

# Physiologic and pathophysiologic roles of AKAP12

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## Abstract

A kinase anchoring protein (AKAP) 12 is a scaffolding protein that improves the specificity and efficiency of spatiotemporal signal through assembling intracellular signal proteins into a specific complex. AKAP12 is a negative mitogenic regulator that plays an important role in controlling cytoskeletal architecture, maintaining endothelial integrity, regulating glial function and forming blood-brain barrier (BBB) and blood retinal barrier (BRB). Moreover, elevated or reduced AKAP12 contributes to a variety of diseases. Complex connections between AKAP12 and various diseases including chronic liver diseases (CLDs), inflammatory diseases and a series of cancers will be tried to delineate in this paper. We first describe the expression, distribution and physiological function of AKAP12. Then we summarize the current knowledge of different connections between AKAP12 expression and various diseases. Some research groups have found paradoxical roles of AKAP12 in different diseases and further confirmation is needed. This paper aims to assess the role of AKAP12 in physiology and diseases to help lay the foundation for the design of small molecules for specific AKAP12 to correct the pathological signal defects.

## Keywords

AKAP12, physiological function, CLDs, inflammatory disease, cancer

## Introduction

A-Kinase Anchoring Proteins (AKAPs), a family of scaffolding protein, regulate intracellular signal transduction through sequestering protein kinases, phosphatases, and signal termination molecules, with their target substrates.<sup>1–4</sup> AKAP12, also known as Gravin in human or Src-suppressed C kinase substrate (SSECKS) in rodents, was originally isolated from a patient with myasthenia gravis.<sup>5–7</sup> AKAP12, a member of the AKAPs family, modulates cell cycle and cytoskeletal architecture

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through binding the regulatory subunit of cAMP-dependent protein kinase (PRKA), protein kinase C (PKC), protein phosphatase 2B, and calmodulin via a C terminal amphipathic helix.<sup>8-12</sup> Moreover, AKAP12 improves the specificity and efficiency of spatiotemporal signal through assembling intracellular signal proteins into a specific complex.<sup>13,14</sup>

## Expression, distribution and physiological function of AKAP12

### Expression and distribution

AKAP12 has three isoforms, which are encoded by three independent mRNAs ( $\alpha$ ,  $\beta$  and  $\gamma$ ) located at 6q24-q25. Among them, AKAP12/A is 305 kDa, AKAP12/B is 287 kDa, and AKAP12/C is 250 kDa respectively.<sup>15,16</sup> Three isoforms have more than 95% amino acid sequence homology except N-terminal sequence. The N-terminal myristylation motif of AKAP12 $\alpha$  is required for the targeted expression of the AKAP12 $\alpha$  isoform into the endoplasmic reticulum.<sup>17</sup>

Three isoforms are expressed differentially in different organs. AKAP12 $\alpha$  is widely expressed except in liver, while the distribution of AKAP12 $\beta$  is similar to AKAP12 $\alpha$ , but to a lesser extent. AKAP12 $\gamma$  is mainly expressed in testis.<sup>17</sup> In addition, the expression of AKAP12 is mainly observed on fibroblasts, neurons, cells from the neural crest such as glia, adrenal chromaffin cells, whereas the expression on endothelial cells is only found on liver sinusoidal endothelial cells (LSECs) and endothelial of intestinal lacteals.<sup>18</sup> The expression of AKAP12 in hepatic sinusoidal is related to long-term exposure to intestinal bacterial endotoxin and inflammatory mediators released by mucosal and hepatic immune system cells in response to endotoxin.<sup>18</sup> The distribution of three isoforms of AKAP12 in organs and the expression of AKAP12 in different cells are summarized in Table 1.

AKAP12 expression can be induced by phorbol ester and lysphosphatidylcholine.<sup>5,6,19</sup> The expression of AKAP12 increases transiently in early G1 phase under mitogenic stimuli and decreases in the late G1 phase.<sup>20</sup> AKAP12 is hyperphosphorylated on serine residues in G1/S phase, but not in G2/M phase.<sup>21,22</sup> The tyrosine phosphorylation of AKAP12 may be directly modulated by EGF/PDGF dependent and Src independent proliferation pathways.<sup>23-25</sup> Moreover, the expression of AKAP12 is orchestrated by ARHGEF18/p114RhoGEF, a tight junction-associated RhoA activator.<sup>26</sup> To ensure

**Table 1.** The distribution of three isoforms of AKAP12.

Isoforms	Expression in organs	Expression on cells	References
AKAP12 $\alpha$	Expressed broadly except in liver	neurons, cells from neural crest such as glia and adrenal chromaffin cells, fibroblasts,	17,18
AKAP12 $\beta$	Similar to AKAP12 $\alpha$ and to a less extent	endothelial cells including LSECs and endothelial of intestinal lacteals	
AKAP12 $\gamma$	Mainly expressed in testis		

normal primary cilia length and renal epithelial morphogenesis, the expression of AKAP12 is regulated by Notch signaling.<sup>27</sup>

### *Physiological function*

AKAP12 is a negative mitogenic regulator, which is located in the whole cytoplasm and enriches in podosomes and cell margins, and it plays a part in controlling cytoskeletal architecture. AKAP12 shifts from the plasma membrane to the periphery of nucleus coincident with a loss of actin stress fibers, when administrated with phorbol ester for a short time<sup>5,25,28</sup> Instead of directly inhibiting src activity, AKAP12 quarantines the active enzyme from its downstream effectors.<sup>29</sup> AKAP12 mainly causes the initial dissolution of actin, followed by the reappearance of stress fiber, so it does not inhibit the formation of actin-based structure. The serine phosphorylation of AKAP12 regulated by PKC and other kinases changes its interaction with the cytoskeleton matrix and its ability to control mitosis. Cell flattening induced by AKAP12 over-expression is associated with early G1 phase growth arrest of untransformed cells<sup>20</sup> Therefore, by reestablishing the actin cytoskeleton, AKAP12 is ready for subsequent cell division.<sup>30,31</sup>

AKAP12 plays a pivotal role in the maintenance of endothelial integrity during vascular development through regulating the expression of p21-activated protein kinase (PAK2), an actin cytoskeletal regulator, and Afadin (AF6), a connector of intercellular adhesion molecules and the actin cytoskeleton. Without AKAP12, zebrafish embryos would display severe hemorrhages partly due to disorganized interendothelial cell-cell adhesions.<sup>32</sup>

Moreover, AKAP12 is a key factor in regulating glial function. In mice, the expression level of AKAP12 in the corpus callosum is higher than in the cortex and decreases gradually with age. It is worth noting that AKAP12 is mainly expressed on postnatal astrocytes, not on oligodendrocyte precursor cells (OPC), another major type of glia in the developing corpus callosum. Compared to wild-type mice, AKAP12 knockout mice have fewer astrocytes and OPC, and the development of corpus callosum slows down after birth.<sup>33</sup> AKAP12 regulates two processes of the blood-brain barrier (BBB) formation, including angiogenesis and tight junction formation. AKAP12 decreases the expression of vascular endothelial growth factor (VEGF) through activating protein-1 (AP-1) reduction and increases angiopoietin-1 (Ang-1) expression, an antipermeability factor in astrocytes.<sup>34</sup> AKAP12 also induces the formation of blood retinal barrier (BRB) by enhancing Ang-1 in astrocytes and reducing the level of VEGF.<sup>35,36</sup> The physiologic role of AKAP12 is summarized in Table 2.

## **Role of AKAP12 in chronic liver diseases (CLDs)**

### *Role of AKAP12 in hepatic fibrosis*

Recent research has increasingly focused on the relationship between AKAP12 and hepatic fibrosis. AKAP12 participates in a variety of factors including activation of hepatic stellate cells (HSCs), capillarization of LSECs, endothelial injury and hypoxia to promote fibrosis progression.

**Table 2.** Physiologic and pathophysiologic roles of AKAP12

Conditions	Role of AKAP12	References
<b>Physiology</b>	<p>Negative mitogenic regulator</p> <p>Controlling cytoskeletal architecture</p> <p>Quarantines the active enzyme from its downstream effectors</p> <p>Inducing cell flattening over-expression</p> <p>Maintaining endothelial integrity</p> <p>Regulating glial function</p> <p>Decreasing VEGF and AP-1, Increasing Ang-I</p> <p>Activating HSCs in hepatic fibrosis induced by CCl4</p> <p>Be involved in the process of actin skeleton remodeling</p> <p>Up-regulating Coll<math>\alpha</math>1, elastin and EpCAM</p> <p>Reducing angiogenesis, ET-1</p> <p>Inhibiting ECM accumulation and vascular remodeling</p> <p>Hindering PFs activation</p> <p>Promoting fibrosis resolution</p> <p>Improving vascular endothelial dysfunction</p> <p>Reducing ROS</p> <p>Increasing eNOS</p>	<p>5,20,23,28,29,32-34</p> <p>37-55</p> <p>56,57</p>
<b>CLDs</b>	<p><b>Hepatic fibrosis</b></p>	
	<p><b>NAFLD</b></p> <p>Promoting plaque formation in the aorta.</p> <p>Enhancing lipid accumulation and damage in the liver</p> <p>Promoting hyperlipidemia and atherosclerosis</p>	58
	<p><b>ALD</b></p> <p>Hindering liver fibrosis through impeding HSP47-collagen interaction</p> <p>Decreasing in Ang II-induced cardiac injury</p> <p>Attenuating oxidative stress, inflammation, apoptosis, autophagy and severe tissue damage</p> <p>Alleviating myocardial fibrosis through inhibiting TGF-<math>\beta</math>1 pathway</p> <p>Improving cardiac histologic alterations, and cardiac dysfunction and heart failure</p> <p>Be related to the presence of extensive colitis</p>	59-61
<b>Inflammatory Diseases</b>		

(Continued)

Table 2. (continued)

Conditions	Role of AKAP12	References
<b>Various Cancers</b>		
<b>HCC</b>	Inhibiting growth and metastasis of tumor	62-65
<b>Lung Tumor</b>	Impairing the activity of telomerase Inhibiting lung tumorigenesis and aggressiveness Be a tumor promoter	66-69
<b>Meningioma</b>	Inhibiting proliferation, migration, invasion	70-72
<b>Colorectal Carcinoma</b>	Reducing tumor volume Promoting apoptosis	73-76
<b>Breast Cancer</b>	Suppressing tumor growth Suppressing cell migration	77,78
<b>Gastric Cancer</b>	Increasing relapse-free survival	79
<b>Prostate Cancer</b>	Suppressing the invasion and metastasis	80-84
<b>Myeloid malignancies</b>	suppressing invasion, metastasis and cancer recurrence Be related to DTX-resistance Prolonging cell cycle Inhibiting cell proliferation Inducing apoptosis	85,86
<b>Reproductive system tumor</b>	Inhibiting cell division of seminiferous tubules in the testis	87,88
<b>Other Cancers</b>	Be a poor prognosis and predictor of PFS and OS in serous ovarian cancer Inhibiting Lung Metastasis And Colonization Of Metastatic Melanoma Inhibiting Tumor Viability In Fibrosarcoma HT1080 Cells	89-91

AKAP12 helps activate HSCs, which can regulate the formation of liver regeneration or liver fibrosis after various injuries.<sup>37</sup> The expression of AKAP12 rises in both liver tissues of acute liver failure and activated HSCs induced by CCl<sub>4</sub>, and may also be involved in the process of actin skeleton remodeling in HSCs.<sup>37,38</sup> Platelet-derived growth factor (PDGF), a growth factor promoting HSCs proliferation and playing an important role in progression of liver fibrosis,<sup>39–41</sup> is able to induce AKAP12 tyrosine phosphorylation and rapid rearrangement of the cytoskeletal network in rat HSCs, which is mediated by PKC through Rho protein.<sup>42</sup>

Similarly, the expression of AKAP12 on LSECs increases significantly after the hepatic injury stimulated by lipopolysaccharide (LPS).<sup>43</sup> However, after 8 weeks of thioacetamide (TAA) administration, the expression of AKAP12 drops in capillary endothelium. AKAP12 reduces the expression of collagen type 1  $\alpha$ 1, elastin and encoding epithelial cell adhesion molecule (EpcAM), but no significant change in extracellular matrix (ECM) accumulation is observed.<sup>44</sup> And with liver fibrosis progression, AKAP12 expression on portal fibroblasts (PFs) and LSECs diminishes gradually. AKAP12 reduces angiogenesis and endothelin-1 (ET-1) expression, inhibits ECM accumulation and vascular remodeling, hinders the activation of PFs, promotes fibrosis resolution and normalizes myofibroblasts and capillarized sinusoids in a DDC-induced biliary fibrosis model.<sup>45</sup> The aforementioned paradox results reflect the complexity of AKAP12 regulation in the development of liver fibrosis.

In addition, AKAP12 is correlated with vascular integrity which plays an important role in the development of liver fibrosis.<sup>34,46</sup> AKAP12 is conducive to endothelial barrier function and is essential for cAMP-mediated barrier stabilization.<sup>8,47,48</sup> AKAP12 also improves vascular endothelial dysfunction induced by LPS, reduces the level of reactive oxygen species (ROS) and pro-inflammatory factors, increases endothelial nitric oxide synthase (eNOS), and promotes transcriptional activity of extracellular-signal-regulated kinase 5 (ERK5) through inhibiting PKC $\zeta$ .<sup>49</sup> AKAP12 may play a role in endothelial injury healing by targeting PKA and PKC to specific membrane associated sites.<sup>21</sup> Past results suggest that PKC promotes hepatic fibrogenesis and its inhibitor can hinder liver fibrosis. The level of oxidized diacylglycerol (DAG), which is a type of activator of PKC, elevates in the mouse model induced by CCl<sub>4</sub>.<sup>50–52</sup> The expression of AKAP12 is higher on VEGF stimulated endothelial cells with active migration, but lower in quiescent endothelial cells.<sup>53,54</sup>

Hypoxia, another important factor related to the development of liver fibrosis, can induce the expression of AKAP12. There are 2 binding sites for hypoxia-inducible factor (HIF) in AKAP12 and the most distal HIF-binding site is key to hypoxia-induced AKAP12 expression. AKAP12 inhibits angiogenesis, enhances junctional permeability in a hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ )-dependent manner and acts as a “brake” system for angiogenesis. Furthermore, AKAP12 controls the response of endothelial barrier function to PKA agonists.<sup>55</sup> The roles of AKAP12 in hepatic fibrosis are summarized in Table 2.

### **Role of AKAP12 in NAFLD**

AKAP12 is involved in the development and progression of non-alcoholic steatohepatitis (NASH) and may represent potential targets of therapy for NASH-related

inflammation.<sup>56</sup> Fan and McConnell's team recently reported that the role of AKAP12 in a mouse model with atherosclerosis induced by HFD. AKAP12-mediated signaling complex increases plaque formation in the aorta, enhances lipid accumulation and damage in the liver of HFD mice and promotes hyperlipidemia and atherosclerosis by inhibiting the expression of sterol regulatory element-binding protein-2 (SREBP-2) and liver 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA).<sup>57</sup> The roles of AKAP12 in NAFLD are well documented in Table 2.

### **Role of AKAP12 in ALD**

Liver injury induced by alcohol exposure increases the phosphorylation of AKAP12. Evidentially, elevated phosphorylation of AKAP12 is found in ALD/alcoholic hepatitis patients. AKAP12 inhibits the activation of HSCs and the interaction between AKAP12 and heat shock protein 47 (HSP47) hinders liver fibrosis through impeding HSP47-collagen interaction. Augmented phosphorylation of AKAP12 induced by ethanol can down-regulate the scaffolding activity of AKAP12 for PKC/cyclin-D1 in HSCs but not in hepatocytes. Ethanol promotes the activation of HSCs by increasing the phosphorylation of AKAP12 and up-regulating the interaction between HSP47 and collagen.<sup>58</sup> Table 2 demonstrates the roles of AKAP12 in ALD.

### **Role of AKAP12 in inflammatory diseases**

Dysregulated angiotensin II (Ang II) is a key effector of hypertension and cardiac fibrosis that could lead to a series of inflammatory responses. The expression of AKAP12 decreases in Ang II-induced cardiac injuries and the number of inflammatory cells increases in AKAP12 knock-out mice. Moreover, AKAP12 attenuates oxidative stress, inflammation, apoptosis, autophagy and alleviates myocardial fibrosis by inhibiting the TGF- $\beta$ 1 pathway. AKAP12 depletion worsens cardiac histologic alterations and then leads to cardiac dysfunction and heart failure.<sup>59</sup> However, heat shock protein A12B (HSPA12B) over-expression shows cardioprotection along with reduced fibrosis, and increased capillary and arteriolar density in a rat model of diabetic myocardial infarction through down-regulating the expression of AKAP12 and up-regulating VEGF and thiorodoxin 1 (Trx1) expression.<sup>92,93</sup>

Similarly, increased AKAP12-positive cells in the new tissue formation stage attenuate excessive inflammation and severe tissue damage, and express junction proteins to form a physical barrier after central nervous system (CNS) injury.<sup>60</sup>

However, the over-expression of AKAP12 in patients with ulcerative colitis (UC) is related to the presence of extensive colitis. The expression of AKAP12 in the colonic mucosa of patients with active UC up-regulates, while that in patients with UC remission down-regulates.<sup>61</sup> In addition, elevated AKAP12 level induced by IL-1 $\beta$  and TNF- $\alpha$  in rat pulmonary microvascular endothelial cells is correlated with the endothelial hyperpermeability in the inflammatory process and aggravates endothelial barrier dysfunction.<sup>94</sup> The roles of AKAP12 in inflammatory diseases are illustrated in Table 2.

## Role of AKAP12 in various cancers

AKAP12 functions as a tumor suppressor in a variety of cancers that can block the cell cycle and inhibit angiogenesis proliferation, chemotaxis and invasion of cancer cells by hindering PKC activation.<sup>73,87,95</sup> The expression of AKAP12 declines in various human cancers, including hepatocellular carcinoma (HCC),<sup>62</sup> breast cancer,<sup>77</sup> gastric cancer,<sup>79</sup> prostate cancer,<sup>80</sup> myelodysplastic syndromes (MDS),<sup>96</sup> colon cancer,<sup>55,97,98</sup> skin cancer,<sup>99</sup> and seminoma,<sup>100</sup> etc.

Over-expression or deficiency of AKAP12 in cells changes susceptibility to the progression of malignancy or metastasis and AKAP12-deficient mice also show higher tumor incidence.<sup>40</sup> The anti-proliferative effect of colchicine on HCC cells partially correlates with the expression of AKAP12.<sup>101</sup> MiR-103 or MiR-1251-5p promotes cell proliferation and inhibits apoptosis of HCC cells by suppressing the expression of AKAP12 and encouraging protein kinase C $\alpha$  (PKC $\alpha$ ) activities.<sup>62,102</sup> In meningioma, levels of expression of AKAP12 and long non-coding RNA maternally expressed gene 3 (MEG3) decreases and miR-29c increases. Elevated levels of MEG3 and the absence of miR-29c can diminish cell cycle, migration, invasion, and proliferation in meningioma cells. The expression of AKAP12 is co-regulated by MEG3/miR-29c axis and AKAP12 depletion restores the above inhibitory effects induced by miR-29c absence *in vitro*.<sup>70</sup> Down-regulated expression of AKAP12 in patients is related to tumor recurrence and progression and indicates poor prognosis.<sup>71</sup> Low AKAP12 expression through AKAP12 knockdown in benign meningioma cells SF4433 can promote proliferation, migration, invasion, and confer an anaplastic profile. Furthermore, low AKAP12 helps differentiate grade II from grade I meningiomas.<sup>72</sup> The expression of AKAP12 is down-regulated and is related to the overall survival (OS) of patients with breast carcinoma.<sup>78</sup> Patients with AKAP12 expression have higher relapse-free survival. AKAP12 knockdown induces cell migration but does not alter cell proliferation, thus AKAP12 acts as a potential metastasis suppressor in breast cancer.<sup>77</sup> AKAP12A may function as an important negative regulator of the survival pathway in human gastric cancer. AKAP12 is weakly expressed in gastric cancer and can suppress the invasion and metastasis in gastric cancer cells.<sup>79</sup> The expression of AKAP12 significantly diminishes in myeloid malignancies including acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and chronic myeloid leukemia (CML).<sup>85</sup> MiR-144 reduces AKAP12 expression through bounding to AKAP12 3'UTR in hematopoietic cells.<sup>96</sup> Compared to normal skin tissue, AKAP12 is significantly down-regulated in cutaneous squamous cell carcinomas (cSCCs).<sup>99</sup> AKAP12 expression in retinoblastoma patient tissue reduces significantly, while the expression of VEGF increases.<sup>35</sup> The content of AKAP12 in human seminoma cells is lower than that in normal cells. In mice lacking AKAP12, cells in the area called seminiferous tubules in the testis divide faster, which is a hallmark of cancer. The loss of AKAP12 is accompanied by the reduction of two important cell cycle regulatory kinases Aurora A and Plk.<sup>100</sup> In addition, both over-expression of AKAP12 and down-regulation of PKC $\alpha$  can inhibit the growth and metastasis of the tumor by impairing the activity of telomerase.<sup>102</sup>

Promoter hypermethylation rises as the basis for the loss of AKAP12 expression in a variety of cancers and is an underlying biomarker for cancer progression and metastasis.<sup>63</sup> AKAP12 is down-regulated by promoter hypermethylation or 6q24-25.2 deletion in HCC tissues and hypermethylation of the promoter of the AKAP12 gene has been



observed in 85% of HCC tissues.<sup>62–64</sup> AKAP12 DNA methylation is closely related to the low risk of recurrence and long-progression-free survival of patients with HCC.<sup>65</sup> The high percentage of methylated AKAP12 in patients with advanced colorectal cancer indicates that AKAP12 methylation can be used as a marker to monitor the progression of colorectal cancer.<sup>74–76</sup> The 5' CpG islands of both AKAP12A and AKAP12B are often hypermethylated in gastric cancer cells. DNA methylation can inhibit the expression of AKAP12 in gastric cancer cells through transcriptional silencing. Suppressing DNA methylation leads to the restoration of AKAP12 expression, followed by reducing the formation of the colon and promoting apoptotic cell death.<sup>103</sup> AKAP12 is expressed and characterized by an unmethylated 5' CpG island in normal hematopoietic progenitors but is transcriptionally silent and characterized by hypermethylation in leukemic blasts. Moreover, AKAP12 hypermethylation is also observed in refractory anemia with excess blasts (RAEB) and acute myeloid leukemia (AML).<sup>86</sup> AKAP12 methylation is significantly higher in Barrett's esophagus patients than in controls.<sup>104</sup> Hypermethylation frequency is zero in normal esophagus but is elevated early during neoplastic progression, to 38.9%, 52.5% and 52.2% in the patients with Barrett's alone, dysplastic Barrett's metaplasia, and esophageal adenocarcinoma (EAC) respectively.<sup>105</sup>

In addition, AKAP12 can suppress tumor growth by regulating cytokinesis progression. AKAP12 localizes to the cell periphery during interphase, and localizes to the actomyosin contractile ring during cytokinesis. The inhibition of myosin light chain kinase (MLCK), a key regulator of actomyosin contractility, removes AKAP12 from the cell periphery during interphase and from the contractile ring during cytokinesis, suggesting that AKAP12 might be one of the downstream effectors of MLCK. AKAP12 depletion increases the number of multinucleated cells, and disrupts the completion of cytokinesis.<sup>106</sup> Up-regulation of AKAP12 can prolong the cell cycle, inhibit cell proliferation, and induce apoptosis.<sup>96</sup>

AKAP12 can reduce tumor volume and promote apoptosis of colorectal cancer, which helps suppress tumor growth and improves the survival of human colorectal cancer.<sup>73,97,98</sup> AKAP12 inhibits lung metastasis and colonization of metastatic melanoma by reducing the expression of selectin adhesion protein.<sup>89,90</sup> AKAP12 impedes peritoneal metastasis induced by B16F10, a type of murine melanoma cell line, by reducing the secretion of CXCL9/10 by resident fibroblasts.<sup>16</sup> In fibrosarcoma HT1080 cells, AKAP12 inhibits tumor viability by inducing apoptosis via caspase-3, which is related to the Bcl-2 expression down-regulation and Bax expression up-regulation.<sup>91</sup> Moreover, phosphorylation can change the scaffold activity of AKAP12 and inhibit its binding with PKC, thus enhancing PKC activities.<sup>47</sup> The association between the 6q25.1 locus and breast cancer risk may be mediated through single nucleotide polymorphisms (SNPs) that regulate the expression of the AKAP12 gene.<sup>107</sup>

AKAP12 regulates endothelial cell migration by inhibiting the expression of matrix metalloproteinase 9 (MMP-9) in tumor cells, which plays an important role in the degradation of ECM molecules followed by tumor metastasis and angiogenesis.<sup>108</sup> Different roles of AKAP12 in regulating MMPs may be involved in the different substrates specificities between the endothelial cell and vascular smooth muscle cells (VSMCs).<sup>57,109</sup> By reducing MMP-9 and HIF-1 $\alpha$ , AKAP12 can regulate angiogenesis in NIH3T3 cell lines.<sup>110</sup>

It is noteworthy that the roles of AKAP12 in lung tumors, prostate cancer and ovarian cancer are controversial. Different research groups have made opposite conclusions on the

role of AKAP12 played in lung cancer.<sup>66-69,111</sup> Ma et al. observed down-regulation of AKAP12, up-regulation of VEGF and angiopoietin-1 in mice with lung tumors.<sup>66</sup> AKAP12 $\alpha$  expression is regulated by DNA methylation and reduced expression is observed in lung cancer cells. Compared to normal tissues, the AKAP12 $\alpha$  promoter is more frequently methylated in tumors and AKAP12 $\alpha$  promoter methylation is associated with lung cancer prognosis.<sup>67,68</sup> Transcription factor activated enhancer-binding protein 2C (TFAP2C) can promote lung tumorigenesis and aggressiveness by inducing the overexpression of oncogenic microRNA (miRNA)-183 and then blocking AKAP12-mediated cyclin inhibition.<sup>69</sup> Contrary to the above-mentioned results, Chang et al. group demonstrated that AKAP12 was a tumor promoter in the development of lung adenocarcinoma. Elevated miR-338-3p inhibited the expression level of AKAP12 in lung cancer cells and helped improve the prognosis.<sup>111</sup>

The expression of AKAP12 reduces in human prostate cancer cell lines including PC-3, PPC-1, LNCaP, DU145, and TSU and rat prostate cancer cell lines such as AT3.1 and MatLyLu. Loss of AKAP12 is related to the increased metastatic progression of human prostate cancer.<sup>80</sup> AKAP12 has been reported to suppress invasion, metastasis and cancer recurrence by inducing heterotypic repulsion between human prostate cancer and microvessel endothelial cells, inhibiting VEGF expression and enhancing soluble anti-angiogenic factors.<sup>81,82</sup> The combined loss of AKAP12 and Rb in the prostate leads to early metastasis to the lymph node in prostate cancer.<sup>83</sup> By inducing AKAP12 promoter demethylation and then increasing the expression of AKAP12, peroxisome proliferator-activated receptor gamma 2 (PPARG2) inhibits cell migration, colony formation, and invasion of prostate cancer cells in vitro.<sup>84</sup> However, there is another result indicating the roles of AKAP12 in promoting prostate cancer progression. The expression of the long noncoding RNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) enhances in docetaxel (DTX)-resistant prostate cancer cells. MiR-145-5p is a target of MALAT1, and AKAP12 is a target of miR-145-5p. Over-expression of MALAT1 promotes proliferation, migration, and invasion of prostate cancer cells and inhibits expression of miR-145-5p in prostate cancer cells, then enhances their chemoresistance to DTX. Over-expression of AKAP12, is related to chemoresistance to DTX in prostate cancer cells, can be suppressed by miR-145-5p.<sup>112</sup> Interestingly, AKAP12 is highly expressed in paclitaxel resistant advanced serous ovarian cancer cells and is a poor prognosis and predictor of progression-free survival (PFS) and OS in serous ovarian cancer patients.<sup>88</sup>

The roles of AKAP12 in various cancers including HCC, lung tumor, meningioma, colorectal carcinoma, breast cancer, gastric cancer, prostate cancer, myeloid malignancies, reproductive system tumor, etc. are summarized in Table 2.

## Conclusion and future perspectives

AKAP12 is a negative mitogenic regulator and is crucial in controlling cytoskeletal architecture, maintaining endothelial integrity, regulating glial function and forming the BBB and BRB. AKAP12, a scaffolding protein, can improve the specificity and efficiency of spatiotemporal signals by assembling intracellular signal proteins into a specific complex.

AKAP12 has exhibited paradoxical results and complex relationships with a variety of diseases including CLDs, inflammatory diseases and various cancers. AKAP12 expression

increases in activated HSCs stimulated by CCl<sub>4</sub> and in LSECs stimulated by LPS; paradoxically, the expression of AKAP12 decreases in capillarized endothelium in liver fibrosis induced by TAA and DDC. AKAP12 is related to normalizes myofibroblasts, capillarized sinusoids and fibrosis resolution. In addition, AKAP12 inhibits angiogenesis, enhances junctional permeability in a HIF-1 $\alpha$ -dependent manner and acts as a “brake” system for angiogenesis. Therefore, further research is necessary to investigate the role of AKAP12 in the development and progression of liver fibrosis, especially within patients with liver fibrosis. AKAP12 is also involved in the development and progression of NASH and may represent potential targets of therapy for NASH-related inflammation. Ethanol promotes the activation of HSCs by increasing the phosphorylation of AKAP12 and up-regulating the interaction between HSP47 and collagen in ALD. In a word, the role of AKAP12 in CLDs is not consistent and needs to be addressed further.

In inflammatory diseases, AKAP12 attenuates oxidative stress, inflammation, apoptosis, autophagy and alleviates myocardial fibrosis, however, HSPA12B plays a cardioprotective role by reducing AKAP12 levels and the over-expression of AKAP12 in patients with UC is related to the presence of extensive colitis. Further elucidation is needed to understand the inconsistencies.

As a tumor suppressor, AKAP12 expression decreases in patients with HCC, meningioma, colorectal carcinoma, breast cancer, gastric cancer, myeloid malignancies, seminoma, and etc. Promoter hypermethylation is the most important reason for the lower expression of AAKP12. However, AKAP12 has exhibited mixed effects on lung cancer, prostate cancer and ovarian cancer, which deserves further investigation.

Ultimately, the role of AKAP12 in various diseases has generated wide interest that could lead to the design of small molecules for specific AKAP12 to correct the pathological signal defects in a variety of diseases.

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## Conflicts of interest

Hui li declare that there is no competing interest

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## Author biography

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