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Review Article

Role of A-Kinase Anchoring Proteins in Respiratory Disorder

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ABSTRACT

Protein kinase A, plays a crucial role in cAMP signaling and its further downstream regulation of received stimuli. A kinase anchoring protein (AKAP); a binding protein provides a platform to the substrates to perform signaling events. AKAP serve its role in cAMP signaling by interacting with GPCR, PKA, ACs, Epac or PDE. More than 70 AKAP have been identified from which role of some AKAPs have been identified. AKAPs are found in heart, brain, testis, skeletal muscle, pancreas, placenta, oocytes, thyroid, kidney, liver, lungs. Amongst which the regulatory role of some AKAPs like AKAP149, AKAP5, AKAP4 and AKAP18 has been reported in mitochondrial function, recycling of β1-adrenoceptors, sperm motility, and insulin secretion respectively; whereas AKAP149 interaction is involved in reverse transcriptase activity of HIV; mutation in AKAP9 isoform causes prolonged QT interval, AKAP10 causes arrhythmia, risk of colorectal cancer and familial breast cancer. Although its dominating role is majorly reported in heart and brain, few reports are available regarding its role in respiratory system. The probable action of AKAP is via IL-8 release; IL-10, IL-6 and iNOS synthesis; mitochondrial function mediation, ROS generation and apoptosis. In the current review, attempt has been made to explore the general role of AKAPs with special emphasis in respiratory system.

Keywords: Anchoring protein, Cyclic adenosine monophosphate, Protein kinase A, QT interval, Inflammatory mediators.

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INTRODUCTION

Protein Kinase A (PKA), a holoenzyme plays crucial role in protein phosphorylation. Protein Kinase A upon activation by cyclic adenosine monophosphate (cAMP) mediates downstream regulation of the stimuli received by the receptor. Interaction of PKA to the A kinase anchoring protein(AKAP) require for the further signaling.[1]

AKAP is a family of scaffolding protein which is structurally diverse but functionally similar and executes its action by binding to PKA. Numerous AKAP family members have been identified,[2] out of which role of some AKAPs have been identified. Structure of AKAP comprises of targeting domain and binding domain (Figure 1). PKA contains two regulatory subunits which are Regulatory subunit I (RI) and Regulatory subunit II (RII). RII subunit of PKA preferentially binds with the binding domain of AKAPs due to presence of amphipathic helix consisting of 14-18 amino acids. Although some AKAPs have been found which binds specifically to the RI subunit of PKA. Targeting domain is unique property to each of AKAP for restricting its location within the cell.[3] It directs AKAP/PKA complex to the defined location in the cell.

Basic function of AKAP is to coordinate the downstream regulation of the intracellular pathways. The pathways which triggers via receptor by extracellular signals such as neurotransmitter, hormones, etc. AKAPs exhibits significant role in cAMP signaling by interacting with G protein coupled receptors (GPCRs), PKA, Adenylyl cyclase (ACs), Exchange protein directly activated by Protein kinase (Epac) or Phosphodiesterase (PDEs).[4] Along with other signaling proteins AKAPs also provides a pathway to direct signaling events by forming multicomponent complexes. The examples of signaling proteins such as protein phosphatases or protein kinases such as Akt/Protein kinase B, Protein kinase c, Protein kinase D, Protein kinase N, Extracellular signal regulated kinase 1/2(ERK1/2), or glycogen synthase kinase 3 β (GSK3β).[5] AKAP also provides the basis of cAMP compartmentalization and molecular architecture.[6] The role of AKAPs is dominantly reported in heart and brain, its presence is also found in testes, skeletal muscle, kidney and lungs. Amongst these few research articles are available for the effect on lungs. In the current review attempt has been made to explore the role of AKAPs in respiratory system.

Nomenclature of AKAPs

Formerly the various types of AKAPs were named based on their molecular weight, which was characterized with the help of Sodium Dodecyl sulfate (SDS) gel electrophoresis. For example, AKAP79 type found in human was named because of its migration at 79 kDa in SDS Polyacrylamide gel electrophoresis (PAGE). The other examples are Bovine AKAP75 and Murine AKAP150. However, later the existing AKAPs were renamed by Human genome organization nomenclature committee (HGNC) by numbers in chronological order starting from AKAP1 to AKAP14. Thus, formerly known AKAP350 or AKAP450 is now alternatively known as AKAP9 as per Human Genome Organization Nomenclature Committee (HGNC). However molecular weight based names are more commonly preferred in practice in spite HGNC recommendation.[5]

Distribution

AKAPs have been identified in various cellular compartments such as dendrites, mitochondria, centrosomes, endoplasmic reticulum, vesicles, plasma membrane with the help of immunohistochemical studies and subcellular fractionation. The precise details of targeting have been determined for only a few molecules. For example, AKAP15/18 and mAKAP are distributed in plasma membrane and perinuclear location respectively (Table 1).

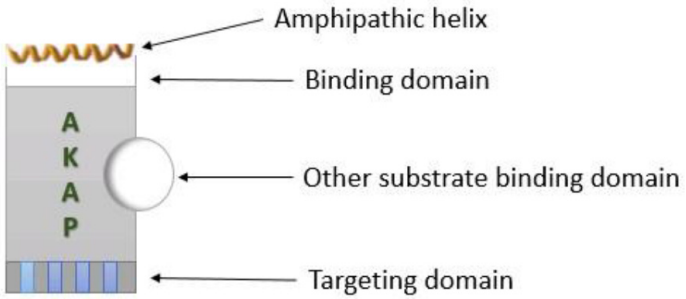

Figure 1: Structure of AKAP.

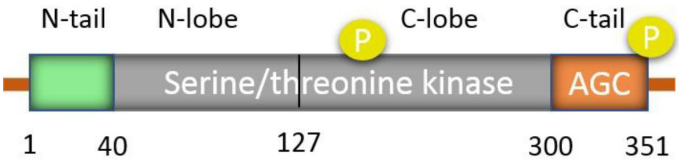

Figure 2: Catalytic subunit.

PROTEIN KINASE A

PKA is a serine/threonine kinase, which is inactive as tetrameric structure[6] and a member of AGC kinase family. AGC kinase family includes PKA (cAMP dependent protein kinase A), PKG (cGMP dependent protein kinase G), and PKC (Phospholipid dependent protein kinase G).[7] PKA holoenzyme complex consisting of two regulatory (R) subunit and two catalytic subunit (C) comprised of lobes and tails (Figure 2). The genes encode various catalytic subunit isoforms are Cα, Cβ and Cγ. From which Cα and Cβ are the ubiquitous and Cγ are found predominantly in the testis. Regulatory subunits are of two types, RI subunit and RII subunit. These subunits are encoded by 4 genes: RIα, RIβ, RIIα and RIIβ. Depending upon the type of subunit present in PKA, it is classified as PKA I (RI subunit) and PKA II (RII subunit).[8] Catalytic subunits enfolds the regulatory subunits and prevent enzyme activity.

Mostly AKAPs anchor the RII subunit of PKA to the subcellular structures.[9] Specific physiological responses are contributed differently by cAMP due to variation in affinity of cAMP for both PKA. Amongst these, PKAI is predominantly cytoplasmic and PKAII is associated with specific cellular structure and organelles.

Catalytic subunit is composed of two lobes, N-lobe and C-lobe, which is surrounded by two tails, N-terminal tail and C-terminal tail. N-terminal tail is specific for PKA whereas C- terminal tail is common to all AGC kinase (Figure 2). Regulatory subunit consists of Dimerization/Docking domain (DD) is the docking site for AKAP, a linker region and Cyclic nucleotide binding domain (CNBA and CNBB). N-terminus of the R subunit creates Dimerization/Docking domain (a hydrophobic groove) which facilitates binding of amphipathic helix of AKAP[10,11] (Figure 3).

Functions of AKAP by regulating PKA

Regulatory subunit of PKA binds to AKAP which locate the PKA holoenzyme in specific subcellular regions.[12,13] Amphipathic α-helix of 14-18 amino acid of AKAP (RIIBD) binds with D/D domains of PKA regulatory subunit which is formed by four helix bundle.[5] (Figure 4). In response to cAMP production, AKAPs bind with the inactive PKAs (which is in tetrameric form).[14] By increase in cAMP level, two cAMP unit binds with the PKA regulatory subunits which acts as sensors for

DD, Dimerization/Docking domain; IS, Inhibitory substrate motif; CNBA, cyclic nucleotide binding domain A; CNBB, Cyclic nucleotide binding domain B

Figure 3: Regulatory subunit.

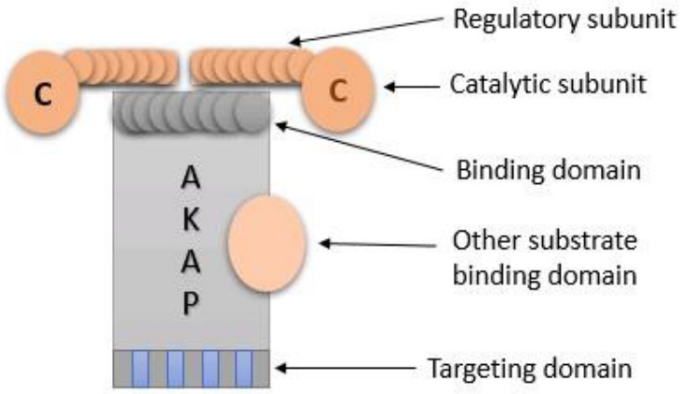

Figure 4: AKAP/PKA complex.

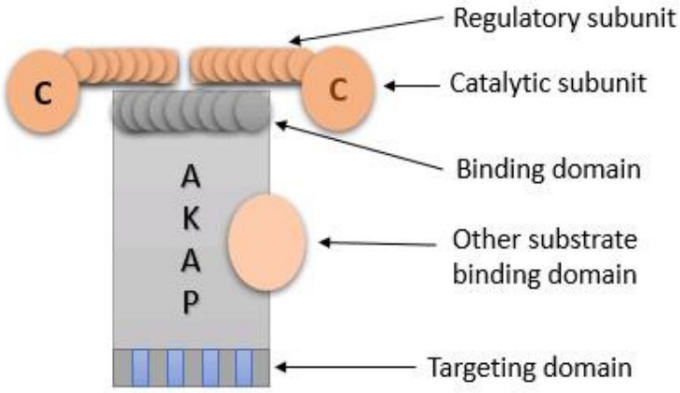

Figure 5: Structural illustration of AKAP-PKA binding.

intracellular cAMP[15] Catalytic subunits are released from the cAMP – PKA complex and this unit phosphorylates the close substrates. In addition to this, PKA R subunit interacts with the AKAPs.[16] In presence of cAMP, both the Cyclic nucleotide binding domain are in the close contact forming kinked helix structure and in absence of cAMP helix straightens separating the two (Figure 5).

Generally, AKAPs anchor RII subunit of PKA predominantly. But, some favor the AKAP-RI association. Biochemical evidence also suggest that dual function AKAPs family can binds to either RI or RII.[17]

Besides AKAP involvement in signal transduction it is also able to recruit multiple signaling enzymes and connect both upstream as well as downstream in signal transduction process. These includes AKAP79, Yotiao, AKAP220, Gravin, verprolin-homology domain containing protein (WAVE) and mAKAP.[18]

Table 1: Various types of AKAPs and its role in physiology.

Sr. No.	AKAP Name	Role in Physiology	Location
01	AKAP1/AKAP121/AKAP84/D-AKAP1/ AKAP149/ S-AKAP84	Mitochondrial function regulation, Regulates nuclear envelope integrity, binds HIV-1 reverse transcriptase	Ubiquitous, high expression in testis, thyroid, oocytes
02	AKAP2	Kallmann syndrome due to interruption of the AKAP2 gene	Kidney, lung, thymus, cerebellum, heart
03	AKAP3/ AKAP110	Structural sperm protein	Testis
04	AKAP4/ AKAP82	Sperm motility	Testis
05	AKAP5/ AKAP79(human)/AKAP150 (murine)/ AKAP75 (bovine)	Regulation of synaptic plasticity, Regulation of multiple ion channels and receptors, required for recycling of β1-ARregulation of insulin secretion	Ubiquitous, high expression in brain
06	AKAP6/ mAKAP/ AKAP100	Phosphorylates PKA / activate RyR; communicate negative feedback inhibition of AC5 by PKA and ERK5-induced cardiac hypertrophy	Heart, brain and skeletal muscle
07	AKAP7/ AKAP15/ AKAP18 (Isoform α)	Lipid-anchored to plasma Membrane, enhances glucose-stimulated insulin Release	Heart, kidney, lung, Brain, Pancreas
	AKAP18 β	Lipid-anchored to plasma membrane; function unknown	Kidney, Brain
	AKAP18γ	Inhibits glucose-stimulated insulin release	Heart, brain, placenta, lung, pancreas
	AKAP18δ	Maintains cardiac function	Heart, kidney inner Medulla
08	AKAP8/ AKAP95	DNA replication during mitosis	Ubiquitous
09	AKAP9/ AKAP350/ AKAP450/ CG-NAP	Regulates microtubule dynamics	Ubiquitous
	Yotiao (Isoform of AKAP9)	Modulates NMDA receptor currents, Yotiao mutation S1570L in KCNQ1-binding site causes long QT syndrome, facilitates bradykinin-induced PKA phosphorylation of IP3R1	Heart, Brain, Placenta, lung, Skeletal muscle, Pancreas
10	AKAP10/ D-AKAP2	Activation can lead to abrupt mortality risk due to cardiac dysrhythmia and, also involved in colorectal cancer and familial breast cancer	Ubiquitous
11	AKAP11/ AKAP220	Facilitates GSK3β Phosphorylation, Mediates GABAc-dependent PKA activation, overexpressed in oral squamous cell carcinomas	Heart, lung, testis, Brain, kidney
12	AKAP12/ AKAP250/ Gravin/ SSeCKS	Autoantigen in myasthenia Gravis, in cell cycle Regulation, tumor suppressor protein, important in resensitization of receptor	Ubiquitous except for liver
13	AKAP13/AKAP-Lbc	Mediates catecholamine-induced cardiac hypertrophy	Ubiquitous
14	AKAP14/ AKAP28 (Human)/ TAKA80 (rat)	Probably involved in the regulation of ciliar/flagellar beat	Lung (AKAP28), Testis (TAKAP80)
15	AKAP78/ Ezrin	Interacts with CFTR, mediates inhibition of T cell immune functions by PKA	Blood cells, placenta, secretory epithelia, brain
16	WAVE-1	Regulates actin cytoskeleton dynamics, regulates apoptosis and glycolysis	Brain, Platelets, Liver

INVOLVEMENT IN DISEASE

Protein phosphorylation regulated by protein kinases and protein phosphatases is primary mechanism for the regulation of enzymatic activity and also for protein-protein interaction. This bi-directional process is a flexible means of influencing cellular activity. Thus, disruption in this signal transduction may lead to pathophysiological outcome and development of disease. As described earlier anchoring of protein kinase and also other substrates is important step in the physiological means for functioning of a cell. Disruption in AKAP-PKA complex or alteration in expression profile of AKAP generally leads to the Pathological means of disease. AKAP12/AKAP250/Gravin was first identified as an autoantigen in myasthenia gravis. Down regulation of AKAP12 have been reported to cause abnormal cell cycle regulation, leading to prostate hyperplasia, myelodysplastic syndrome, and several types of cancer, such as esophageal and colon cancer, gastric carcinoma and pulmonary adenocarcinoma. Ezrin involved in increasing the malignancy including uveal malignant melanoma, uterine cervical cancer, hepatocellular carcinoma, tongue squamous cell carcinoma, brain astrocytoma.

RESPIRATORY DISORDER

A few reports are available on the role of AKAP in respiratory disorder. In 2005 Wang et. al. raised the questions about expression of AKAP79 and AKAP 250, and their function in coordination for switching of the downstream regulation of signaling and recycling/resensitization of the β-receptor as well. But they were unable to answer all the questions. In 2012, Horvert *et al.* suggested role of AKAPs in compartmentalization of cAMP signaling transduced by β-adrenergic receptors. Subsequently, Han *et al.* reported action of AKAP in contraction and proliferation of bronchial smooth muscle. Oldenburger *et al.* proposed role of AKAP in contributing epithelial function loss. Although, AKAP interact with

PKA and coordinate with the stabilization of endothelial barrier, the functional relevance of these interactions on bronchial epithelial barrier is unknown. Poppinga *et al.* defined its role in airway smooth muscle (ASM) remodeling, Inflammation and contraction. Norala *et al.* reported AKAP gene importance in decreasing in hyperopia induced acute lung injury. Li *et al.* demonstrated role of AKAP4 in occurrence, proliferation and metastasis of tumor by controlling intracellular signaling. Allen *et al.* introduced AKAP13 involvement in Idiopathic Pulmonary Fibrosis pathogenesis. Hence, the attempt has been made to summaries the general role of AKAP with special emphasis on respiratory disorders.

In general, Stimulation of Gs coupled receptor (e.g. β_2-adrenoceptor, Adenyl cyclase (ACs)) activates, and synthesize cAMP from adenosine triphosphatase(ATP). PDEs tightly control the cAMP levels by hydrolyzing cAMP to 5'-AMP and ultimately terminating the signal. AKAPs namely AKAP2, AKAP3, AKAP79, AKAP9, Gravin, Ezrin and Microtubule associated protein 2B(MAP2B) are present in airway smooth muscle. Generally, balance between AKAP12, AKAP5 and AKAP78 (Ezrin) determines the β_2-adrenoceptor function. Epac, cAMP gated ion channels and PKA in association with ACs and PDEs regulates intracellular cAMP signaling in lungs, including airway relaxation, reduction of inflammation and fibrosis. Moreover, AKAPs also control specific response by directly binding to PKA and its other substrates, locating multiple complexes to its specific location and therefore generation of spatiotemporal signaling complex.

AKAP5 is essential for the functioning of β_2-adrenoceptor, facilitating signal transduction and also recycling of β_2-adrenoceptor. AKAP78 (Ezrin) is important for β_2-adrenoceptor internalization and AKAP12 requires for recycling of β_2-adrenoceptor (Figure 6).

Bronchial Inflammation

Roscioni *et al.* demonstrated an increase in Interleukin-8(IL-8) release via induction of Gq protein couple receptor in response to direct activation of both PKA and Epac. Silencing of the Epac expression reduced IL-8 secretion and also PKA inhibition by Rp-8-cpf-cAMPs reduced IL-8 release.[19]

Furthermore, PKA-AKAP interaction disruption using Stearated form of peptide Ht-31 (St-Ht31) recommends that Epac and PKA both regulates the IL-8 release via AKAP.[20]

But, other related study, showed that fenoterol (β_2-agonist) inhibited Cigarette smoke extract (CSE) induced IL-8 release, seemingly via PKA and Epac. The possible proposed mechanism may be that Epac inhibits cigarette smoke extract (CSE) induced IL-8 release by inhibiting the activation of Nuclear factor Kappa-B (NF-κB) and PKA does the same by inhibiting ERK activation.[21]

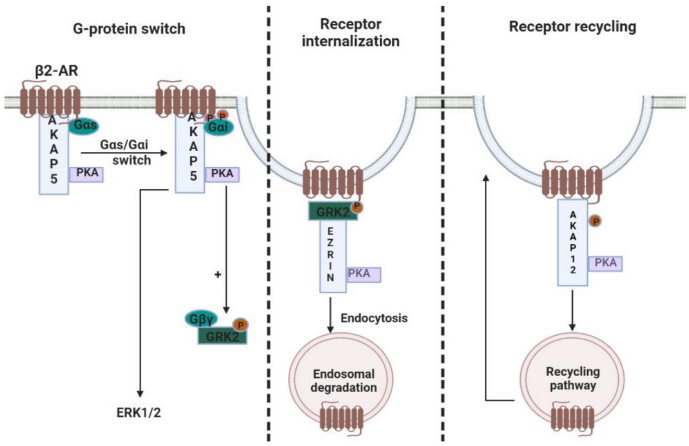

Figure 6: AKAPs in regulation of β2-AR signaling.

Asthma and COPD

β_2 adrenergic agonist, Theophylline, muscarinic receptor antagonist, etc. are used in asthma and chronic obstructive pulmonary disease (COPD). β_2-adrenoceptors and other GPCR function by cAMP production and downstream regulation of it can be highly compartmentalized. AKAPs play a central role in such cAMP compartmentalization. AKAPs mediates localization of substrates such as ACs, PKA, PDEs and phosphatases and determines both signaling and termination of receptor activity.

A study considering role of PDE activity and subsequent β_2 adrenoceptor desensitization by PKA mediated stimulation was done by Horvat *et al.* AKAP-PKA complex was disrupted using st-Ht31. cAMP response observed in Isoproterenol induced Human ASM cells. Decay in cAMP response was observed with Isoproterenol induced Human ASM, which possibly due to receptor desensitization (or decrease in synthesis of cAMP) or increase in the PKA mediated PDE activities and subsequent hydrolysis. While in the cells treated with st-Ht31, broadening of cAMP response observed presumably due to reduction in localization of PKA by st-Ht31. Reduction in AKAP/PKA complex mediated stimulation of PDE is likely to believe for cAMP accumulation. Based on this finding, AKAPs can be a Pharmacological target for β2-adrenoceptors.[22]

AKAPs in Innate Immunity

Alveolar macrophages as a part of innate immunity possess proinflammatory program directed by Toll-like receptors (TLR). TLR4 via its ligand Lipopolysaccharide induces generation of Prostaglandin E2 (PGE2). PGE2 mediates shapes the nascent TLR response, though mechanism is poorly understood. PGE2 is known to increase the cAMP production and this leads to production of Nitric oxide (NO). It has been demonstrated that AKAP10 mediates potentiation of Inducible nitric oxide (iNO) and NO, IL-10 and IL-6 induced by TLR-4. However, it was also suggested that activation of NF-κB, cAMP response element binding protein (CREB) transcriptionally upregulates iNOS, IL-6 and IL-10, speculating role of AKAP10 by activating CERB directly or indirectly.[22] AKAP11, here mediates IL-6 production but lesser involved in NO synthesis.

The study suggesting potential role of AKAPs so far done by disrupting AKAP-PKA complex, either by using RII/AKAP disrupter peptide Ht31 (attenuated IL-10 and IL-6 production) or RI/AKAP disrupter peptide (RIAD) (attenuated NO production).[22]

Also, Tumor necrosis factor-α (TNF-α) generation is mediated by PGE2, which is believed to be mediated by PKARII-AKAP complex.[23]

AKAPs in Epithelial Barrier Changes

Airway epithelium not just being a physical barrier also is a part of innate immune system. Bronchial epithelium provides protection against inhaled pollutants or any other substance. It includes junctions, tight junction and gap junction. This epithelial barrier is strengthened by E-cadherin which interacts with α-catenin or β-catenin and link to actin cytoskeleton ultimately provides strong adhesion between the epithelial cells.[24] Also, the proteins occludin and claudin in tight junction connected by the ZO-1 (Zonula occludens) to actin cytoskeleton.[25] After injury modification in epithelial cells structure and function occurs either to repair or to adapt to the changes in the injured area. (Figure 7) Cigarette smoke induces structural changes in the epithelial barrier and disturbs the function such as increasing permeability and aberrant repair of epithelial cells.[26-28]

An *in vitro* study demonstrated disruption in expression of ZO-1, in cigarette smoke extract treated cells. Using human bronchial epithelial

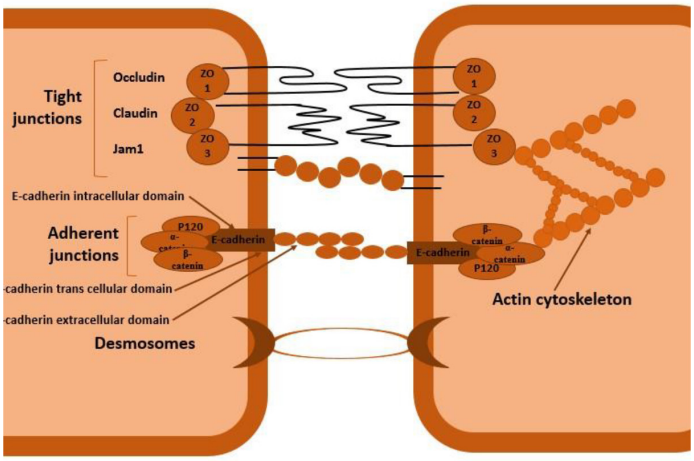

Figure 7: Maintenance of epithelial barrier function.

cell line (16HBE) it was concluded that cigarette smoke extract (CSE) exposure, induces the delocalization of ZO-1 and occludin (Components of tight junction).[29] Downregulation of E-cadherin and ZO-1 believed to be involved in this damage due to cigarette smoking. Oldenburger et.al. also tried to find out an actual role of AKAP9. They observe disruption in the AKAP-PKA complex by using st-Ht31, prevents the cigarette smoke extract induced loss of E-cadherin expression in the membrane. However, E-cadherin protein expression was not changed in cytosolic fraction and as well at mRNA level. By using 16HBE cell they confirmed colocalization of AKAP9 and E-cadherin in the cell membrane of epithelial cells, and silencing of AKAP9 reduced the epithelial barrier function. Also, reduced expression of AKAP9 at mRNA levels was observed in the COPD patients but there was no difference in the AKAP9 expression at epithelium between COPD patients and normal control ones.[30]

AKAPs in Acute Lung Injury

Acute lung injury (ALI) is associated with increased pulmonary vascular permeability, edema and apoptosis of epithelial cells. Severe ALI is manifested as Acute respiratory distress syndrome (ARDS).[31] Histological presentation is diffuse alveolar damage (DAD) in both the disease. Severe alveolar damage is characteristic of HALI (Hyperoxia induced acute lung injury), which is generally induced by hyperoxic treatment in acute respiratory failure.[32] AKAPs, namely AKAP121, AKAP100 and AKAP84 are present in mitochondria have been reported to be involved in cAMP signal transmission to the mitochondrial membrane. Reports also mentioned that Akap1 gene products generated by alternative splicing,[33] AKAP121 has important role in regulation of mitochondrial function, reactive oxygen species (ROS) generation and apoptosis. It anchors PKA close to the several mitochondrial substrates. AKAP121 improves cardiomyocyte hypertrophy.[34] Based on these findings, a study was done to check the effect of Akap1 gene in Hyperoxia induced acute lung injury (HALI). Study used wild type mice and Akap1$^{-/-}$ mice and 100% O_2 for 48 hr provided to them. Significant increase in total cell number and neutrophil and macrophage levels as well in the Akap1$^{-/-}$ mice promoted alveolar leakage in airspace by deletion of Akap1 gene.[34]

Thus, protective role of AKAP was established in lung. In light with this study, it can be predicted that Akap1 gene may represent the novel target in the inflammatory lung disease.[35]

AKAPs in Tumor Growth

The Myc Protein is the family of transcriptional factors that regulates cell growth and cell cycle progression. It is a powerful oncogene which enhances in all type of human cancers.[36] Mammalian target of rapamycin (mTOR) is a member of kinase family which regulates protein synthesis, transcription, autophagy, cell growth, cell motility and cell survival.[37] Increased activity of both Myc and mTOR observed in tumor growth. AKAP1 is a transcriptional target of Myc, and ultimately Myc overexpression induces upregulation of AKAP1. Further, AKAP1 interacts with sestrin2. Sestrin2 is a negative inhibitor of mTORC1 pathway.[38] Thus, by limiting the activity of sestrin2 AKAP1 indirectly enhances tumor growth by activating mTOR pathway.

Accordingly, downregulation of AKAP1 further promotes oxidative stress and mitophagy and eventually leads to apoptosis.

Besides, AKAP4 has been identified as novel cancer testis antigen (CTA) and associated with multiple myeloma, prostate cancer, ovarian cancer and breast cancer.

In a study, higher AKAP4 expression was observed in lung adenocarcinoma tissues and in the other study in a sera of lung adenocarcinoma patients. Hence, AKAP4 can be used as a diagnosis marker or prognosis marker.[38]

AKAP in Fibrosis

In normal cells PGE2 has the ability to suppress the fibrotic functions of activated fibroblasts by binding to its G protein-coupled receptor EP2. But, in idiopathic pulmonary fibrosis (IPF) this function is dysregulated. Further, Upregulation of PGE2 synthesis by plasmin provides protection from lung fibrosis in alveolar epithelial cells and in lung fibroblasts.[39] Next, a study conducted by Okunishi *et al.* to identify the role of AKAP in mediating the PGE2 synthesis by Plasminogen activation. AKAP1 and AKAP9 were mainly focused due to their known ability to interact with both PKA-RII and PP2A. To which, silencing of AKAP9 produced promising data showing importance of PKA-RII interaction with AKAP9 in modulating plasminogen mediated PGE2 synthesis. However, PGE2 synthesis is independent of this AKAP-PKA-RII interaction in normal fibroblast.[40]

CONCLUSION

A kinase anchoring protein is a family of scaffolding protein which is structurally diverse but functionally similar and exerts its action by interacting with Protein kinase A. Despite of its effect being dominating in heart and brain it also found to be present in testis, skeletal muscle, kidney and lungs. It functions to regulate synaptic plasticity, T cell immune response, sperm motility, several exocytic process, cardiomyocyte contractility, apoptosis, insulin secretion, etc. Different members of AKAP family are situated in different locations. For example, AKAP3 and AKAP4 in testis, AKAP5, AKAP12, AKAP78 in lungs, mAKAP, AKAP-Lbc, Yotiao, AKAP18 and its isoforms in heart, etc. As AKAPs involved in physiological functions its signal transduction disruption may lead to disease occurrence. Several knockout study and *in vitro* studies suggested pathological role in heart disease, cancer, human immunodeficiency virus (HIV), neurodegenerative disease, etc. In respiratory system, cells which possess AKAP like airway smooth muscle, epithelial barrier, alveoli are involved in pathological means of disease. For example, AKAP mediates IL-8 release induced by activation of both PKA and Epac. As a part of innate immunity, AKAP helps in synthesis of IL-10, IL-6, iNOS and NO. AKAP mediates Loss of E-cadherin occur due to cigarate smoking. Also, AKAP9 silencing reduces the epithelial barrier function. Some researchers also suggest its important role in improving hyperoxia induced acute lung injury

(HALI). AKAP121 reported to be regulating mitochondrial function, ROS generation and apoptosis. AKAP helps in improving disease pathology and also mediates lung tumor growth. As AKAP has both the role in physiology and disease pathology as well, further studies should focus on AKAP as therapeutic target.

ABBREVIATIONS

AKAP: A kinase Anchoring Protein; PKA: Protein Kinase A; **cAMP:** Cyclic adenosine monophosphate; **RI:** Regulatory subunit I; **RII:** Regulatory subunit II; **GPCR:** G protein coupled receptor; **AC:** Adenylyl cyclase; **Epac:** Exchange protein directly activated by Protein kinase; **PDE:** Phosphodiesterase; **GSK3β:** Glycogen synthase kinase 3 β; **SDS PAGE:** Sodium Dodecyl sulfate – Polyacrylamide gel electrophoresis; **HGNC:** Human genome organization nomenclature committee; **DD:** Dimerization/Docking domain; **CNBA:** Cyclic nucleotide binding domain A; **CNBB:** Cyclic nucleotide binding domain B; **IS:** Inhibitory substrate; Wiskott-Aldrich syndrome, **WAVE-1:** verprolin-homology domain containing protein; **PP2B:** Protein phosphatase 2 B; **RyR2:** Ryanodine receptor; **TCR:** T cell receptor; **TCR/CD3 complex:** T cell receptor/Cluster of differentiation complex; **PKD/HDAC5/MEF2 pathway:** Protein kinase D/Histone deacetylase 5/Myocyte enhancer factor-2 pathway; **MAP2B:** Microtubule associated protein; **RT:** Reverse transcription; **ATP:** Adenosine triphosphatase; **IL-8:** Interleukin-8; **Rp-8-cpf-cAMPs:** Inhibitor of cAMP; **St-Ht31:** Stearated form of peptide Ht-31; **CSE:** Cigarette smoke extract; **NF-κB:** Nuclear factor Kappa-B; **ERK:** Extracellular signal regulated kinase; **COPD:** Chronic Obstructive pulmonary disease; **PGE2:** Prostaglandin E2; **NO:** Nitric oxide; **iNO:** Inducible nitric oxide; **CREB:** cAMP response element binding protein; **IL-6:** Interleukin-6; **IL-10:** Interlukin-10; **RIAD:** RI/AKAP disrupter peptide; **TNF-α:** Tumor necrosis factor-α; **ZO:** Zonula occludens; **16HBE:** Human Epithelial bronchial cell line; **ALI:** Acute lung Injury; **ARDS:** Acute respiratory distress syndrome; **DAD:** Diffuse alveolar damage; **HALI:** Hyperoxia induced acute lung injury; **mTOR:** Mammalian target of rapamycin; **CTA:** Cancer testis antigen; **IPF:** Idiopathic pulmonary fibrosis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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