ADAM9 in Cancers

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ADAM9 plays an important role in tumor biology. It is overexpressed in several cancer types and is correlated with tumor aggressiveness and poor prognosis. Through either proteolytic or non-proteolytic pathways, ADAM9 promotes tumor progression, therapeutic resistance, and metastasis of cancers. Therefore, comprehensively understanding the mechanism of ADAM9 is crucial for the development of therapeutic anti-cancer strategies.

Keywords: ADAM9 ; cancer ; metastasis

1. Introduction

The “a disintegrin and metalloproteases” (ADAMs) family, a subset of the zinc protease superfamily, consists of transmembrane proteins with a multidomain extracellular region, a single transmembrane sequence, and a relatively short cytoplasmic domain [1][2]. So far, around 40 family members have been identified in the mammalian genome, and among them, 22 are expressed in humans [3]. Extracellular regions of ADAMs contain several distinct domains: A prodomain followed by metalloproteinase, disintegrin, and cysteine-rich domains [4]. A majority of ADAMs—all except ADAM10 and ADAM17—also have an epidermal growth factor (EGF)-like domain, whose function is yet to be clarified [2][5][6]. ADAM proteins have been reported in numerous biological functions involving development, fertility, ectodomain shedding, cell adhesion, cell–cell interaction, vascular endothelial cell function, inflammation, immunity, signaling transduction, neurodegenerative disease, and cancer biology [1][7][8][9]. Therefore, ADAMs have important roles in diverse physiological contexts.

ADAM9 (also known as metalloprotease/disintegrin/cysteine-rich protein 9 (MDC9) or meltrin-γ), one of the ADAM proteins, was first identified in 1996 in breast carcinoma [10]. It is widely expressed in human tissues, and shows an abundant increase in pathological conditions [11]. ADAM9 expression is detected in multiple cell types, including monocytes [12], macrophages [13], neutrophils [14], keratinocytes [15], and fibroblasts [16]; and in multiple tissues, including lung [17], colon [18], kidney [19], vascular smooth muscle [20][21], nervous system [1][22], reproductive system [23], and secretary organs [24]. This indicates that ADAM9 is involved in a multitude of biological functions as well as pathophysiological conditions, such as inflammation and tumorigenesis [25][26].

In inflammation, ADAM9 contributes to monocyte fusion, mediating the conversion of monocytes-macrophages to multinucleated giant cells (MGCs) as a response to foreign bodies or bacteria; the resulting granulomatous lesions help to isolate the pathogens and also enhance phagocytotic activity [12]. ADAM9 also stimulates the inflammatory process through polymorphonuclear leukocytes, macrophages, and epithelial cells in some inflammatory diseases, such as acute lung injury or chronic obstructive pulmonary disease (COPD) [11][13][14][27]. ADAM9 is also expressed in the epidermis, where it delays wound healing by increasing collagen XVII shedding and matrix metalloproteinase-9 (MMP-9) secretion to decrease keratinocyte migration [28]. ADAM9 promotes neuropilin-1 proteolysis in the angiogenic signaling pathway of vascular endothelial cells [29]. ADAM9 has been demonstrated to be involved in neurodegenerative disease by regulating the cleavage of amyloid precursor protein (APP), which might be relevant in Alzheimer’s disease [4][30][31]. ADAM9 was also shown to be involved in myogenesis and formation of myotubes, which might contribute to the endocardial cushion during embryonic development [32]. Recently, ADAM9 was reported to shed the interleukin-11 receptor, which is involved in inflammatory conditions, bone homeostasis, hematopoiesis, and fertility [33]. Altogether, ADAM9 is expressed broadly in human tissues, and participates in the development, inflammatory processes, and degenerative diseases.

Despite its wide distribution in mammalian tissue and its regulatory function in development, the *Adam9*$^{-/-}$ mouse model showed no apparent morphological changes or histopathological defects during development and adult life [34]. Therefore, the effects of ADAM9 deficiency might be compensated by other ADAM family members, but no further investigation to address the potential ADAM family members [21]. However, subsequent animal studies demonstrated that the deletion in the ADAM9 induced photoreceptor degeneration of both retinal rods and cones, resulting in visual acuity impairment in young canine models. Malformation of retinal pigment epithelium, disrupted contact with photoreceptor outer segments,

and abnormal gaps between retinal layers were demonstrated, leading to the degeneration of the retina [35][36]. These mice showed less ocular neovascularization than wild-type mice during the pathological neovascularization, which was not associated with developmental retinal angiogenesis. Furthermore, ADAM9 null mutations were shown to cause retinal degeneration in human patients, leading to cone–rod dystrophy (CRD) [36]. In the opposite direction, overexpression of ADAM9 enhances angiogenesis by increasing the shedding of several angiogenesis-related endothelial membrane proteins including Tie-2, vascular endothelial growth factor receptor-2, VE-cadherin, ephrin type B receptor 4 (EphB4), CD40, and vascular cell adhesion molecule 1 (VCAM-1) [37].

2. Role of ADAM9 in Cancers

ADAM9 participates in the regulation of various tumor processes. In addition to metastasis, ADAM9 also plays an important role in tumor proliferation, angiogenesis, and even immune evasion (Table 1).

Table 1. Studies of ADAM9 in various cancers.

Type	Role of ADAM9 in Cancer		Reference
Lung Cancer	Clinical Significance	Overexpressed in cancer	[25][26][38][39]
		Negative correlation with OS	[25][38][39][40][41][42]
	Mechanism	ADAM9-tPA-CDCP1-Metastasis	[25]
		ADAM9-ANGPT2-Metastasis	[26]
		ADAM9-IL8/VEGFA-Angiogenesis	[26][40]
Prostate Cancer	Clinical Relevance	Overexpressed in cancer	[43][44]
		Negative correlation with RFS	[43]
	Mechanism	Naa10p-ADAM9-Tumorigenesis/Metastasis	[45]
		ADAM9-Integrin Degradation	[46]
	Clinical Relevance	Negative correlation with immunotherapy response	[47][48]
Liver Cancer	Mechanism	ADAM9-MICA cleavage-immune evasion	[48]
		IL-6-ADAM9-JNK-Metastasis	[49]
Breast Cancer	Clinical Relevance	Overexpressed in cancer	[50]
		Positive correlation with progression	[51]
	Mechanism	NSD2-ADAM9-Tumorigenesis	[52]

Pancreatic Cancer		Overexpressed in cancer	[24][53]
	Clinical Relevance	Positive correlation with progression	[54]
		Negative correlation with OS	[24][53]
		KRAS-ADAM9-Tumorigenesis	[55]
	Mechanism	ADAM9-MEK-ERK-Tumorigenesis	[24]
		Circ-ADAM9-ERK-Tumorigenesis	[56]
Brain Cancer	Clinical Relevance	Overexpressed in cancer	[57][58]
		Negative correlation with OS/PFS	[57][58]
	Mechanism	TNC-ADAM9-Metastasis	[58]

OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival.

2.1. Lung Cancer

In lung cancer, the dysregulation of ADAM9 was documented long ago. Various studies demonstrate that ADAM9 is a major player in lung cancer progression and metastasis [25][26]. Studies show the overexpression of ADAM9 shortens overall survival, and the same pattern was found in various cohorts by different groups [38][39][40]. By immunohistochemical staining, high protein expression of ADAM9 was found to be correlated with a poor 5-year survival rate in an Asian cohort (10/17, 59%) [25], and in resected stage I lung cancer (29/63, 46%) [41][42].

Metastasis is the leading cause of lung cancer-related death, and nearly 50% of late-stage patients with lung cancer exhibit brain metastasis. ADAM9 has been reported as a major player in several steps of this process [59]. Shintani et al. first described that overexpression of ADAM9 promotes the adhesion of tumor cells to vascular endothelial cells, which suggests the importance of ADAM9 during metastasis. In addition, ADAM9 enhances cell migration and anoikis resistance to promote metastasis by a novel mechanism. Silencing ADAM9 down-regulates the RNA expression of CUB domain-containing protein 1 (CDCP1) and tissue-type plasminogen activator (tPA) but up-regulates the expression of plasminogen activator inhibitor-1 (PAI-1) [25]. Moreover, ADAM9 enhances the activity of tPA to cleave CDCP1, resulting in CDCP1 activation that promotes metastatic processes of cell migration and anoikis resistance. Thus, ADAM9 promotes the CDCP1 activation for lung cancer metastases to the brain through a tPA-based pathway.

This ADAM9-CDCP1 axis to lung cancer metastasis is also validated in several other reports as well [60][61]. The ADAM9-CDCP1 axis was confirmed to be necessary for lung cancer cell migration and survival in vitro and in vivo; and moreover, the authors demonstrated that ADAM9 decreases the expression of miR-1 and miR-218, which target the 3′-UTR of CDCP1 to suppress its expression. Thus, ADAM9 promotes the elevated protein levels of CDCP1. To achieve brain metastasis, the disruption of the blood–brain barrier is necessary for tumor cell entry. ADAM9 also participates in this process by up-regulating angiopoietins 2 and tPA. Silencing ADAM9 enhances the membrane expression of VE-cadherin, which is responsible for maintaining the restrictive barrier between endothelial cells and reduces the cell permeability of endothelial cells in vitro [26]. These findings illustrate the multiple roles of ADAM9 in lung cancer metastasis.

The essential role of angiogenesis in tumor progression is well-defined in numerous cancer types, including lung cancer, and chemical stimulation performed by various angiogenic proteins is crucial and necessary. Meanwhile, the conditioned medium from ADAM9-silenced cells suppresses tube formation of human umbilical vein endothelial cells; moreover, silencing ADAM9 inhibits angiogenesis in vivo. By angiogenesis antibody array and further ELISA, a previous study identified that ADAM9 mediates the expression of angiogenesis factor, interleukin 8 (IL-8). And IL-8 is known to bind and then activate its high-affinity receptor, C-X-C Motif Chemokine Receptor 2 (CXCR-2). Moreover, the neutralizing antibody of CXCR-2 reverses the ADAM9-mediated HUVAC tube formation. These evidences suggest a possible mechanism of ADAM9-mediated angiogenesis through the IL-8-CXCR2 axis [40]. In another study, vascular endothelial growth factor, a

well-known angiogenic protein, was down-regulated in the ADAM9-silenced cell-conditioned medium [26]. Taken together, these results suggest that ADAM9 participates in tumor angiogenesis by increasing the activity of various angiogenic proteins in lung cancer.

Micro-RNAs (miRNAs), such as miR-425, miR-488 and miR-590, have been reported as regulators of ADAM9 in lung cancer. Via prediction tools and luciferase reporter assay, the 3′-UTR of ADAM9 is identified as the target sites of 3 micro-RNAs to down-regulate ADAM9 mRNA expression [38][62][63].

2.2. Prostate Cancer

Fritzsche et al., demonstrated that both mRNA and protein overexpression of ADAM9 is correlated with poor relapse-free survival of prostate cancer [43]. By immunohistochemistry, more than 60% of recurrent prostate tumors have elevated protein expression of ADAM9 [44].

The progression and growth of prostate cancer is dependent on androgens; thus, androgen deprivation by castration or target therapy has become the predominant therapies for advanced prostate cancer. However, tumors treated in this way develop into a more aggressive and castration-resistant type, called androgen-independent prostate cancer (AIPC). Lin et al., uncovered the mechanism of maintaining ADAM9 protein stability in AIPC. N-α-Acetyltransferase 10 protein (Naa10p) has been identified as an oncoprotein in prostate cancer [45]. Silencing Naa10p down-regulates the protein expression of ADAM9 to suppress tumor growth and metastasis in vitro and in vivo. Silencing Naa10p also accelerates ADAM9 protein degradation, and the direct interaction between Naa10p and ADAM9 has been confirmed by co-immunoprecipitation. Taken together, the protein stability of ADAM9 is highly maintained by Naa10p to drive AIPC tumor outgrowth and metastasis. And this Naa10p-mediated stabilization of ADAM9 maybe exist in other cancer types to drive tumorigenesis as well.

ADAM9 regulates prostate cancer progression and outcome in other ways as well. Silencing ADAM9 impairs the endocytosis of integrin β1 to increases its expression on cell membrane to enhance the integrin-mediated cell adhesion and suppress cell migration in vitro. Notably, metalloproteinase inhibitors (Batimastat or GM6001) cannot reverse the integrin β1 expression or integrin-mediated migration effects, which suggests the proteolytic activity of ADAM9 is dispensable for this mechanism. In contrast, the direct interaction between ADAM9 and integrin β1 has been confirmed by co-immunoprecipitation, and both proteins co-localize on early endosomes in vitro. These findings suggest ADAM9 mediates integrin β1 stability in a non-catalytic manner [46].

MiRNAs also play a role in regulating ADAM9 in prostate cancer, especially miR-126. Hua et al. identified the binding site and the effect of miR-126 on reducing ADAM9 expression via luciferase reporter assay. And silencing ADAM9 by miRNA has similar inhibitory effects on cell proliferation, migration, and invasion in vitro as did miR-126 overexpression [47].

2.3. Liver Cancer

Several pieces of evidence suggest the overexpression of ADAM9 contributes to poor patient outcomes and lower response to immune checkpoint blockade therapy [47]. Kohga et al. identified MHC Class I polypeptide-related sequence A (MICA), which is a ligand on cancer cells to elicit attack by natural killer cells, as a novel target of ADAM9. Membrane-bound MICA (mMICA) can be cleaved by ADAM9 to release soluble MICA (sMICA) by ADAM9 as an immunological decoy to suppress immune surveillance. The knockdown of ADAM9 up-regulates the expression of mMICA on the cell membrane and down-regulates sMICA in culture supernatant in vitro [48].

Metastasis is also an urgent issue in liver cancer therapy. IL-6 is a major mediator of invasion and metastasis in liver cancer [81,96]. Dong et al. have demonstrated that IL-6 enhances ADAM9 expression through activating the JNK pathway in vitro. Silencing ADAM9 not only reduces the primary tumor size but also suppresses the metastasis rate to lung; in contrast, overexpressing ADAM9 accelerates primary tumor growth and promotes the metastasis to the lung [49].

Numerous studies identify the negative regulation of ADAM9 by miRNAs in liver cancer. MiR-126 [64]. miR-203 [65], and miR-488 [66], target the 3’-UTR of ADAM9 and down-regulate ADAM9 to suppress cell migration and invasion in vitro.

2.4. Breast Cancer

In breast cancer, the expression of ADAM9 is up-regulated compared to normal tissue [50]. ADAM9 also contributes to disease progression by promoting tumor extravasation and migration ability [51]. An upstream role of ADAM9 in the trans-endothelial migration pathway was suggested by Micocci et al. Knockdown of ADAM9 down-regulates the mRNA expression of ADAM15 and MMP2 but not ADAM10, ADAM17, or MMP9 in vitro [67].

Triple-negative breast cancer (TNBC) is the most aggressive type of breast cancer. In some subtypes of TNBC, methylation deregulation causes the overexpression of EGFR to enhance cell proliferation and survival. ADAM9 shares EGFR's methyltransferase, according to chromatin precipitation assays, and nuclear receptor-binding SET domain protein 2, a member of the histone methyltransferase family, up-regulates the expression of both ADAM9 and EGFR and promotes TNBC cell resistance to EGFR inhibitors [52].

Several miRNA expression profiles and target sites on ADAM9 have been studied in breast cancer, including miR-126 [68][69], miR-154 [70], and miR-33a [71]. The binding sites of these miRNAs are located on 3′-UTR of ADAM9, and lower expression of these miRNAs results in the overexpression of ADAM9 and promotes cancer cell migration and invasion in vitro.

2.5. Pancreatic Cancer

In recent years, several studies have suggested that elevated mRNA expression of ADAM9 shortens the overall survival of pancreatic cancer patients [53], a finding that was confirmed by immunohistochemistry [24]. Increased ADAM9 expression also correlates with higher tumor grade and progression [54].

KRAS signaling is necessary to maintain tumorigenesis in pancreatic cancer. Yuan et al. discovered that dysregulated KRAS signaling enhanced the expression of ADAM9 via NF-kB cascade [55]. Notably, the knockdown of ADAM9 suppresses the downstream pathway of KRAS and MEK-ERK signaling as well [24]. Taken together, a feedback loop between ADAM9 and KRAS is implied.

Circular RNA, a type of single-stranded RNA produced by non-canonical linear splicing, called back-splicing, takes on a covalently closed-form in the cytoplasm and regulates biological function by acting as a micro-RNA or protein inhibitor [72]. Studies have demonstrated that circular ADAM9 (circ-ADAM9) is up-regulated in pancreatic cancer cells and is correlated with poor prognosis. Circ-ADAM9 absorbs and inhibits miR-127, which is a tumor suppressor. Overexpressing circ-ADAM9 increases ERK signaling to promote cell proliferation and migration in vitro, and silencing circ-ADAM9 delays pancreatic tumor growth in vivo [56].

ADAM9 is also regulated by various miRNAs in pancreatic cancer. MiR-489 [55], miR-126 [73][74], and miR-502f [53] target the 3′-UTR of ADAM9 and down-regulate ADAM9 directly to suppress cell migration and invasion in vitro.

2.6. Glioma

Glioma causes nearly 8% of all cancer-related deaths every year, and glioblastoma (GBM) is an advanced and aggressive glioma that has only a 10% 5-year survival rate. Based on the RNA-seq data from 303 glioma patients, the elevated mRNA expression of ADAM9 is correlated with poor progression-free survival and overall survival [57]. In addition, both mRNA and protein expression of ADAM9 are up-regulated in GBM patients and correlated with short overall survival in different cohorts as well [58].

Tumor invasion highly depends on the interaction between the ECM and tumor cells for most cancer types. Tenascin-C (TNC), a major component of the ECM, activates the JNK pathway to promote tumor invasion in GBM. One study demonstrated that both mRNA and protein expression of ADAM9 are up-regulated in TNC-treated GBM cells [58]. Moreover, treatment with JNK inhibitor (SP600125) inhibited TNC-induced ADAM9 expression, and silencing ADAM9 in TNC-treated GBM cells suppressed cell migration and invasion.

ADAM9 regulation by miRNAs is also well-studied in glioma. MiR-543 [75] and miR-140 [76] are two down-regulated miRNAs in GBM tumor tissue. Similar to other miRNAs in various tumor types, the binding sites are located in the 3′-UTR of ADAM9. Overexpression of ADAM9 reverses the inhibitory effects of miR-543 and miR-140 on cell proliferation, migration, and invasion of GBM cells in vitro.

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