

# Physiological and pathological roles of Hic-5 in several organs (Review)

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**Abstract.** Integrins allow cells to adhere to the extracellular matrix and promote the recruitment of other integrins, resulting in the formation of focal adhesion sites at the binding sites. Focal adhesion sites play essential roles in the assembly of the cytoskeleton and are vital in shaping the structure of cells. They also play other regulatory roles by influencing numerous biological functions, such as cell proliferation and apoptosis. Hydrogen peroxide-inducible clone 5 (Hic-5) is a member of the Paxillin family of proteins and is an adhesive plaque scaffolding protein. Its expression can be detected in both vascular and smooth muscle cells. Thus, it plays an essential role in vascular remodeling, as well as in fibrotic diseases. Hic-5 functions as a coactivator of steroid receptors, thus playing a role in steroid hormone-dependent diseases. It also plays a vital role in the invasive metastasis of various types of cancer. Moreover, several studies have demonstrated that Hic-5 plays a critical role in transcriptional regulation, as well as in numerous signaling pathways. Therefore, the inhibition of the functions of Hic-5 may prevent the development or halt the progression of several diseases. Its use as a therapeutic target in future investigations may thus aid in the treatment of several diseases, including various types of cancer. The present review article focused on the expression and functions of Hic-5 in different organs, with the aim of highlighting novel possibilities for future research.

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## 1. Introduction

Hydrogen peroxide-inducible clone 5 (Hic-5) was isolated from a transforming growth factor- $\beta$  (TGF- $\beta$ ) or hydrogen peroxide-inducible gene clone by ablative hybridization in 1994 by Shibanuma *et al* (1). Subsequently, after studying Hic-5 at the molecular and cellular level, it was found that Hic-5 is a homolog of Paxillin and is currently considered a member of the Paxillin protein family (2). The Paxillin family includes Paxillin, Leupaxin and Hic-5, and they function as molecular adapters that deliver signals when the cellular adhesion environment changes (2).

Hic-5 has a high degree of homology with Paxillin and its intracellular localization is similar (Table I) (2-19). It is primarily restricted to focal adhesion sites, and sites of adhesion with the extracellular matrix (ECM) via integrins (2). In contrast to the abnormal development of extra-embryonic tissues, and the segmentation of the heart and body in mouse fetuses following the knockout of Paxillin in mice (20), no effects on homeostasis and development were observed in Hic-5 knockout mice (13). This indicates that Hic-5 is not required for development, and suggests that Paxillin and Hic-5 have different physiological functions. Hic-5 expression has been detected in smooth muscle cells (SMCs) of various tissues (21), and a higher level of expression has been observed in the lungs and spleen (1). Hic-5 expression has been assessed and shown to vary in several cell lines (2). It is highly expressed

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in mesenchymal cell lines, such as fibroblasts, whilst it exhibits lower levels of expression in epithelial cell lines (2). The fact that Hic-5 expression can be detected in different tissues and cells also implies that it plays a central role in the pathophysiology of different organs.

However, the physiological and pathological roles of Hic-5 have not yet been systematically clarified. Therefore, the present review summarized the expression of Hic-5 in different organs and its role in various diseases.

## 2. Structure and function of Hic-5

Hic-5 has a molecular weight of 55 kDa and consists of 444 amino acids; its gene is located in chromosome 16p11 in humans and in chromosome 7 mice (3). A long intron can be found in the genetic structure of Hic-5 between the N-terminal and C-terminal structural domains (22). Hic-5 consists of four Leu- and Asp-rich LD domains in the N-terminal region; LD1 is missing in one isoform; and there are four LiM domains with two zinc fingers in the C-terminal region (2). Hic-5 also includes multiple phosphorylation sites; tyrosine phosphorylation can occur in response to stimuli, such as osmotic pressure, serum factors, lysophosphatidic acid (LPA) and endothelin (8,23), which further regulate signaling associated with lamellar pseudopodia formation to influence cell motility (24). The structural domains involved in protein interactions include the LD and LiM structural domains, and these allow Hic-5 to function as a junction molecule and thus facilitate protein-protein interactions. It can also serve as a docking site for signaling proteins, such as vinculin and focal adhesion kinase (FAK) (25,26). Additionally, Hic-5 can function as a linker molecule in the integrin substrate complex and can modulate integrin signaling through interactions with binding molecules (2). Under normal culture conditions, the majority of cellular behaviors are almost unaffected by Hic-5 expression (2). When healthy adhesion maintenance is compromised under conditions of stress that affect focal adhesion sites, Hic-5 may inhibit adhesion and excessive changes in cytoskeletal structure by antagonizing Paxillin (21,27).

There is a nuclear export signal (NES) that overlaps with the amino-terminal LD structural domain, and this allows Hic-5 to enter the nucleus from the cytoplasm via an oxidation-sensitive NES (28). Hic-5 is transferred from a focal adhesion site to actin stress fibers in the presence of organic stress, thereby regulating cell contractility (21). In various pathophysiological processes, Hic-5 functions primarily through two different pathways. First, it can affect the transcriptional levels of several nuclear receptors (29), including the glucocorticoid receptor (GR) (4,30), the androgen receptor (AR) (31) and the progesterone receptor (13). Hic-5 may affect the genomic occupancy of GR, as well as the assembly of transcriptional complexes and may thus function as a glucocorticoid regulatory switch for several genes (30). After entering the nucleus, Hic-5 can regulate the expression of several genes through transcriptional regulation (4-6). For example, it can repress *Lef/Tcf*-driven transcription. Multiple sequences upstream of *c-fos* (such as *GC/Spl* and *Ets*, amongst others) can activate Hic-5 (Fig. 1) (5). The P21 promoter region can also respond to Hic-5 in the nucleus, which can bind to *Spl*, *Smad3*, and *p300* to create a transcriptional complex (6). Hic-5 also interacts

with glucocorticoid response promoters (such as TIF-2 and p300, among others) and coactivators, and thus functions as a steroid receptor coactivator (6,32-34). In addition, Hic-5 acts in conjunction with various structural and signaling molecules (such as FAK, vinculin and PtP-PEST, amongst others) to form a scaffold for integrin signaling (Fig. 2) (8-10,14). Hic-5 has been shown to be essential to the adhesion formation of the three-dimensional (3D) structure of the ECM (35). Moreover, when Hic-5 expression is low, fibroblasts exhibit higher migratory capacity, and when its expression is high, the migratory capacity of fibroblasts is reduced and the contractile capacity is increased, increasing the contraction and matrix remodeling of the ECM (36). This allows Hic-5 to function as a key factor in various types of fibrotic diseases (7,11,37).

## 3. Hic-5 and the regulation of signaling pathways

A main mechanism through which Hic-5 exerts its effects is via the activation of various signaling pathways (Fig. 3). It can induce the formation of abdominal aortic aneurysm (AAA) by promoting the activity of the JNK pathway (38). The TGF- $\beta$ /Smad pathway is a crucial factor in fibrotic diseases (39,40), and TGF- $\beta$  can promote Hic-5 expression (1). Previous studies have also demonstrated that Hic-5 can promote the development of liver fibrosis and pancreatic fibrosis via the activation of *Smad2/Smad3* and inhibition of *Smad7* (7,41). It also inhibits the apoptosis of prostate cancer cells by binding and interacting with *Smad1* (42). Hic-5 inhibits  $\beta$ -catenin function upon interaction with *Smad4*, thereby promoting the proliferation and inhibiting apoptosis of osteosarcoma (OS) cells (43). Hic-5 can also promote inflammation by activating the activity of the NF- $\kappa$ B pathway (44) and can promote cell apoptosis through the Toll-like receptor 4 (TLR4)/Fas-associated protein with death domain (FADD) signaling pathway (45). Hic-5 can promote hepatocarcinogenesis by activating the reactive oxygen species (ROS)/JNK pathway (46), while in a variety of tumors, Hic-5 can induce epithelial-mesenchymal transition (EMT) by activating *RhoA/ROCK I* signaling, thus promoting invasion and metastasis (12,47,48). Hic-5 may play a critical role in other signaling pathways; however, current research is limited, and further research is required to elucidate the roles of Hic-5 in other signaling pathways.

## 4. Role of Hic-5 in the cardiovascular system

A high expression of Hic-5 has been detected in both vascular and visceral SMCs in mice and humans (49); under physiological conditions, Hic-5 expression has been shown to play a very limited role in intravascular homeostasis (13). Moreover, it has been demonstrated *Hic-5<sup>-/-</sup>* mice do not exhibit any notable abnormalities compared with the wild-type mice in terms of arterial structure and function (3). However, other researchers have found a reduced endothelial cell (EC) expansion in capillaries and an impaired structural organization of cells on basement membrane extracts following the knockdown of Hic-5 (50). Hic-5 has also been found to be expressed in mouse ECs, which are involved in both EC spreading and migration (3). In ECs, the knockdown of Hic-5 has been found to reduce EC sprouting and lumen formation, whereas the sprouting deficiency is restored upon the

Table I. Characterization and expression of Paxillin and Hic-5.

Protein	Molecular weight (kDa)	Chromosome	Domain structure	Expressing tissues or cells	Functions	Related disease	(Refs.)
Hic-5	55	16p11 (human) 7 (mouse)	Four LD motifs Four LIM domains	Widespread high level of expression in SMCs, platelets, and fibroblasts, etc.	Regulation of the expression of multiple genes through transcriptional regulation. Interacts with multiple structural and signaling molecules	Vascular injury, fibrosis, cancer, etc.	(2-14)
Paxillin	68	12q24.2 (human) 5 (mouse)	Five LD motifs Four LIM domains	Universally expressed	Embryogenesis, involved in the adhesion and metastasis of tumor cells, regulates signaling pathways, etc.	Cancer, inflammation, etc.	(15-19)

Hic-5, hydrogen peroxide-inducible clone 5.

re-expression of Hic-5. Hic-5 can interact with membrane type-1 matrix metalloproteinase (MT1-MMPs) under the stimulation of pro-angiogenic factors (51). During EC sprouting, the expression of MT1-MMPs and Hic-5 complexes increases, and this promotes the formation of MT1-MMPs and FAK complexes, thus playing a role in EC matrix proteolysis and cell motility (51). All types of vessels contain ECs and vascular SMCs (VSMCs); this suggests that Hic-5 functions as an essential factor in all types of vascular diseases.

*Hic-5 and vascular injury.* A previous study on Hic-5 found that it carried out a regulatory function in the activation of integrin  $\alpha$ IIb $\beta$ 3 and platelet aggregation in mice (52). However, a subsequent study found that the knockdown of Hic-5 did not affect hemostasis and experimental thrombosis (53), possibly as the function affected by Hic-5 absence was compensated for by Paxillin and Leupaxin, which are also expressed in mouse platelets (54).

In a previous study, in a rat model of wire-mediated femoral artery injury, the expression of Hic-5 was significantly downregulated after 4 days, followed by a gradual recovery to normal levels after 2 weeks, suggesting that Hic-5 expression is downregulated during the acute phase of vascular injury (13). By contrast, in Hic-5<sup>-/-</sup> mice, a significant reduction in the arterial mesangial area with vascular injury was observed along with the accelerated formation of neointima and promotion of chronic apoptosis of VSMCs (13). Similarly, in another study, in the mouse SM SV30 cell line, the expression of Hic-5 was notably increased after differentiation above undifferentiated levels, and furthermore, in a rat model of acute vascular injury following the local delivery of Hic-5 using an adenoviral vector, neointima formation was inhibited, primarily by reducing the migration of vascular SM cells (55). However, further investigations are required to explore the specific underlying mechanisms.

*Hic-5 and atherosclerosis.* The adhesion of monocytes and ECs is a key factor in the development of atherosclerotic plaques (56,57). The APOE<sup>-/-</sup> model is currently the most well-recognized and widely used model for studying atherosclerosis. Arita-Okubo *et al* (58) extracted the aortas of APOE<sup>-/-</sup> and LDLR<sup>-/-</sup> mice and found that Hic-5 deficiency inhibited the adhesion of THP-1 monocytes to the aorta typically stimulated with TNF- $\alpha$  or oxidized low-density lipoprotein. Electron microscopic analysis of aortas extracted from APOE<sup>-/-</sup> mice revealed that Hic-5 deletion significantly inhibited TNF- $\alpha$ -induced microvilli-like structures. Further experiments revealed that the knockdown of Hic-5 significantly inhibited atherosclerotic changes in mice. The same reduction in the number of surface microvillus-like structures was found in human umbilical vein ECs (HUVECs) in which Hic-5 was knocked down, while the number of surface microvillus-like structures was significantly increased in HUVECs after overexpression of Hic-5 (58). These findings indicate that Hic-5 in ECs not only promotes the formation of microvillus-like structures, but also promotes the recruitment of monocytes, which ultimately leads to atherosclerosis (58). However, the exact role of Hic-5 has not yet been determined, thus the mechanisms through which Hic-5 affects atherosclerosis warrant further investigations in future studies.

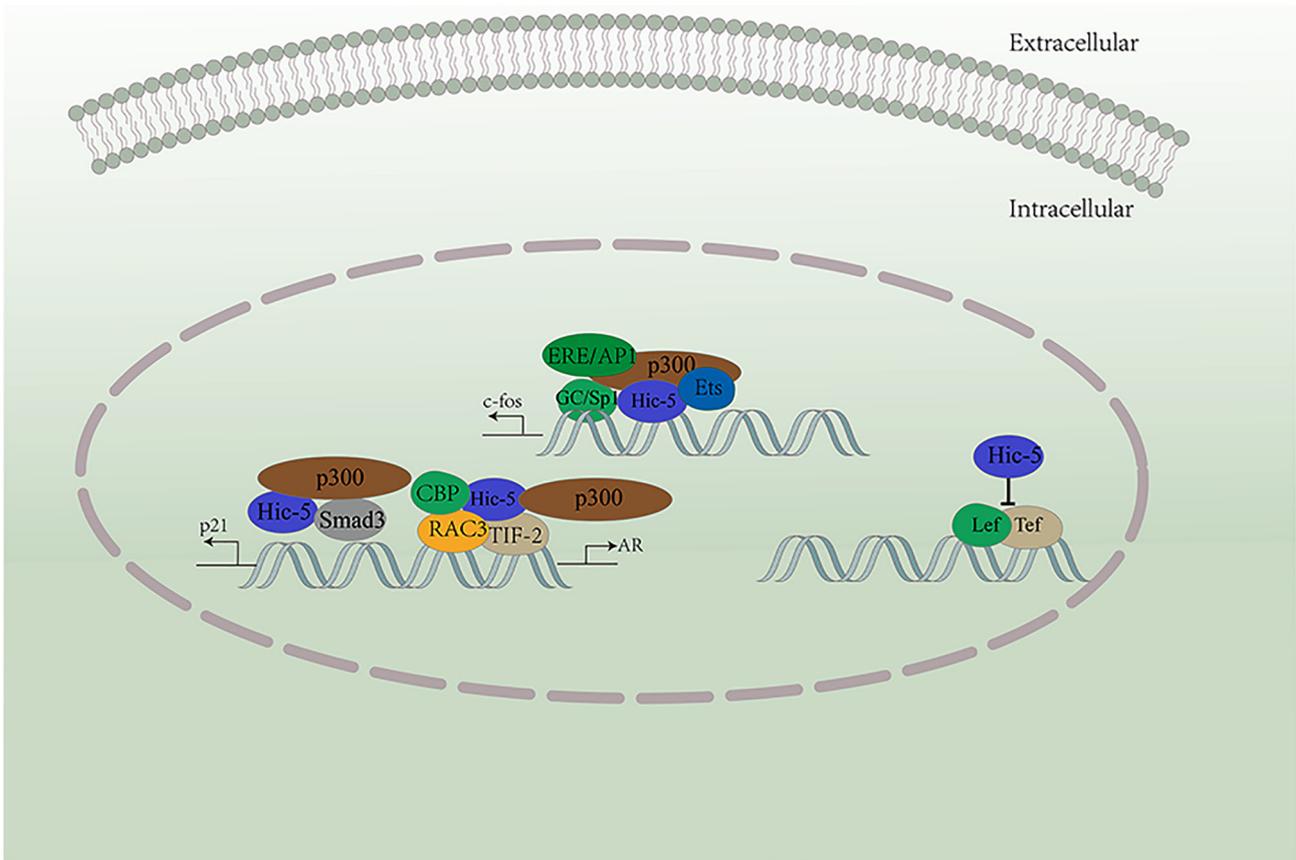


Figure 1. Hic-5 as a transcriptional co-activator. GC/Sp1, Ets and ERE/AP-1 interact with Hic-5 to activate c-fos. Sp1, Smad3, and p300 interact with Hic-5 to activate p21. TIF-2, RAC3, CBP, and p300 interact with Hic-5 to activate GR. Hic-5 can repress Lef/Tcf transcription. Hic-5, hydrogen peroxide-inducible clone 5.

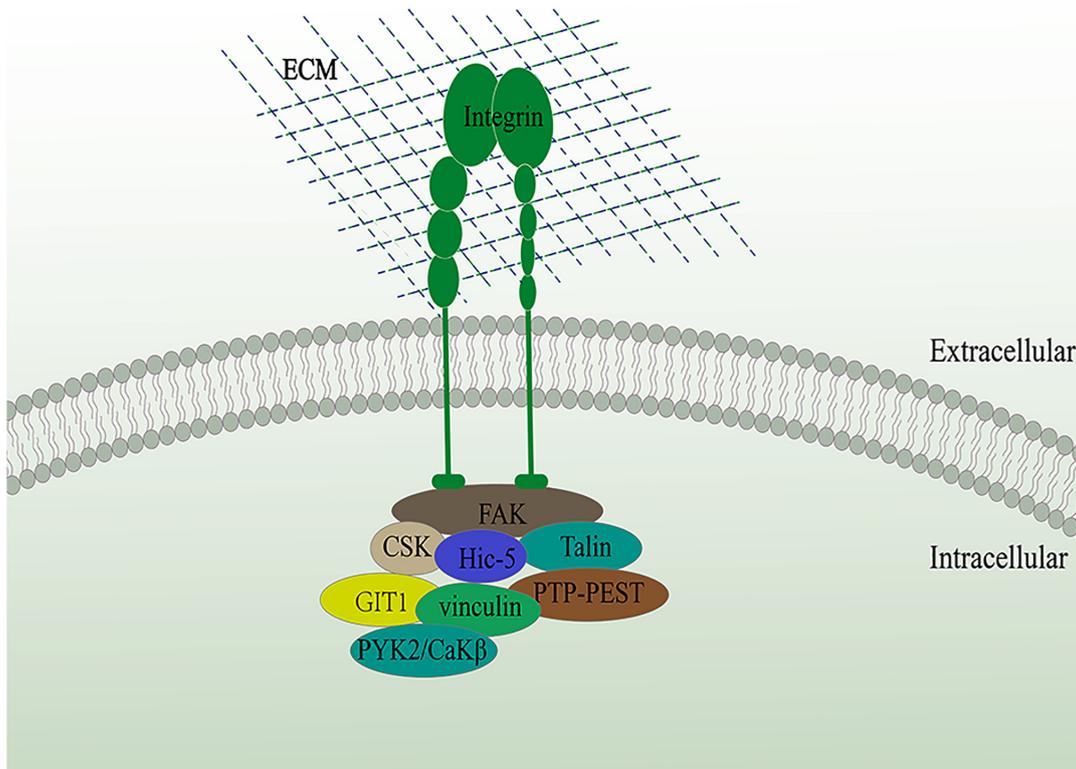


Figure 2. Hic-5 functions as an adaptor for recruitment of several signaling molecules, including FAK, Talin, vinculin, Csk, GIT1 and PTP-PEST. Hic-5, hydrogen peroxide-induced clone 5; Csk, C-terminal Src kinase; GIT1, G protein-coupled receptor kinase interacting ArfGAP 1; PTP-PEST, protein-tyrosine phosphatase PEST.

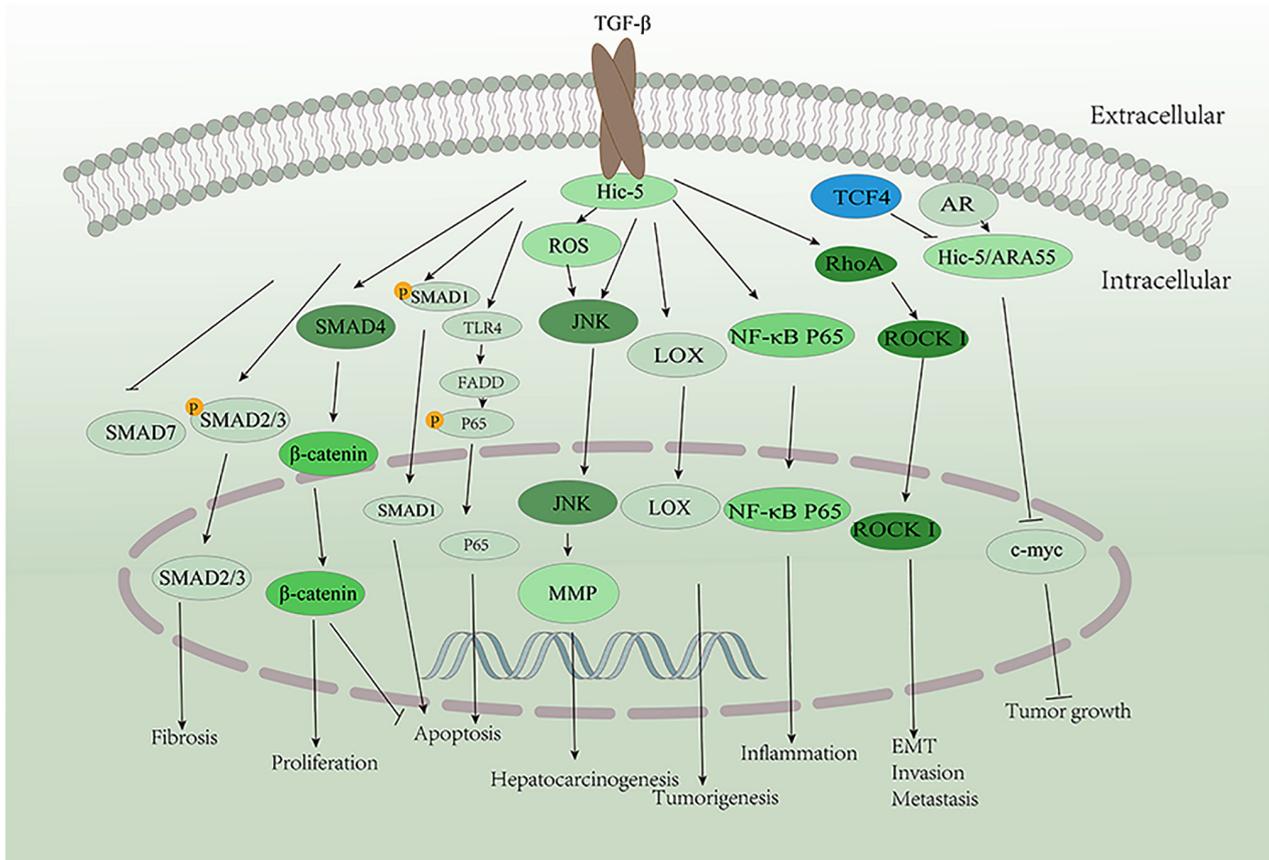


Figure 3. Hic-5 can affect multiple signaling pathways. Hic-5 promotes fibrosis by activating the TGF- $\beta$ /Smad, while inhibiting Smad7. Hic-5 binds and interacts with Smad1 to inhibit apoptosis of prostate tumor cells. Hic-5 inhibits  $\beta$ -catenin upon interaction with Smad4, thereby promoting the proliferation of OS cells and inhibiting apoptosis. Hic-5 promotes inflammation via the NF- $\kappa$ B pathway and apoptosis via the TLR4/FADD pathway. Hic-5 promotes hepatocarcinogenesis via the ROS/JNK pathway. Hic-5 induces EMT by activating RhoA/ROCK I, thus promoting invasion and metastasis. Hic-5/ARA55 inhibits prostate cancer growth by suppressing the expression of c-myc. Hic-5, hydrogen peroxide-induced clone 5; OS, osteosarcoma; EMT, epithelial-mesenchymal transition; TLR4, Toll-like receptor 4; FADD, Fas-associated protein with death domain; ROS, reactive oxygen species.

**Hic-5 and AAA.** In a previous study in which models of AAA were constructed by the administration of angiotensin II in APOE<sup>-/-</sup> and APOE<sup>-/-</sup> Hic-5<sup>-/-</sup> mice, it was found that Hic-5<sup>-/-</sup> mice exhibited a significantly lower degree of AAA and had smaller maximum aortic diameters (38). Abdominal artery rupture and mass hemorrhaging were observed in the APOE<sup>-/-</sup> mice, but not in the APOE<sup>-/-</sup> Hic-5<sup>-/-</sup> mice, indicating that the knock-down of Hic-5 prevented AAA formation and rupture (38). Further mechanistic analyses revealed that Hic-5 promoted the activation of the JNK pathway, subsequently increasing MMP expression and promoting the development of AAAs (38).

**Hic-5 and hypertrophic heart disease.** Hic-5 has also been shown to be expressed in neonatal rat ventricular myocytes (NRVMs) (59). In NRVMs, epinephrine induced the expression of Hic-5, and Hic-5 overexpression significantly increased the number of cells with organized cytoskeleton (59). Mechanistically, Hic-5 exerted its effects via regulation of the ERK1/2 signaling pathway (59). Increased levels of Hic-5 were found in a mouse model of hypertrophic heart disease established using thoracic aortic constriction (59). However, the elevated of Hic-5 in the model alone did not suggest that it played a role in the development of hypertrophic heart disease; thus, future investigations are required to determine its role in hypertrophic heart disease.

## 5. Role of Hic-5 in the digestive system

### Hic-5 and the liver

**Hic-5 and liver fibrosis.** Previous studies have demonstrated that Hic-5 is not expressed in quiescent hepatic stellate cells (HSCs), although its expression is significantly increased following HSC activation (7,60). The significant upregulation of HIC-5 expression has also been found in liver tissues from patients with fibrosis, or in mice subjected to bile duct ligation or mice with CCl<sub>4</sub>-induced mouse liver fibrosis, as well as in activated HSCs (7). It has been revealed that HSCs from Hic-5<sup>-/-</sup> mice exhibit a significantly reduced activation when cultured (7). Additionally, Hic-5 has been found to promote fibrosis by activating the TGF- $\beta$ /Smad2 pathway, while inhibiting Smad7 (7).

**Hic-5 and hepatic ischemia-reperfusion injury (HIRI).** In a previous study, Hic-5 expression was shown to be increased in models of HIRI, and the expression of inflammatory chemokines was found to be decreased in a Hic-5<sup>-/-</sup> HIRI mouse model, while the extent of liver injury was found to be reduced compared with wild-type mice (45). Further experiments revealed that Hic-5 activated the NF- $\kappa$ B signaling pathway to enhance the inflammatory response, and activated the TLR4/FADD pathway to increase hepatocyte apoptosis, which

ultimately led to the exacerbation of the lesions in mice (45). This suggests that *Hic-5* targeted therapy may be beneficial for liver transplantation-induced HIRI. Similarly, *Hic-5* may play a role in ischemia-reperfusion injury in other organs (such as the lungs); however, further studies are required to confirm this.

*Hic-5 and chronic pancreatitis (CP)*. Similar to liver fibrosis, pancreatic fibrosis is also primarily caused by the activation of pancreatic stellate cells (PSCs) (61). A high expression of *Hic-5* was likewise found in pancreatic tissues of patients with CP and was primarily expressed in activated PSCs (41). In a previous study, by culturing pancreatic primary PSCs, it was found that the knockdown of *HIC-5* inhibited PSC activation. The same study subsequently found a significant attenuation of pancreatic fibrosis in *Hic-5*<sup>-/-</sup> mice in a model of caerulein-induced CP, suggesting that *Hic-5* can promote the development of CP (41). By culturing primary PSCs, *Hic-5* was shown to increase the activation of PSCs by increasing the phosphorylation of Smad2, ultimately promoting the development of CP (41). Another study also found that the knockdown of *Hic-5* inhibited NF- $\kappa$ B/p65 expression (44). This also suggested that *Hic-5* can be used as a diagnostic marker and a potential therapeutic target in CP.

## 6. *Hic-5* and the urinary system

*Hic-5 and the kidneys*. In rat kidneys, *Hic-5* expression has been detected in mesenchymal cells, mesangial cells and ECs (62). This suggests that *Hic-5* may be involved in the development of glomerulosclerosis (11). Another study also demonstrated that the increased expression of *Hic-5* in glomerular mesangial cells was not dependent on the TGF- $\beta$ -induced pro-sclerotic phenotype (63); however, that study only illustrated the increased expression of *Hic-5* in glomerulosclerosis, which does not yet indicate a role in the development of glomerulosclerosis, and therefore further studies are required to determine this.

*Hic-5 in the prostate*. Previous research detected *Hic-5* expression in the normal prostate mesenchyme and exhibited a lesser reduction in the tumor-associated mesenchyme (31). *Hic-5* expression was subsequently found in both the normal and tumor prostate epithelium, as well as in prostate cancer cells and prostate cancer tissues (42,64,65). *Hic-5* regulates the transcription of AR (31). When steroid ligands are absent, *Hic-5* can interact with nuclear receptor co-blockers to inhibit transcription (34,66). In prostate myofibroblasts, *Hic-5* rapidly translocates to the nucleus in response to the action of androgens, consistent with the increased phosphorylation of adherent spot kinase. *Hic-5* acts as a co-regulator and AR can lead to androgen-induced transcriptional enhancement through interaction with the coactivator, *Hic-5*/ARA55, thereby affecting androgenic effects on growth, cell adhesion, motility and invasion regulation (67). It was similarly found that the mRNA levels of *Hic-5*/ARA55 in normal or benign prostate hypertrophy tissues were reduced in hormone-independent prostate cancer tissues (12,64); in normal prostate tissues, it was primarily expressed in the interstitium (31,68), and in prostate cancer tissues it was also expressed in the interstitium. *Hic-5*/ARA55 was also observed in the cytoplasm and focal adhesion sites of the prostate mesenchymal cell line,

WPMY-1 (31). *Hic-5*/ARA55 activates AR activity by interacting with the endogenous androgen response promoter (31). CYP24A1 encodes the 1,25D3 metabolizing enzyme 24-hydroxylase (69). *Hic-5* is a coactivator of the vitamin D3 receptor (VDR) and can limit the negative feedback circuit of VDR activity by participating in VDR-mediated transcription of CYP24A1 (69).

## 7. *Hic-5* and tumors

Tumor cells exhibit two interchangeable patterns of cell movement, mesenchymal or amoeboid; during invasion, tumor cells can migrate to different 3D microenvironments through these two switchable motility modes, and this allows them to invade the tumor stroma and circulatory system (35,70). Gulvady *et al* (71) found that the expression levels of *Hic-5* varied greatly by analyzing the expression of Paxillin and *Hic-5* in a variety of tumor cells, while the levels of Paxillin were relatively stable. It was also found that cancer cell lines with low *Hic-5*:Paxillin ratios lacked the ability to efficiently convert to a mesenchymal phenotype, while cell lines with a high *Hic-5*:Paxillin ratios were able to adequately switch from an amoeboidal to a mesenchymal phenotype. In a variety of tumors, *Hic-5* has been shown to induce EMT by activating RhoA/ROCK I signaling, thus promoting invasion and metastasis (12,47,48), which highlights its potential as a biomarker for metastasis in several tumors and as a therapeutic target.

*Hic-5 and hepatocellular carcinoma (HCC)*. *Hic-5* is also involved in HCC progression. The upregulation of proline-rich tyrosine kinase 2 (Pyk2) is expressed in HCC liver tissues and is associated with a worse prognosis (72). Other studies have demonstrated that Pyk2 upregulates the activation and localization of *Hic-5* (73). In another study, Wu *et al* (46) found that *Hic-5* expression was upregulated in HCC cell lines that originated from high motility cancers, but not in HCC cells originated from low motility cancers when they analyzed liver tissues from patients with HCC, suggesting that its overexpression was closely associated with the metastasis of HCC. This suggests that *Hic-5* may be used as a biomarker for metastasis in with HCC. The same authors also found that the knockdown of *Hic-5* in high motility-derived HCC cells significantly reduced the invasive ability of HCC cells (46). Further analyses revealed that *Hic-5* affected HCC progression through the ROS/JNK pathway (46). However, that study was limited to assessing the progression of HCC *in vitro*, and further studies are thus required to confirm its role *in vivo* and to elucidate the specific underlying mechanisms.

*Hic-5 and pancreatic cancer (PC)*. In a previous study, the upregulated expression of *Hic-5* was detected in PC, and the knockdown of *Hic-5* revealed that PC cell (PCC) proliferation was suppressed and apoptosis was increased, while PCC invasion and migration were reduced (74). The same study also found that patients with a high expression of *Hic-5* in PC had lower survival rates (74). However, there are fewer studies investigating the role of *Hic-5* in PC; thus, further cellular and animal models are required to examine the mechanisms through which *Hic-5* specifically affects PC and to identify novel strategies for the management of PC.

**Hic-5 and esophageal cancer.** The tumor microenvironment plays an essential role in tumor development and metastasis (75); cancer-associated fibroblasts (CAFs) are an important component of the tumor microenvironment (76) that release cytokines into the ECM, thereby promoting circulating tumor metastasis (77,78). In a previous study, the high expression of Hic-5 was detected in the CAFs of esophageal squamous cell carcinoma (ESCC) (79). That study further demonstrated that the invasion and migration of cells was inhibited following the knockdown of Hic-5 in KYSE150/TE1 esophageal cancer cells co-cultured with CAFs (79). RNA-seq revealed that Hic-5 in CAFs may promote tumor progression by regulating cytokines (such as CCL2) and altering the ECM (79). The same study also found an association with esophageal cancer lymph node metastasis through survival analysis (79). This suggests that the levels of Hic-5 may be used as a marker of lymph node metastasis in ESCC. The effect of Hic-5 on the biological behavior of esophageal cancer cells has only been demonstrated *in vitro*; thus, *in vivo* models are warranted to explore the role of Hic-5 and its specific mechanisms of action in esophageal cancer.

**Hic-5 and colon cancer.** PPAR $\gamma$  is a major regulator of adipocyte differentiation (80). Hic-5 has been shown to bind to and activate PPAR $\gamma$ , and both Hic-5 and PPAR $\gamma$  are expressed in normal and malignant intestines (33). In a mouse colon cancer model, the expression of both PPAR $\gamma$  and Hic-5 has been found to be notably decreased (33). Hic-5 has also been found to enhance PPAR $\gamma$ -mediated epithelial gene induction in colon cancer cells (33).

The high expression of Hic-5 was also previously detected in CAFs of tumor tissues from patients with colon cancer (81). The addition of CAF supernatant to normal fibroblasts induced the expression of Hic-5 (81). Following the establishment of a mouse colon tumor model by azoxymethane induction, no tumors were found in Hic-5<sup>-/-</sup> mice compared with wild-type mice, where tumors were found in 55% of mice after 20 weeks; proliferative polyps were found in only one location after 24 weeks, and advanced adenocarcinomas was only observed in wild-type mice (81). Further analyses revealed that HIC-5 induced lysyl oxidase (LOX) expression following nucleation, and LOX promoted the cross-linking of collagen fibers and thus increased the stiffness of ECM, which eventually promoted tumor progression (81). This suggests that Hic-5 may serve as a therapeutic target for the management of colon cancer.

**Hic-5 and prostate cancer.** Previous research has shown that Hic-5 can interact with Smad1 to inhibit the apoptosis of prostate cancer cells (42). LNCaP is a prostate epithelial cell line that does not express Hic-5. Hic-5 overexpression using lentiviral transfection and subsequent administration in mice has been shown to result in the inhibition of tumor growth (64). Further mechanistic research has revealed that Hic-5/ARA55 can inhibit c-Myc expression in an androgen-dependent manner (65). The expression of c-Myc is increased when deprived of androgens, and Hic-5/ARA55 also inhibits c-Myc expression by suppressing it in a TCF4-dependent and non-dependent manner (64).

Hic-5 could interact with 1,25D3 to inhibit prostate cancer cell proliferation. Following androgen deprivation, Hic-5 induces different responses in prostate tumors to 1,25D3,

particularly during androgen deprivation therapy (69). Hic-5 can play a differential role in the adjuvant treatment of VDR activity in prostate cancer. This suggests that patients with prostate cancer with a downregulated expression of Hic-5 may benefit more from treatment with VDR ligands (69).

**Hic-5 and breast cancer.** Gulvady *et al* (71) found that the expression of Hic-5 in breast cancer cells was upregulated. They further constructed a mouse polyoma middle T-antigen breast cancer model and found that CAFs in Hic-5<sup>-/-</sup> mice could not effectively form fibrillar adhesion in both 2D and 3D (82). Using bioinformatics analysis, it was found that the high expression of Hic-5 in patients with breast cancer was negatively associated with the distant metastasis-free survival (DMFS) of patients (83).

**Hic-5 and ovarian cancer.** The high expression of Hic-5 was previously found in advanced ovarian cancer, and EMT independent of TGF $\beta$ -1 was induced by the overexpression of Hic-5 in the ovarian cancer cell line, A2780 (which is typically morphologically epithelial), accompanied with enhanced cell proliferation and migratory/invasive ability, as well as increased resistance to chemotherapeutic agents (48). In addition, in epithelial ovarian cancer cells, the knockdown of Hic-5 inhibited its proliferation, migration/invasion and induced mesenchymal-epithelial transition, and it was further shown that it may promote EMT in ovarian cancer via the regulation of the RhoA/ROCK signaling pathway (48). However, further *in vivo* studies are required to investigate the role of Hic-5 in ovarian cancer.

**Hic-5 and osteosarcoma (OS).** The high expression of Hic-5 was previously detected in both OS tissues and cells, and a higher percentage of low-grade OS tissues exhibited an upregulated expression of Hic-5 (46.7%), while its expression was reduced in the majority of high-grade OS patient tissues (53.3%) (43). The knockdown of Hic-5 suppressed the proliferation of OS cells, whereas it promoted apoptosis. Additionally, it was found that Hic-5 expression in exosomes was similarly reduced following the knockdown of Hic-5, and it was further found that Hic-5 interacted with Smad4 through the exosomal pathway to promote the activation of  $\beta$ -catenin, thus promoting the proliferation of OS cells (43).

**Hic-5 and melanoma.** Hic-5 expression was previously detected in both human melanoma cells and murine B16-F1 cells (84). The knockdown of Hic-5 in murine melanoma B16-F1 cells was shown to result in reduced cell proliferation and migration, and significantly inhibited tumor growth and lung metastasis in further subcutaneous tumorigenesis assays in mice (84). It was also found an increase in RhoA activity upon the knockdown of Hic-5, accompanied by an altered amoeboid-like phenotype, leading to a loss of cell plasticity, which may also be responsible for its effect on cell motility (84). This suggests that Hic-5 may influence melanoma development via modulation of the RhoA/ROCK signaling pathway.

## 8. Hic-5 and other diseases

**Hic-5 and Alzheimer's disease (AD).** In a previous study using a model AD, an increased expression of Hic-5 was detected

in pyramidal neurons in the CA1 region of the hippocampus (85). It is possible that Hic-5-mediated intracellular signaling in the ECM is involved in the pathogenesis of AD. However, to the best of our knowledge, no further studies have been performed to date to confirm whether Hic-5 is involved in AD development, and thus further research is required to determine this.

**Hic-5 and osteoarthritis.** A mouse model of osteoarthritis of the knee was previously established by surgical induction, and a significantly lower degree of cartilage degradation was observed in Hic-5<sup>-/-</sup> mice than in wild-type mice after 8 weeks (86). Furthermore, by extracting primary chondrocyte cultures, it was found that Hic-5 promoted the development of osteoarthritis primarily by promoting the expression of inflammatory cytokines, or mechanical load-induced MMP13, and a disintegrin and metalloproteinase with thrombospondin type 1 motif 5 (86).

**Hic-5 and skin.** Hic-5 modulates androgen sensitivity in hair follicle papillae (87), while in scar-forming myofibroblasts, autocrine TGF- $\beta$  upregulates Hic-5 expression, further downregulating the autocrine loop of Hic-5 and collagen synthesis (88). The overexpression of Hic-5 in keloid-derived fibroblasts was previously found to increase collagen expression in keloid scars (89). Similarly, Hic-5 was confirmed to be expressed in keloid specimens (8/15) using immunohistochemistry, and was not observed in normal tissues; its expression was shown to be primarily localized in the nucleus where it stimulated Smad2/3 expression via other pathways not dependent on Smad7 thus promoting scar formation (89). Hic-5 expression was found to be increased in patients with systemic sclerosis (SSc) and SSc dermal fibroblasts. In addition, in SSc fibroblasts, the knockdown of Hic-5 reduced the production of type I collagen by >50%. This suggests that Hic-5 can promote the formation of fibrosis in SSc, indicating that it may be a therapeutic target for the management of SSc fibrosis (90). However, that study had a small clinical sample; thus, further clinical samples are warranted to confirm these findings and the underlying molecular mechanism need to be assessed.

**Hic-5 and the eyes.** Aqueous humor (AH) homeostasis is critical for maintaining normal intraocular pressure (91). By contrast, increased obstruction or resistance to the atrial fluid flow through the trabecular meshwork (TM) causes increased intraocular pressure and is a major risk element for primary intraocular pressure elevation (92). In a previous study, in human TM (HTM) cells, Hic-5 expression was limited to the focal adhesion of HTM cells, as well as throughout the TM and AH efflux pathways of the Schlemm's canal; the administration of recombinant Hic-5 was found to result in the redistribution of actin stress fibers, focal adhesion and  $\alpha$ v integrins in the focal adhesion, along with an increase in  $\alpha$ -SMA, and increased collagen-1 expression, whereas the knockdown of Hic-5 reversed these effects. In the presence of dexamethasone, Hic-5 in TM increased resistance to AH efflux via the trabecular pathway, which suggests that Hic-5 plays a critical role in regulating eye AH outflow through the TM (93).

## 9. Perspectives of Hic-5 in clinical applications

TGF- $\beta$  plays a key role in the progression of various diseases. Hic-5 expression can be induced by TGF- $\beta$ , plays a key role in various diseases (Table II) (7,11,13,31,38,41-46,48,55,58-60, 64,71,74,79,81,83-86,90,94-122) and the negative effects of its knockdown are limited and not severe; thus, targeting Hic-5 may be a suitable approach for the management of several diseases. Hic-5 expression was previously found to be significantly elevated in liver fibrosis, pancreatic fibrosis, HIRI, glomerulosclerosis and SSc, while disease pathology was reduced following the knockdown of Hic-5 (7,11,41,44,45,88,90), which also suggests its potential use as a biomarker for the diagnosis of fibrotic diseases and as a potential therapeutic target. The role of Hic-5 in other fibrotic diseases likely promotes fibrosis via the activation of the TGF- $\beta$ /Smad pathway.

In tumors, the high expression of Hic-5 was found to promote the transformation of tumor cells with an amoeboid phenotype to a mesenchymal phenotype and promote EMT through the RhoA/ROCK pathway, thus promoting tumor cell plasticity and invasiveness (12,47,48), which also suggests that Hic-5 may be used as a biomarker for tumor metastasis. Related studies have demonstrated that Hic-5 expression is upregulated in HCC with a low migratory capacity and is also associated with lymph node metastasis in patients with esophageal cancer (46,79). Therefore, it may be used as a biomarker for the detection of metastases in patients with HCC, and lymph node metastases in patients with esophageal cancer. It is also negatively associated with the survival of with PC and the DMFS of patients with breast cancer and may serve as a biomarker for predicting a poor prognosis of patients with PC and breast cancer. The knockdown of Hic-5 in HCC cells, PC cells, esophageal cancer cells, ovarian cancer, melanoma and cholangiocarcinoma cells led to the inhibition of tumor cell invasion and migration (43,46,48,74,79,84,123), and the knockdown of Hic-5 in HuCCT1 cholangiocarcinoma cells was also found to inhibit cholangiocarcinoma migration in a concentration-dependent manner (123). This suggests that it may be possible to inhibit tumor metastasis in these tumors by targeting Hic-5. However, the effects of the knockdown of Hic-5 were only verified at the cellular level in these tumors, and further *in vivo* experiments are thus required to confirm these results. In addition, the knockdown of Hic-5 was previously found to suppress tumorigenesis in mouse models of colon and breast cancer (81,82). In patients with PC, those with a downregulated HIC-5 expression were found to benefit more from VDR ligand therapy (69). Furthermore, the majority of research has focused on the effects of Hic-5 on tumor metastasis, and thus further studies are required to explore the effects of Hic-5 on tumorigenesis.

In future studies, drugs targeting Hic-5 need to be investigated, which may provide novel options for the treatment of tumors. Moreover, Hic-5 promotes CAF protofibril adhesion by direct interaction with Tensin1, and the interaction is through a phosphorylation-dependent mechanism (83). Therefore, Hic-5 plays a key role in CAFs, and future research on drugs targeting the tumor microenvironment using Hic-5 as a target may provide novel avenues for the management and treatment of several types of cancer.

Table II. Role of Hic-5 and TGF- $\beta$  in different diseases.

Disease	Hic-5	TGF- $\beta$	(Refs.)
Vascular injury	<ul style="list-style-type: none"> <li>• Expression was downregulated during the acute phase of vascular injury.</li> <li>• Hic-5<sup>-/-</sup> mice exhibited a significant reduction in the arterial mesangial area as well as accelerated neonatal intima formation and increased levels of chronic apoptosis of vascular SMCs.</li> </ul>	<ul style="list-style-type: none"> <li>• Increased expression after vascular injury.</li> <li>• Promotes the proliferation of neoplastic endothelium.</li> </ul>	(13,55,94,95)
Atherosclerosis	<ul style="list-style-type: none"> <li>• Plays an essential role in the formation of microvillous structures of endothelial cells.</li> <li>• Promotes atherosclerosis by recruiting monocytes and interacting with monocytes.</li> </ul>	<ul style="list-style-type: none"> <li>• Decreased TGF-<math>\beta</math> levels in patients with advanced atherosclerosis.</li> <li>• Promotes the development of atherosclerosis.</li> </ul>	(58,95,96)
Abdominal aortic aneurysm	<ul style="list-style-type: none"> <li>• Activates the JNK pathway to enhance MMP expression in VSMCs and promote AAA formation.</li> </ul>	<ul style="list-style-type: none"> <li>• Decrease aneurysm formation and progression.</li> <li>• TGF-<math>\beta</math>1 can decrease pseudoaneurysm formation and progression.</li> </ul>	(38,96,97)
Hypertrophic heart disease	<ul style="list-style-type: none"> <li>• Overexpression of Hic-5 increases the number of cells in the cytoskeletal tissue.</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>	(59)
Liver fibrosis	<ul style="list-style-type: none"> <li>• Expression is upregulated in patients with liver fibrosis and in mouse models.</li> <li>• Exerts its effect by activating the TGF-<math>\beta</math>/Smad2 pathway while suppressing Smad7.</li> </ul>	<ul style="list-style-type: none"> <li>• Activation of hepatic stellate cells through the TGF-<math>\beta</math>/Smad signaling pathway, thereby promoting liver fibrosis</li> </ul>	(7,60,98,99)
Hepatic ischemia-reperfusion injury (HIRI)	<ul style="list-style-type: none"> <li>• Highly expressed in HIRI models.</li> <li>• Promotes hepatocyte apoptosis through the TLR4-FADD pathway and inflammation through the NF-<math>\kappa</math>B pathway.</li> </ul>	<ul style="list-style-type: none"> <li>• Serum TGF-<math>\beta</math>1 levels are upregulated in the HIRI mouse model.</li> </ul>	(45,100)
Hepatocellular carcinoma (HCC)	<ul style="list-style-type: none"> <li>• Highly expressed in HCC cells originating from cells with a high degree of motility.</li> <li>• Promotes HCC development through the ROS-JNK signaling pathway.</li> </ul>	<ul style="list-style-type: none"> <li>• Limiting hepatocyte proliferation under normal conditions, but enabling chemically induced HCC in the heterozygous state.</li> <li>• Promotes HCC progression and immune escape.</li> </ul>	(46,99,101-103)
Chronic pancreatitis	<ul style="list-style-type: none"> <li>• Highly expressed in patients with CP.</li> <li>• Exerts its effect by activating the TGF-<math>\beta</math>/Smad2 signaling pathway and NF-<math>\kappa</math>B signaling pathway.</li> </ul>	<ul style="list-style-type: none"> <li>• Highly expressed in a mouse model of CP.</li> <li>• Promotes CP progression.</li> </ul>	(41,44,104)
Pancreatic cancer	<ul style="list-style-type: none"> <li>• Highly expressed in pancreatic cancer.</li> <li>• Promotes the proliferation of PCCs, reduces apoptosis and promotes the invasion and migration of PCCs.</li> </ul>	<ul style="list-style-type: none"> <li>• Increased expression in patients with pancreatic ductal adenocarcinoma (PDAC).</li> <li>• Inhibition of TGF-<math>\beta</math> receptor inhibits tumor growth and metastasis.</li> </ul>	(74,99,105)
Esophageal cancer	<ul style="list-style-type: none"> <li>• Highly expressed in ESCC.</li> <li>• Promotes invasion and migration of esophageal squamous carcinoma cells. Could be used as a marker of lymph node metastasis in ESCC.</li> </ul>	<ul style="list-style-type: none"> <li>• Associated with the overall survival time in esophageal cancer.</li> </ul>	(79,99,106)

Table II. Continued.

Disease	Hic-5	TGF- $\beta$	(Refs.)
Colorectal cancer	<ul style="list-style-type: none"> <li>Highly expressed in the CAFs of patients with CRC.</li> <li>Promotes the expression of LOX, promotes the cross-linking of collagen fibers, and thus increases the stiffness of the ECM, ultimately promoting tumor progression.</li> <li>Increased expression in a rat model of glomerulosclerosis.</li> <li>Kidney fibrosis can be reduced by targeting TGF-<math>\beta</math> downstream molecules.</li> <li>Expressed in tumor prostate epithelium, AR-deficient prostate cancer cells, and in tissue from untreated stage IV prostate cancer.</li> <li>Interacts with Smad1 to inhibit apoptosis.</li> <li>Increased expression in breast cancer cells.</li> <li>Negatively associated with the DMFS of breast cancer patients.</li> </ul>	<ul style="list-style-type: none"> <li>Highly expressed in CRC.</li> <li>Inhibition of TGF-<math>\beta</math> signaling inhibits CRC metastasis</li> </ul>	(81,99,107,108)
Glomerulosclerosis	<ul style="list-style-type: none"> <li>Increased expression in a rat model of glomerulosclerosis.</li> <li>Kidney fibrosis can be reduced by targeting TGF-<math>\beta</math> downstream molecules.</li> </ul>	<ul style="list-style-type: none"> <li>Highly expressed in various kidney diseases associated with fibrosis.</li> </ul>	(11,109,110)
Prostate cancer	<ul style="list-style-type: none"> <li>Expressed in tumor prostate epithelium, AR-deficient prostate cancer cells, and in tissue from untreated stage IV prostate cancer.</li> <li>Interacts with Smad1 to inhibit apoptosis.</li> <li>Increased expression in breast cancer cells.</li> <li>Negatively associated with the DMFS of breast cancer patients.</li> </ul>	<ul style="list-style-type: none"> <li>Inhibits proliferation in early stages of prostate cancer, promotes proliferation and metastasis in advanced stages.</li> </ul>	(31,42,64,111-113)
Breast cancer	<ul style="list-style-type: none"> <li>Increased expression in breast cancer cells.</li> <li>Negatively associated with the DMFS of breast cancer patients.</li> </ul>	<ul style="list-style-type: none"> <li>TGF-<math>\beta</math>1 activated cancer-associated fibroblasts to promote breast cancer invasion, metastasis and EMT</li> </ul>	(71,83,114)
Ovarian cancer	<ul style="list-style-type: none"> <li>Highly expressed in ovarian cancer.</li> <li>Promotes EMT in ovarian cancer via RhoA/ROCK signaling.</li> </ul>	<ul style="list-style-type: none"> <li>Induces metastasis or EMT in advanced ovarian cancer</li> </ul>	(48,115)
Osteosarcoma	<ul style="list-style-type: none"> <li>Highly expressed in the osteosarcoma.</li> <li>Activates <math>\beta</math>-catenin by interacting with smad4 to promote osteosarcoma cell proliferation and inhibit osteosarcoma apoptosis.</li> </ul>	<ul style="list-style-type: none"> <li>Serum levels are increased in patients with osteosarcoma.</li> </ul>	(43,116,117)
Melanoma	<ul style="list-style-type: none"> <li>Expressed in human melanoma cells.</li> <li>Promotes proliferation and migration.</li> </ul>	<ul style="list-style-type: none"> <li>Promotes invasion and metastasis.</li> <li>Promotes the invasion and metastasis of melanoma cells.</li> </ul>	(84,118)
Alzheimer's disease	<ul style="list-style-type: none"> <li>Increased expression in a rat model of AD</li> </ul>	<ul style="list-style-type: none"> <li>Serum levels are increased in patients with AD.</li> <li>Reduce amyloid <math>\beta</math>-protein (A<math>\beta</math>) pathology of brain parenchyma.</li> <li>May be a useful biological marker for patients with AD.</li> </ul>	(85,119,120)
Osteoarthritis	<ul style="list-style-type: none"> <li>Promotes the development of osteoarthritis by increasing the expression of MMP13 and ADAMTS5</li> </ul>	<ul style="list-style-type: none"> <li>Serum levels are increased in patients with osteoarthritis.</li> </ul>	(86,121)
Systemic sclerosis	<ul style="list-style-type: none"> <li>Increased expression in systemic sclerosis skin.</li> </ul>	<ul style="list-style-type: none"> <li>Promotes osteoarthritis progression.</li> <li>Elevated serum levels in patients with systemic sclerosis.</li> </ul>	(90,122)

Hic-5, hydrogen peroxide-inducible clone 5; SMCs, smooth muscle cells; VSMCS, vascular smooth muscle cells; AAA, abdominal aortic aneurysm; EMT, epithelial-mesenchymal transition; TLR4, Toll-like receptor 4; FADD, Fas-associated protein with death domain; PCCs, pancreatic cancer cells; ESCC, esophageal squamous cell carcinoma; CRC, colorectal cancer; DMFS, distant metastasis-free survival; AD, Alzheimer's disease.

## 10. Conclusions

As an important component of focal adhesion sites, Hic-5 plays an essential role in cell proliferation, migration, differentiation and apoptosis. It also plays a key role in transcriptional regulation, as well as in the regulation of signaling pathways, and in the suppression of its functions can prevent the development of several diseases. Thus, Hic-5 may serve as a diagnostic biomarker, as well as a therapeutic target for a wide range of diseases, including tumors. Several studies have confirmed the expression of Hic-5 in various organs and its pathological roles in different systems; however, the exact physiological and pathological roles of Hic-5 in several other organs remain unclear and additional studies are required to explore its functions. The present review summarized the role of Hic-5 in a variety of organs and their associated diseases with the aim of providing an up-to-date background on the current body of literature from which future studies may be designed.

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## Availability of data and materials

Not applicable.

## Authors' contributions

SY and ZT drafted the manuscript and contributed equally. XY, LiZhang, YZ, LZheng and HW participated in the literature search and analysis of the data to be included in the review. ZY, JA and HJ were involved in the design of the study and assisted in the preparation of the figures and tables. GW and BT edited and revised the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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