/AKT/mTOR signaling effectors, including PI3K inhibitors (idelalisib [204], NVP-BMK120 [205,206], CDUC907 [206] and copanlisib [207]), AKT inhibitor (MK2206 [208]), mTORC1 inhibitors (torin2 [209], ramapycin [210] and RAD001/everolimus [205,210,211]), mTORC1/mTORC2 dual inhibitor (torin2 [209], PP242 [210] and AZT8055/sapanisertib [210,212]), PI3K/mTORC1 dual inhibitor (NVP-BEZ235 [205]), or combination therapy of PI3K inhibitor with JAK1/2 inhibitor [212] or NF-κB inhibitor [207]. These *in vitro* and *in vivo* experimental trials mean indirect evidence of the involvement of the PI3K/AKT/mTOR signaling pathway in oncogenesis of ATL.

On the other hand, expression of AKT and CA9 is correlated with tumorigenicity. Yamaguchi [208] obtained AKT-activated ST1-N1 subclone from ATL patient-derived ST1 cell line [213] by serial transplantation into immune deficient NOG mice and proved correlation of AKT expression with tumorigenicity. Inhibition of AKT by inhibitor MK2206 abrogated tumorigenicity of ST1-N1. Furthermore, Nasu [55] confirmed that the responsible effector of tumorigenicity in ST1 was CA9 and that CA9 was expressed on ATL primary cells in lymph nodes of all the four cases of ATL patients. Tomita [214] demonstrated high expression of AKT and HIF-1α in both ATL cell lines and primary ATL cells. Cell growth inhibition by HIF-1α depletion using siRNA was also shown. These data clearly indicate that CA9 plays a central role in ATL oncogenesis and that CA9 inhibitors are expected to be effective against ATL. In addition, NF-κB plays a plethora of roles in the multistep oncogenesis of ATL at its early stage [215-218] and activation of HIFs by NK-κB has been detected in various mechanisms [39-43]. As a logical consequence, linkage between NK-κB and CA9 via HIFs in ATL oncogenesis is quite possible. In sum, these abundant experimental data strongly suggest that administration of CA9 inhibitors can be a promising novel therapeutic strategy against therapy resistant ATL.

Conclusion

CA9 is involved in oncogenesis of solid tumors and malignant lymphomas by its multifaceted roles in cancer cell proliferation, survival and metastasis and therapy resistance. In consequence of its critical role in malignant progression, CA9 inhibitors have great potentialities targeting therapy resistant TNBC and PDAC. Furthermore, since CA9 is suspected to be a substantial effector in oncogenic processes, a therapeutic strategy by CA9 inhibitors against IPMN and ATL is quite promising. Thus, one should start the *in vitro* experimental therapeutic trials for IPMN and ATL cells.

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Conflicts of Interests

The author declares that there is no conflict of interests.

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