



# Inhibin subunit beta B (INHBB): an emerging role in tumor progression

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## Abstract

The gene inhibin subunit beta B (INHBB) encodes the inhibin  $\beta$ B subunit, which is involved in forming protein members of the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily. The TGF- $\beta$  superfamily is extensively involved in cell proliferation, differentiation, adhesion, movement, metabolism, communication, and death. Activins and inhibins, which belong to the TGF- $\beta$  superfamily, were first discovered in ovarian follicular fluid. They were initially described as regulators of pituitary follicle-stimulating hormone (FSH) secretion both in vivo and in vitro. Later studies found that INHBB is expressed not only in reproductive organs such as the ovary, uterus, and testis but also in numerous other organs, including the brain, spinal cord, liver, kidneys, and adrenal glands. This wide distribution implies its involvement in the normal physiological functions of various organs; however, the mechanisms underlying these functions have not yet been fully elucidated. Recent studies suggest that INHBB plays a significant, yet complex role in tumorigenesis. It appears to have dual effects, promoting tumor progression in some contexts while inhibiting it in others, although these roles are not yet fully understood. In this paper, we review the different expression patterns, functions, and mechanisms of INHBB in normal and tumor tissues to illustrate the research prospects of INHBB in tumor progression.

## Key points

- INHBB is a gene that encodes the inhibin  $\beta$ B subunit, which forms part of the TGF- $\beta$  superfamily of proteins that regulate various cellular processes.
  - INHBB was initially discovered as a regulator of FSH secretion in reproductive organs, but it was later found to be expressed in many other organs and involved in their normal physiological functions.
  - INHBB has an emerging role in tumorigenesis, but the direction of this role is unclear and may vary depending on the tissue type and context.
  - This paper reviews the different expression patterns, functions, and mechanisms of INHBB in normal and tumor tissues, and suggests future research directions for INHBB in tumor progression.

**Keywords** INHBB · Activin · Inhibin · Cancer · Tumor progression

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## Introduction

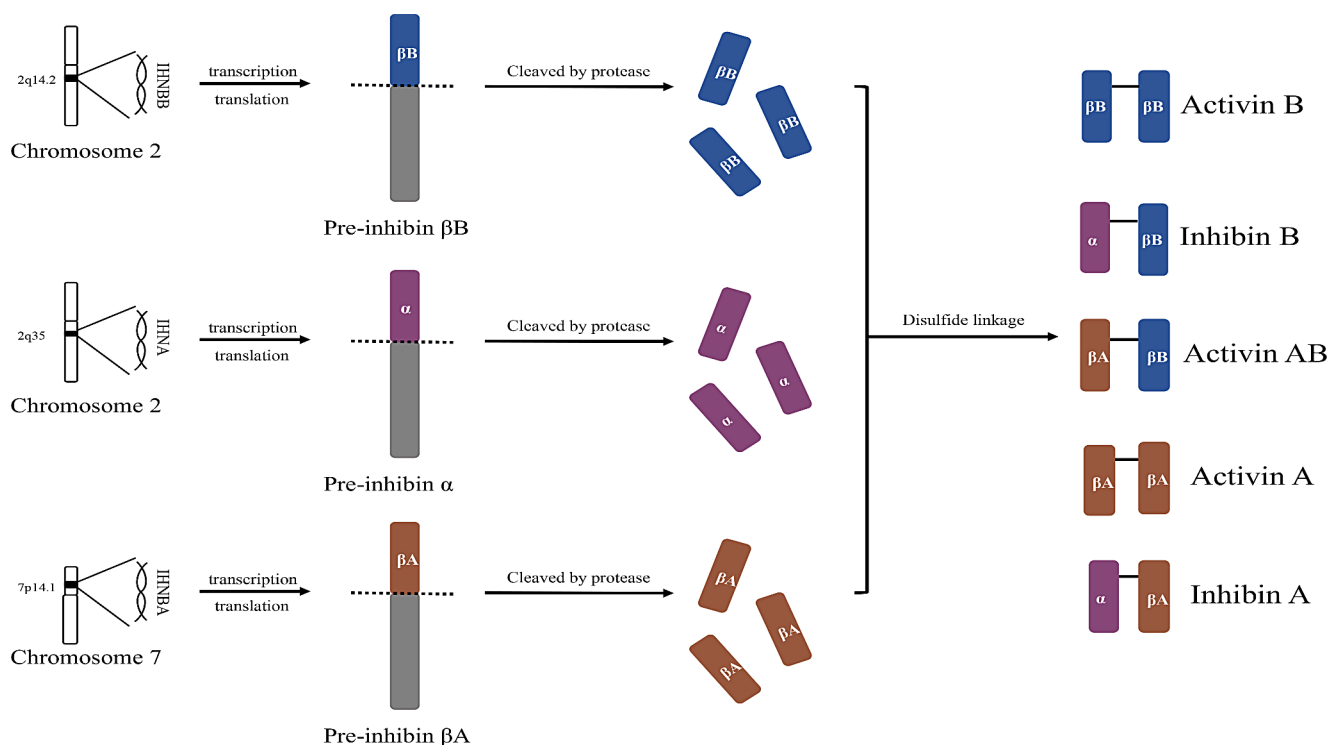
Activins and inhibins are members of the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily that have significant roles in reproduction and development [35, 100]. They were first discovered in ovarian follicular fluid and have been found to function as regulators of pituitary follicle-stimulating hormone (FSH) secretion in vivo and in vitro [57, 101], essential for follicular development. Activins can promote the production of FSH, while inhibins can inhibit it. However, in addition to the regulation of reproductive biology [115], there has been evidence that activins and inhibins exist in a variety of tissues, participating in various biological processes, such as cell proliferation, differentiation, and invasion, to promote the formation and function of many human tissues and organs [5]. More importantly, they appear to play an emerging role in tumor progression [19, 46, 94, 133]. Activins and inhibins are dimeric proteins formed through the disulfide linkage of two inhibin subunits. These inhibin subunits include the inhibin  $\alpha$  subunit and various  $\beta$  subunits, specifically  $\beta$ A,  $\beta$ B,  $\beta$ C, and  $\beta$ E subunits. Inhibins are heterodimers composed of one  $\alpha$  subunit and one  $\beta$  subunit, including inhibin A ( $\alpha/\beta$ A) and inhibin B ( $\alpha/\beta$ B). Activins, on the other hand, are homodimers or heterodimers formed by two  $\beta$  subunits. The activins that have been isolated to date include activin A ( $\beta$ A/ $\beta$ A), activin B ( $\beta$ B/ $\beta$ B), activin AB ( $\beta$ A/ $\beta$ B), activin C ( $\beta$ C/ $\beta$ C), and activin E ( $\beta$ E/ $\beta$ E) [63, 104, 110, 116].

The gene inhibin subunit beta B (INHBB) is located on chromosome 2q14.2. It encodes the inhibin  $\beta$ B subunit, which is involved in the formation of activin B ( $\beta$ B/ $\beta$ B), activin AB ( $\beta$ A/ $\beta$ B), and inhibin B ( $\alpha/\beta$ B) (Fig. 1). On the one hand, INHBB can promote growth and invasion in clear cell renal cell carcinoma [106] and hepatocellular carcinoma [20]. On the other hand, it can inhibit metastasis and promote apoptosis in nasopharyngeal carcinoma [140]. This suggests that it not only has the effect of promoting cancer but also has the effect of inhibiting cancer, similar to TGF- $\beta$  [7, 25].

In the current article, we reviewed the structure, signal pathways, and regulatory mechanisms of INHBB, and compared the different expression patterns of INHBB in normal and tumor tissues to clarify the role of INHBB in tumor progression.

## INHBB signaling mechanism

Like all other members of the TGF- $\beta$  superfamily, the synthesis of activins begins with a larger precursor. The structure of the activin  $\beta$ -subunit precursor includes a signal peptide, a pro-region, and a mature domain, which together determine the synthesis, processing, and function of activins. The signal peptide, located at the N-terminus of the protein sequence, directs the newly synthesized activin precursor to the endoplasmic reticulum and is cleaved at the



**Fig. 1** Synthesis of inhibins and activins

appropriate site to facilitate entry into the cell secretory pathway. Following the signal peptide is the pro-region, a longer sequence crucial for the correct folding of the protein. Its hydrophobic interface promotes a conformation suitable for dimerization assembly. The mature domain is located at the C-terminal of the protein and contains important functional domains, which are key regions for generating biological activity. At the same time, cysteine residues in the mature domain promote protein stability and activity by forming intramolecular and intermolecular disulfide bonds. The mature domain is formed after the precursor protein is cleaved, at which point the dimer is stabilized by disulfide bonds and then released through the cellular secretion pathway to the extracellular space, where it binds to its receptors, triggering downstream signaling pathways [109–111].

Members of the TGF- $\beta$  family signal through pairs of transmembrane serine/threonine protein kinases called type I and type II receptors. The mammalian genome encodes seven type I receptors and five type II receptors, as well as eight small mother against decapentaplegic (SMAD) proteins. In the same manner as other members of the TGF- $\beta$  superfamily, activins function by activating receptor type I and type II serine/threonine kinases. For activins, type II activin receptors (ActRII) are activin A receptor type 2A (ACVR2A) and activin A receptor type 2B (ACVR2B). Type I activin receptor (ActRI), also called activin receptor like kinase (ALK), phosphorylates SMAD proteins in the cytoplasm, which form complex and then translocate to the nucleus, where there, they interact with various other transcription regulators and control the transcription of target genes. Type I receptors of activins are mainly ALK 4 (also known as ACVR1B). Once the activin binds to the type II receptor, the type I receptor is phosphorylated in a juxta membrane domain referred to as the GS box and recruited [9, 13]. In addition, recent studies have also shown that another type I receptor, ALK 7 (also known as ACVR1C), can transmit activin B and activin AB signals, and is insensitive to activin A [9, 99]. Generally, type I receptors ALK 4, ALK 5, and ALK 7 activate the SMAD 2/3 pathway, while type I receptors ALK 1, ALK 2, ALK 3, and ALK 6 activate the SMAD 1/5/8 pathway [123]. Recent studies have also shown that activins can activate the SMAD 1/5/8 pathway through bone morphogenetic protein (BMP) receptor ALK 2 and ALK 3 signaling [83]. Phosphorylated SMAD 2/3 or SMAD 1/5/8 form a complex with SMAD 4 and then enter the nucleus to affect gene expression (Fig. 2). As for inhibins, which are heterodimers composed of an  $\alpha$  subunit and a  $\beta$  subunit, the  $\beta$  subunit of inhibin competitively binds to the ActRII receptor. This binding prevents the recruitment of ActRI and the subsequent activation of downstream signaling cascades, thereby participating in the antagonism of activin activity [55, 94]. Although typical activin signaling

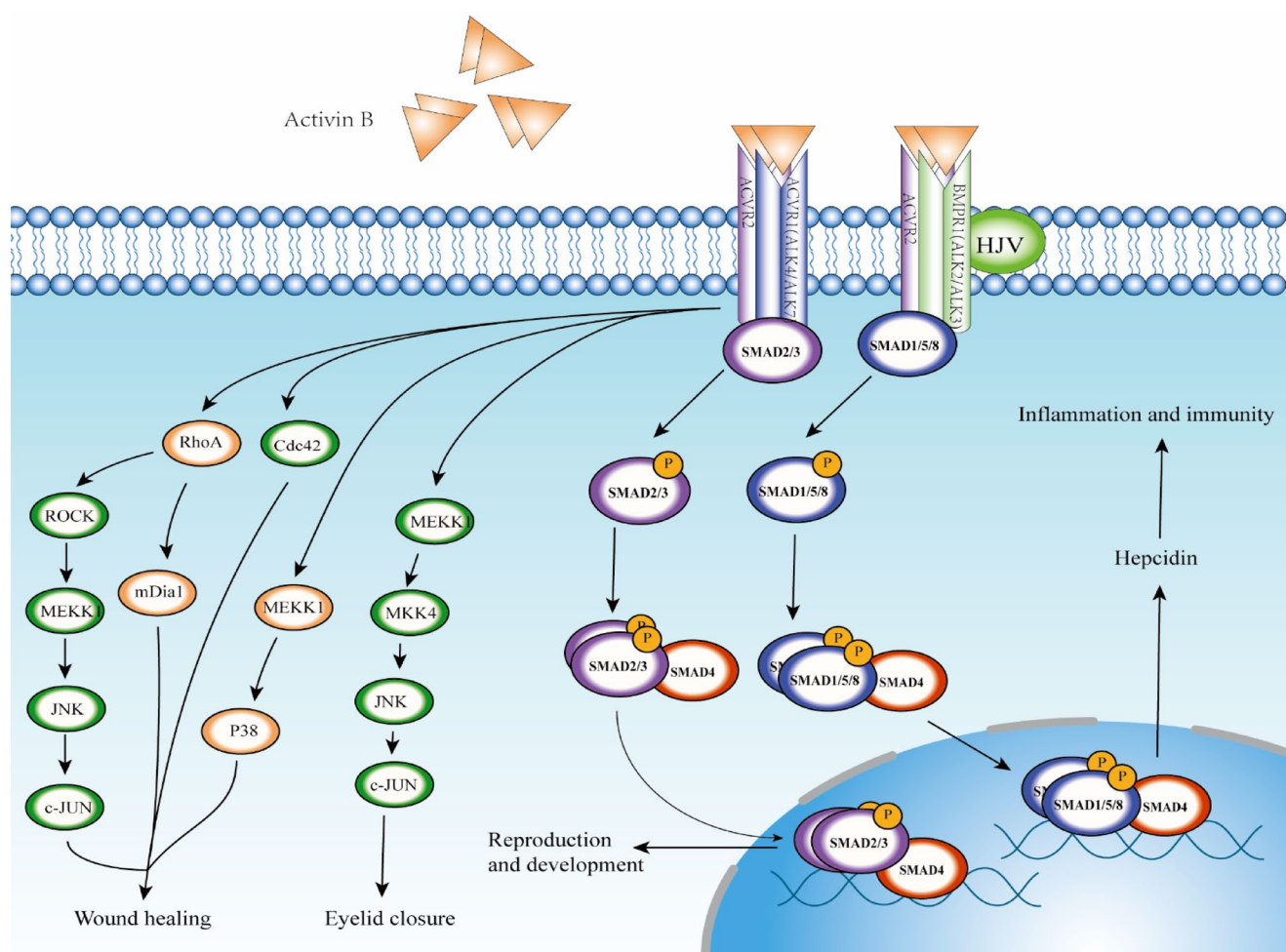
acts through the activation of the SMAD signaling pathway, more and more studies show that there are many other signaling pathways involved in the role of activins and inhibins [61, 72, 81], including RhoA [32, 70, 112, 113, 134, 135], MAPK [6, 50, 118, 121, 138] and JNK [10, 95, 136] signal pathways.

## INHBB in human physiology

In the normal function of INHBB, activins, inhibins, and follistatin could regulate FSH production from the pituitary gland. This triad also affected GnRH secretion from hypothalamic neurons and GnRH receptor expression in pituitary gonadotropes, ultimately regulating LH and FSH secretion. FSH and LH work together to stimulate ovarian follicular development, and ovulation, as well as estrogen and progesterone production [94]. Through the ERK-Elk1 signaling pathway, activin B stimulates hair matrix cell growth, and through the ERK-Cyclin D1 pathway, it accelerates the transition of hair matrix cells from the G0/G1 to the S phase [96]. The RhoA-mDia1 pathway may enhance mesenchymal stromal cell migration induced by activin B by promoting membrane ruffling, microtubule morphology, and focal adhesion signaling dynamics. There is evidence that Cdc42 is related to activin B-induced Golgi complex polarization [113]. Activin B induces RhoA activation by activating the ROCK-MEKK1-JNK-C-JUN pathway. In addition, activin B also induces p38 activity in a MEKK1-dependent pathway through a mechanism independent of RhoA. These pathways jointly lead to actin cytoskeleton recombination and control of epithelial cell migration, thus promoting the physiological and pathological effects of activin on epithelial morphogenesis [134]. Furthermore, activin B can effectively promote the proliferation of keratinocytes and hair follicle cells on wound surfaces, as well as the healing of epithelial wounds [135]. Activin B signal transduction also contributes to the transformation of normal fibroblasts into scar fibroblasts [24]. Together, they participate in the process of activin B-mediated wound healing (Fig. 2).

It is found that INHBB was expressed in both hepatic endothelial cells and Kupffer cells in LPS-treated liver [47]. Under inflammatory conditions, activin B expression in the liver is stimulated. Activin B can induce hepcidin synthesis [31]. Activin B signaling activates SMAD 1/5/8 signal and hepcidin expression through its typical type II receptor, binding to BMP I receptor and co-receptor HJV [18]. Given the important role of hepcidin in iron homeostasis [80], the association of INHBB with hepcidin also suggests its role in inflammation and immunity (Fig. 2).

Furthermore, activin B and its inhibitor follistatin play a role in pancreatic ontogeny. Activin B co-expressed with



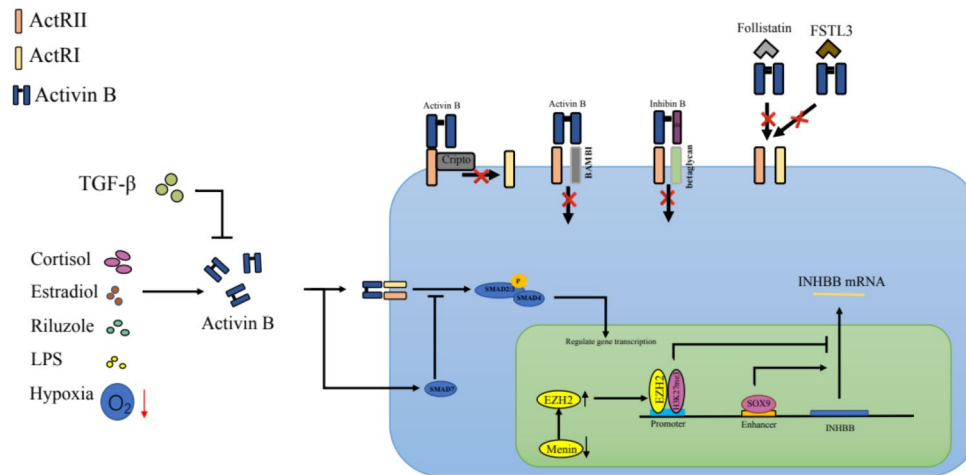
**Fig. 2** Activin B binds to receptors on the cell membrane and affects multiple physiological processes in the cell through both SMAD-dependent and SMAD-independent pathways

glucagon in forming islets, serving as a key regulator of endocrine pancreas formation [64]. Adipocytes express high levels of INHBB and activin B receptors, suggesting a local effect on adipose tissue. By down-regulating adipose triglyceride lipase and hormone-sensitive lipase expression, recombinant activin B decreased lipolysis and increased intracellular triglyceride content [62]. The role of INHBB in glucose metabolism and lipid metabolism underscores its significant impact on regulating human metabolism.

### Regulation of INHBB function

The expression of INHBB is notably widespread, being detected in the uterus, ovaries, prostate, testes, brain, spinal cord, liver, kidneys, and adrenal glands [4, 44, 53, 97, 103]. Given the pleiotropy and extensive expression of INHBB, there are many mechanisms to regulate its bioavailability and participate in the role of INHBB (Fig. 3).

Inhibins were found earlier than activins and can negatively regulate pituitary function, contrary to the action of activins [67]. The inhibin contains a  $\beta$  subunit, which can compete with activins and bind ActRII to block the action of activins, thereby blocking the recruitment of type I receptor [40, 141]. However, the affinity of inhibins for ActRII is about 10 times lower than that of activins. The low affinity of inhibins for ActRII does not support the explanation of its high potency as an activin antagonist [23, 63]. Moreover, there are a large number of cell types in which inhibins can not antagonize the action of activins, indicating that the single competitive binding ActRII model is incomplete [11]. Later studies have also shown that there may be inhibin receptors that selectively bind inhibin components. Betaglycan is a membrane-anchored proteoglycan. It has been demonstrated that it also binds inhibins and can mediate inhibin action. The affinity of inhibins binding to cell membranes co-expressing ActRII and betaglycan was about 30 times higher than that of cell membranes only expressing ActRII [37]. Inhibins compete to bind ActRII more efficiently and



**Fig. 3** Regulation of INHBB function. Activin binds to ActRII and recruits ActRI, which phosphorylates SMAD 2/3. SMAD 2/3 and SMAD 4 assemble into a complex in the nucleus to regulate gene transcription. Cripto binds to activin B and blocks the recruitment of type I receptors. BAMBI competes with type I receptors to bind activin B and block downstream signals. Inhibin B competes to bind ActRII with the help of receptor betaglycan. Follistatin and FSTL3 form a complex

inhibit the action of activins through its binding to ActRII and the co-receptor betaglycan.

Bone morphogenetic protein and activin membrane-bound inhibitor (BAMBI) is a transmembrane glycoprotein. Since BAMBI is highly homologous to the TGF- $\beta$  superfamily type I receptor, it is considered to be a pseudo-receptor and negative regulator of the TGF- $\beta$  signaling pathway [21]. BAMBI negatively regulates TGF- $\beta$  family signaling through a regulatory mechanism of signaling receptor-pseudo-receptor interactions [84].

Cripto is a co-receptor that belongs to the epidermal growth factor/Cripto-1/FRL-1/Cryptic (EGF-CFC) family [36, 49]. It forms a complex with the activin and ActRII that is mutually exclusive with the activin-ActRII-ALK complex, and it inhibits activin signaling [38]. In addition, the antagonistic effect of Cripto on activin B can be reversed by the anti-CFC domain Cripto antibody that blocks Cripto-ALK 4 binding [2].

At the same time, there is also an inhibitor SMAD 7 in the SMAD signaling pathway which acts at the post-receptor level [3, 137]. Activins induce SMAD 7 mRNA expression and SMAD 7 is a potential negative regulator of activin response in the pituitary [12]. This is also considered to be a negative feedback regulation of the activin itself. By preventing SMAD 2 and SMAD 3 from being phosphorylated, it blocks the entire downstream pathway.

Another regulator of activin signaling is follistatin. Follistatin was originally isolated as a component of follicular fluids with the ability to suppress FSH secretion from pituitary cells. It is a monomeric glycosylated polypeptide

with activin B, which prevents activin B from binding to the receptor. TGF- $\beta$  inhibits activin B expression. Cortisol, estradiol, riluzole, and hypoxia promote activin B expression. The deletion of menin caused the recruitment of EZH2, increased the methylation of the INHBB promoter, and inhibited the expression of INHBB. SOX 9 promotes the transcription of INHBB by directly binding to the enhancer of INHBB

that binds and neutralizes activins with high affinity, and the binding is nearly irreversible due to its slow dissociation rate [41]. Meanwhile, the follistatin-related gene (FLRG), also referred to as follistatin-related protein (FLRP) or follistatin-like 3 (FSTL3), is similar in structure and function to follistatin. It is considered to be an important circulating activator-binding protein [98].

Various external stimuli, such as hormonal changes and environmental stressors, have been shown to regulate the activity of INHBB. For example, hypoxia has been reported to upregulate the expression of activin B [107]. The level of extracellular uric acid can affect the sensitivity of prostate cancer cells to activins [93]. For instance, expression of INHBB was up-regulated by cortisol and estradiol in RL-95-2 cells, a type of human endometrial carcinoma cell [105]. There are also reports that expression of INHBB was up-regulated in melanoma cells treated with riluzole, which may be involved in the regulation of SMAD protooncogene function in advanced melanoma [1].

One thing worth noting is that some proteins can affect the expression of INHBB from the level of transcription or epigenetics. H3K27me3, or trimethylation of lysine 27 on histone H3, is an epigenetic mark typically associated with gene repression. This modification is crucial for regulating gene expression by modifying chromatin structure, thereby controlling the accessibility of transcription factors to the DNA [28]. EZH2 (Enhancer of Zeste 2 Polycomb Repressive Complex 2 (PRC2) Subunit) targets INHBB and other genes during the epithelial-mesenchymal transition (EMT) in lung cancer A549 cell lines. Through its role

in methylating histone H3 on lysine 27 (H3K27me3) at the promoter of the *INHBB* gene, *EZH2* facilitates the suppression of *INHBB* expression [54]. What is more, in endocrine pancreatic and testicular tumors, the loss of Menin is directly related to activin B-induced expression, it is related to the Menin protein encoded by tumor suppressor gene *MEN1*. H3K27me3 marks on the *INHBB* locus directly regulate activin B expression in Menin-KO cell lines. Menin binding to the promoter of *INHBB* may promote the recruitment of *EZH2* through the indirect mechanism of AKT phosphorylation [33]. In liver cancer, *Sox9* can promote the transcription of *INHBB* by directly combining with the enhancer of *INHBB* [20].

In this section, we explore various regulatory mechanisms that influence the expression and functionality of *INHBB*. These include transcriptional and epigenetic alterations, interactions with other proteins and receptors, and the effects of external factors such as hypoxia and hormonal fluctuations. Such regulatory processes not only modify the expression of *INHBB* but also adapt its functional effects within specific cellular contexts, thereby highlighting its roles in a range of physiological and pathological conditions.

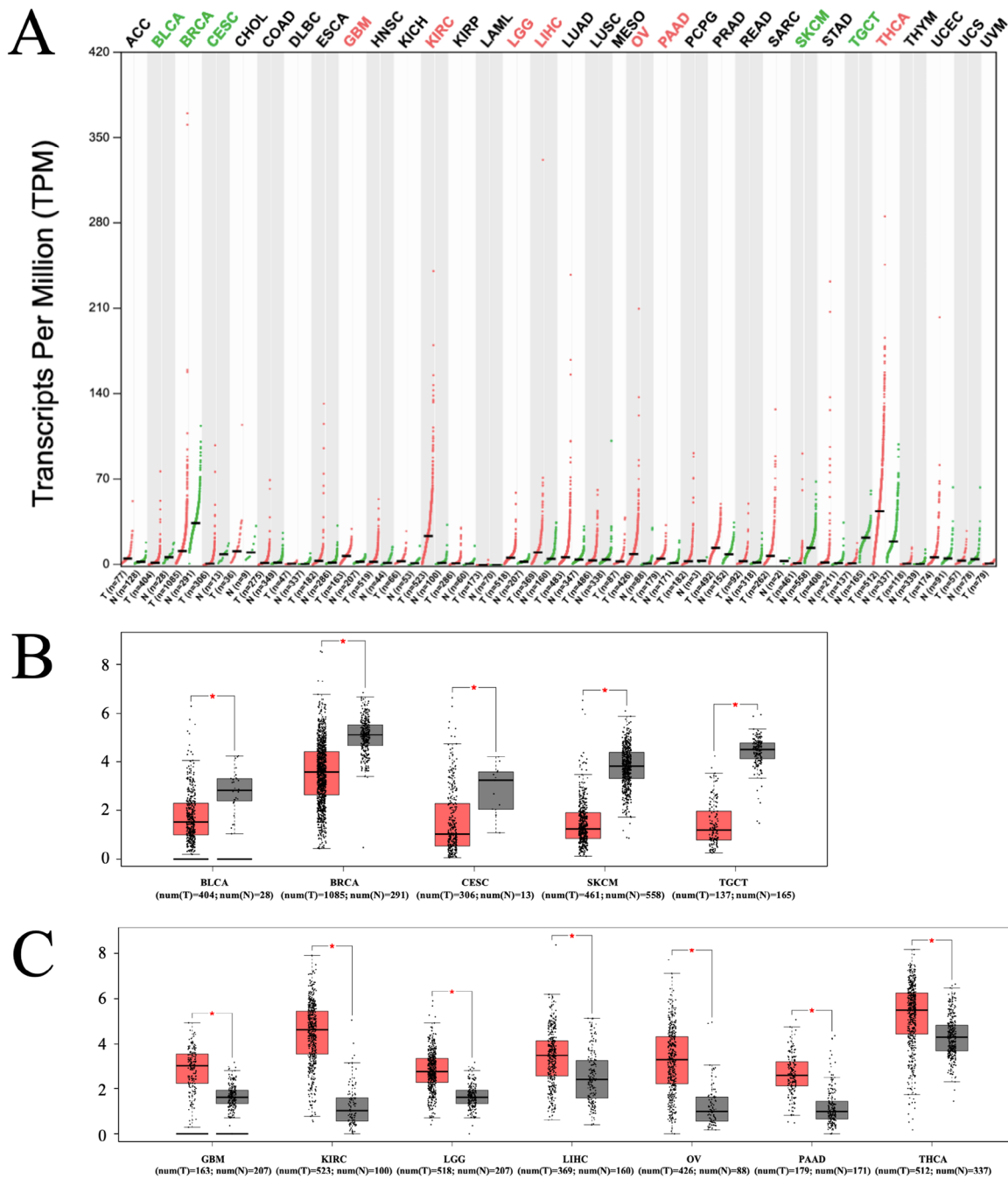
## INHBB in cancer

In cancer, the role of TGF- $\beta$  is complex, changing with the evolution of the tumor over time and space. It can promote apoptosis and inhibit proliferation, acting as an anti-tumor role. As tumors progress, deletions or mutations in TGF- $\beta$  can transform its function, promoting tumor cells to acquire an invasive phenotype [45, 82, 86]. Undoubtedly, it regulates proliferation, differentiation, adhesion, and migration via complex pathways [25]. *INHBB* seems to play a similar role in cancer. On the GEPIA (Gene Expression Profiling Interactive Analysis) website (<http://gepia.cancer-pku.cn/index.html>), we analyzed the expression of *INHBB* across various tumors using data from the TCGA database (Fig. 4A). According to the data collected, mRNA expression of *INHBB* was downregulated in five kinds of tumors (Fig. 4B) and upregulated in seven (Fig. 4C), which also preliminarily confirmed the opposing roles of *INHBB* in different tumors. In the following content, we will discuss the existing research progress of *INHBB* in different tumors. It is important to note that some of the studies mentioned below have measured the expression of either the *INHBB* subunit protein or RNA without distinguishing between inhibin and activin.

## Endometrial cancer

*INHBB* was labeled in normal, hyperplastic, and malignant endometrium [78, 79]. In normal endometrium, *INHBB* mainly locates in the stroma and changes with the menstrual cycle thereby playing an important role in the maturation of the endometrium [76]. The expression of *INHBB* exhibits a distinct cyclical pattern throughout the menstrual cycle. Samples from the endometrium were categorized based on clinical and histological assessments into the proliferative phase (days 1–14), early secretory phase (days 15–22), and late secretory phase (days 23–28). Initially, during the early proliferative phase, *INHBB* levels are low, gradually increasing as the cycle advances towards ovulation. Notably, *INHBB* expression peaks in the late secretory phase. This expression trend underscores the critical role of *INHBB* in regulating the endometrial environment and facilitating conception [76, 91].

Compared to endometrial cancer, hyperplastic tissue showed a higher level of tagging for the presence of *INHBB*, suggesting a significant role in endometrial carcinogenesis and a significant function in endometrial pathophysiology [78]. *INHBB* was highly expressed in endometrial cancer G3 compared with G2 and G1, where G1 represents well-differentiated, G2 moderately differentiated, and G3 poorly differentiated carcinomas as per the World Health Organisation (WHO) histological classification, indicating its effects on the progression of endometrial cancer [79, 117]. Clinically, endometrial carcinoma can be divided into two types according to its pathogenesis and biological behavior. Type I endometrial carcinoma is also called endometrioid adenocarcinoma. It is related to long-term estrogen stimulation. The patients are younger in age, lower in malignancy, and better in prognosis. Type II endometrial carcinoma, also known as non-endometrioid adenocarcinoma (estrogen-independent), is highly malignant. *INHBB* was more likely to be expressed in uterine non-endometrioid cancer compared with endometrial cancer [79]. Also, in patients with uterine non-endometrioid cancer, there is a significant correlation between low expression of *INHBB* and a significantly better cause-specific survival probability, and *INHBB* appeared to be an independent prognostic indicator [73]. The prognostic significance and clinical implications of the *INHBB* in uterine endometrioid adenocarcinomas remain unclear; however, the immunolabelling intensity of the *INHBB* was associated with a slightly worse survival expectation, but not significantly [74]. In summary, *INHBB* has the potential as a tumor biomarker related to the prognosis of endometrial cancer, but histological subtypes must be considered. Clinically, Type II endometrial cancer accounts for 30% of cases, but 75% of deaths, partly because it tends to metastasize. So it is very useful to study the mechanism of



**Fig. 4** Data analyses of INHBB expression in tumor samples and paired normal tissues using GEPIA (<http://gepia.cancer-pku.cn/index.html>). **(A)** The gene expression dot plot across all tumor samples and paired normal tissues; Each dots represent the expression of samples. The red dots represent tumor tissues and the green dots represent paired normal tissues. **(B)** and **(C)** Box plot made on GEPIA.  $|\log_2FC|$  Cutoff=1, p-value Cutoff=0.01. The expression of INHBB was significantly different between normal and tumor tissues. The red box represents tumor tissue, and the gray box represents paired normal tissue. ACC: Adrenocortical carcinoma; BLCA: Bladder Urothelial Carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangiocarcinoma; COAD: Colon adenocarcinoma; DLBC: Lymphoid neoplasm diffuse large B-cell lymphoma; ESCA: Esophageal carcinoma;

GBM: Glioblastoma multiforme; HNSC: Head and Neck squamous cell carcinoma; KICH: Kidney Chromophobe; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute Myeloid Leukemia; LGG: Brain Lower Grade Glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and Paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcoma; SKCM: Skin Cutaneous Melanoma; STAD: Stomach adenocarcinoma; TGCT: Testicular Germ Cell Tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine Corpus Endometrial Carcinoma; UCS: Uterine Carcinosarcoma; UVM: Uveal Melanoma

invasion and metastasis. In HEC-1B and KLE, uterine non-endometrioid cancer cell lines, activin B treatment upregulated integrin  $\beta 3$  expression through the SMAD 2/3-SMAD 4 pathway, leading to an increase of cell migration, invasion, and adhesion to vitreous [120]. This also explains why patients with high expression of INHBB demonstrated poor prognosis. Additionally, activin B treatment significantly decreased E-cadherin expression in KLE and HEC-50 cells. However, knockouts of SMAD 2, SMAD 3, or SMAD 4 did not inhibit this phenomenon. The suppressive effects of activin B on E-cadherin were instead mediated by Snail production induced by MEK-ERK1/2. This signal mechanism independent of the SMAD pathway further confirmed the role of INHBB in endometrial cancer.

### Ovarian cancer

Among ovarian tumors, epithelial tumors are the most common, including serous tumors and mucinous tumors. Specific immunostaining of tumor cells from mucinous adenomas and malignant cystic tumors showed expression of inhibin subunits  $\alpha$ ,  $\beta A$ , and  $\beta B$ . It was also noted that mucinous adenocarcinoma tumor cells were negative for the  $\alpha$  subunits but positive for the  $\beta A$  and  $\beta B$  subunits. Similarly, in the serous tumors such as benign adenomas, borderline malignant cystic tumors, and adenocarcinomas, the  $\alpha$  subunit did not stain, while the  $\beta A$  and  $\beta B$  subunits were seen to stain positively in the serous tumor cells. These results not only indicate differences in activin and inhibin expression across different tissues, but also suggest that the disappearance of  $\alpha$  subunits in mucinous carcinoma indicates an anti-tumor role for inhibin, whereas activin may play a pro-tumor role [125]. Specific immunostaining revealed the presence of the  $\beta B$  subunit in both Leydig and Sertoli tumor cells of ovarian sex cord-stromal tumors, whereas the  $\alpha$  subunit was exclusively found in Leydig cells. mRNA expression of INHBB was confirmed in both granulosa cell and Sertoli-Leydig cell tumors. Serum dimeric inhibin B concentrations were measured in ovarian cancer patients using an enzyme-linked immunosorbent assay (ELISA), which demonstrated elevated levels prior to surgery with a gradual decrease postoperatively. These findings highlight the potential of serum dimeric inhibin B as a tumor marker in this specific patient population [124]. What is more, expression of inhibin  $\alpha$  and  $\beta B$  subunits is positive in malignant germ cell tumors of the ovary and testis [22]. These studies demonstrate that INHBB is widely expressed in ovarian cancer, but the role of activin and inhibin is still not clear due to insufficient research on related dimers. In ovarian cancer patients, Kaplan-Meier analyses demonstrated a gradual decline in the 5-year survival rate with increasing levels of inhibin B [108]. Previous studies have recognized

INHBB as a diagnostic marker for malignant tumors and have identified it as a potential tumor-specific therapeutic target [30].

### Cervical cancer

INHBB is expressed mainly in the basal lamina of normal squamous epithelial cells of the cervix. INHBB subunits were detected in both normal and malignant cervical tissues and cell lines. The expression of INHBB increased significantly in cervical intraepithelial neoplasia (CIN) and cervical cancer compared to normal cervical tissue. Interestingly, the expression of INHBB in CIN2 and CIN3 was significantly higher than in cancer tissues of histological grade 1, suggesting a pivotal role for INHBB in the differentiation of cervical cancer [44]. However, it is worth noting that, unlike in cervical squamous cell carcinoma, the staining intensity of INHBB in adenocarcinoma is significantly lower than that seen in glandular epithelial cells [17]. The role of INHBB in cervical cancer is still unclear, but the synthesis of this subunit in cervical cancer cell lines provides the opportunity to better understand its role in cervical cancer pathogenesis. The levels of INHBB in different stages of cervical cancer do not simply increase or decrease; this suggests that its regulatory functions may vary at different stages through diverse mechanisms.

### Renal clear cell carcinoma

Renal parenchymal carcinoma is an adenocarcinoma that originates from renal tubular epithelial cells, with about 85% being clear cell carcinomas. A mutation in the von Hippel-Lindau tumor suppressor gene (VHL) activates hypoxia-inducible factor (HIF)-mediated gene transcription in clear cell renal cell carcinomas (RCCs). Several VHL/HIF targets, such as glycolysis, angiogenesis, cell growth, and tumor cell chemotaxis, have been implicated in the translational phenotype of RCC. VHL can inhibit key features of cell transformation by downregulating HIF-dependent activin B expression. In VHL-deficient RCC cells, activin B expression is suppressed by restoration of VHL and upregulated by hypoxia. Activin B expression was increased in RCC tumor samples compared to normal kidneys. VHL increased cell adhesion to the extracellular matrix, promoted cell flattening, and decreased invasiveness. Conversely, inhibition of activin B action through RNA interference reversed effects of VHL. Thus, activin B plays an indispensable role in VHL/ HIF-induced renal cell carcinoma transformation [107]. Activin B can mediate the onset of actin stress fiber breakdown, mesenchymal cell morphology changes, and invasion, while activation of RhoA can counteract these effects and vice versa. This



indicates that the two pathways are inversely related. Furthermore, the action of activin B requires the synergistic action of Rac1. Activation of Rac1 triggers the loss of actin stress fibers and promotes the invasion of activin B knock-out cells. These studies underscore the importance of activin B signaling in promoting an aggressive phenotype in clear cell renal cell carcinoma [106].

### Breast cancer

A study of involving 16,175 women of European ancestry revealed that the locus INHBB strongly correlated with breast cancer, estrogen regulation, and breast development [29], indicating that INHBB is an important genetic factor in normal breast development. In later studies, INHBB was reported to be an established ER-negative breast cancer locus associated with breast cancer risk [14] and single nucleotide polymorphisms in INHBB may contribute to the association [58]. Moreover, the results of immunohistochemistry showed that in normal breast tissue, fibrocystic disease, and benign neoplasms, INHBB was weakly positive whereas its expression was negative in carcinoma cells [27]. Furthermore, metastatic lymph nodes exhibited lower INHBB than primary tumors [77], confirming that INHBB may have anti-tumor effects in breast cancer. The growth of breast cancer cells was inhibited by activin B when expressed in the cell culture [2]. The inhibitory effect is mediated by ligands ALK 4 [2] and ALK 7 [71, 132]. At the same time, some molecules regulating the INHBB mechanism have also been found. Activin B induces growth inhibition in breast cancer cells. Cripto, which is a glycosylphosphatidylinositol-linked (GPI-linked) membrane protein, antagonizes the effects of activin B by directly interacting with it [2]. In addition, estrogen has been reported to inhibit the production of activin B by MCF7 breast cancer cells. These studies suggest the importance of activin-estrogen interactions in breast cell growth and carcinogenesis [15]. In conclusion, studies to date have demonstrated that the role of INHBB in tumor suppressor in breast cancer, and the restoration and promotion of its effect may be a new direction of breast cancer treatment.

### Nasopharyngeal carcinoma

INHBB expression is generally low in nasopharyngeal carcinoma (NPC) tissues. Studies have shown that INHBB expression is associated with a better prognosis. Its expression was negatively correlated with lymph node metastasis, clinical progression, tumor size, and invasion. In patients with NPC, the overall survival rate was significantly lower in the INHBB-negative group than in the INHBB-positive group [140]. To investigate the molecular mechanism of

INHBB in NPC, Zou et al. mimicked the high metastatic characteristics of NPC and induced high metastatic cells. Anoikis is a specific form of programmed cell death originating from the extracellular matrix (ECM), and resistance to anoikis is a primary condition for tumor invasion and metastasis. Anoikis resistance enables tumor cells to re-adhere within heterogeneous tissues and organs. The ability of nasopharyngeal carcinoma (NPC) cells to resist anoikis also signifies their highly metastatic characteristics. Zou et al. induced anoikis-resistant cells under non-adherent conditions in NPC cell lines, thereby establishing a model of NPC cell anoikis resistance. In these anoikis-resistant cells, INHBB was either overexpressed or knocked down. In the INHBB-overexpressing cells, there was an increase in apoptotic cells, a decrease in S phase cells, and a downregulation of vimentin, matrix metalloproteinase-9, and vascular endothelial growth factor A, accompanied by an upregulation of E-cadherin expression. Conversely, knocking down INHBB in these cells produced opposite effects. Furthermore, INHBB inhibited anoikis resistance and migration of NPC cells through the TGF- $\beta$  signaling pathway and reduced p53 expression. These phenomena also suggest the possibility of INHBB as a biomarker of nasopharyngeal carcinoma metastasis and prognosis [140].

### Prostatic cancer

In vitro experiments have demonstrated that prostate cancer cell lines were inhibited by activin B [68]. As prostate tumor grade increases, activin B expression increases and activin C expression decreases [88]. Increased activin B and decreased activin C expression is associated with increasing prostate tumor grade. Notably, there is an increase in activin B expression following androgen deprivation therapy (ADT), the first-line treatment for recurrent and metastatic prostate cancer. In a mouse model of ADT-induced sarcopenia, Pan et al. detected an increase in activin B expression, suggesting a potential association between activin B levels and the therapeutic effects of ADT [85]. It has been shown that activin B expression is reduced in high-grade prostate cancer [93]. In prostate cancer, through a comprehensive aCGH approach, after excluding germline copy number polymorphisms, Lee et al. identified 35 regions of recurrent alterations, including INHBB [114]. Epigenetic dysregulation on chromosome 2q14.2 distinguishes normal tissues from prostate cancer and provides a new regional panel of DNA methylation cancer biomarkers, including localized DNA hypermethylation INHBB [26]. The association of INHBB with ADT therapy and its genetic profile in prostate cancer suggests that INHBB could be a potential marker and therapeutic target for prostate cancer.

## Colorectal cancer

In colorectal cancer, miR-34a and miR-34b/c are frequently silenced. INHBB, one of the targets of miR-34, was upregulated in primary colon cancer and had an association with lymph node metastasis [43, 122]. Furthermore, overexpression of INHBB was confirmed to be related to poor overall survival (OS) and recurrence-free survival (RFS) [43, 87]. A 9-gene signature, including INHBB, is helpful in predicting postoperative recurrence of stage II/III colorectal cancer [119]. Additionally, INHBB expression significantly promoted macrophage infiltration while inhibiting the infiltration of memory T cells, mast cells, and dendritic cells [131]. Thus INHBB may play a cancer-promoting role in colorectal cancer and may become a potential prognostic biomarker and a new therapeutic target for colorectal cancer.

The TGF- $\beta$  pathway, a well-recognized signaling pathway, is associated with cancer progression, impacting cell cycle regulation, proliferation, differentiation, and metastasis formation in colorectal cancer [39]. This underscores the vast potential of INHBB, which signals through the TGF- $\beta$  pathway, in colorectal cancer research. Furthermore, INHBB has been identified as a novel biomarker for colorectal cancer metastasis, which is highly deregulated by methylation and closely linked to metastasis. As an emerging DNA methylation biomarker for the prognosis of early-stage colorectal cancer, INHBB requires further clinical trials to refine detection methods and guide the treatment and diagnosis of cancer patients [39].

## Hepatocellular carcinoma

In normal rat liver, INHBB staining was weak and localized to parenchymal cells (PC). However, in fibrotic rat liver, staining of INHBB was observed in stellate cells (SC). It is now known that activation of hepatic stellate cells and the hepatic fibrosis of surrounding tissues contribute to the progression of hepatocellular carcinoma (HCC). This suggests that differential expression of INHBB in SC is likely associated with fibrosis of the liver as well as HCC progression. It has also been reported that the Sox9/INHBB axis is a positive regulator of liver fibrosis, and Sox9 induces the expression of INHBB and promotes the production of activin B by directly binding to the enhancer of INHBB. Further, it could promote the activation of hepatic stellate cells through activin B/SMAD signaling [20]. This revealed that in HCC, INHBB is closely associated with liver fibrosis as well as the progression of HCC.

## Thyroid cancer

In thyroid cancer research, the expression and function of the INHBB gene have gradually revealed its potential role in disease progression. The most common type of thyroid cancer is papillary thyroid carcinoma (PTC), which is often accompanied by mutations in the BRAF gene. In mouse models of PTC with BRAF mutations, INHBB expression is elevated more than 15-fold compared to normal thyroid cells, highlighting its significant role. This substantial increase not only highlights its role in the proliferation of thyroid cancer cells but also suggests that INHBB could promote the phosphorylation of SMAD2/3 by activating its receptor ALK4, thereby influencing the cellular behavior in thyroid cancer [60]. Furthermore, the co-inhibition of the SMAD and MAPK signaling pathways has been found to enhance the uptake of radioactive iodine (124I) in BRAF-mutated thyroid cancers [60], further emphasizing the potential of INHBB as a target in thyroid cancer treatment.

Analysis of human PTC samples has shown that INHBB expression is inversely correlated with the thyroid differentiation score (TDS) [60], implying that INHBB may play a crucial role in the dedifferentiation process of thyroid cancer. Additionally, INHBB expression is significantly higher in follicular adenomas as well as papillary and follicular carcinomas compared to multinodular goiter and normal thyroid tissue [65], supporting its potential impact on thyroid cancer proliferation and tumor processes.

## Oral squamous cell carcinoma

In oral squamous cell carcinoma, activin B is significantly associated with regional lymph node metastasis. Activin B regulates EMT-related proteins, including decreased levels of E-cadherin and Zo-1 and increased levels of Snail, to enable oral squamous cell carcinoma cells to acquire characteristics that are easy to invade and metastasize [52]. This indicates a direct mechanism by which INHBB contributes to cancer dissemination.

## Diverse roles of INHBB in cancer: mechanisms and implications

We summarize the roles of INHBB in different tumors in Table 1, but INHBB plays a role not only in these tumors. For example, the INHBB stained positive in normal adrenal medullary cells and benign adrenal pheochromocytomas, while malignant tumors were almost negative. This suggests that the deletion of INHBB expression in pheochromocytomas may serve as a marker of malignant potential [92]. In islet beta cells, activin B promotes dedifferentiation, revealing unexpected effects of activin B in the loss of beta

**Table 1** Roles of INHBB in different cancers

Tumors/tumor cells	INHBB expression status	Role in cancer (promoting or inhibiting cancer)	Mechanism	Effects on cancer	References
Endometrial cancer	Highly expressed in endometrial cancer G3 compared with G2 and G1; highly expressed in uterine non-endometrioid cancer compared with endometrial cancer.	Promoting	Activin B-SMAD2/3-SMAD4-increase of integrin $\beta$ 3; Activin B-MEK-ERK1/2-Snail- inhibition of E-cadherin	Increase of cell migration, invasion, and adhesion to vitreous.	[79, 117, 120]
Ovarian cancer	Positive in the mucinous adenoma and the cystic tumor with borderline malignancy.	Unclear			[125]
Cervical cancer	Cervical squamous cell carcinoma Cervical adenocarcinoma	Positive at the basal lamina of normal squamous epithelial cells; significantly higher expression in cervical intraepithelial neoplasia (CIN) and cervical cancer than that in normal cervical tissue. Lower expression of INHBB in adenocarcinoma than that of glandular epithelial cells.	Unclear		[17, 44]
Renal clear cell carcinoma	Increased expression of activin B compared to that in the normal kidney.	Promoting	Mutated VHL-activin B- reduced rhoa signaling and promote Rac1 activity	Aggressive phenotype and tumor growth	[106, 107]
Breast cancer	In normal breast tissue, fibrocystic disease, and benign neoplasms, $\beta$ B subunits were weakly positive while the expression of $\beta$ B was negative in carcinoma cells.	Inhibiting	Cripto- directly interacting with Activin B- induced growth suppression; Estrogen- reduce the amount of activin B	Growth suppression	[2, 15, 27]
Nasopharyngeal carcinoma	Downregulated; INHBB expression was negatively correlated with lymph node metastasis, clinical progression, tumor size, and invasion	Inhibiting	INHBB decrease-activate TGF- $\beta$ - SMAD2/3-SMAD4-tumor growth; INHBB decrease-activate TGF- $\beta$ -SNAIL 1/2-EMT	Suppress tumor growth, anoikis resistance, and migration	[140]
Prostatic cancer	Activin B expression was reduced in high-grade prostate cancer.	Inhibiting	Elevated extracellular urate-growth promoting in vitro and antagonized the growth inhibitory effects of activins.	Suppress tumor growth	[88, 93]
Colorectal cancer	Upregulated in primary colon cancer and associated with lymph node metastasis; overexpression of INHBB was confirmed to be associated with poor overall survival (OS) and recurrence-free survival (RFS).	Unclear			[43, 87, 122]
Hepatocellular carcinoma	Upregulated	Promoting	SOX9-INHBB-activin B- SMAD2/3-SMAD4- the activation of hepatic stellate cells and hepatic fibrosis in surrounding tissues	Hepatic fibrosis and progression of hepatocellular carcinoma	[20]
Thyroid cancer	Upregulated	Unclear			[60, 65]

**Table 1** (continued)

Tumors/tumor cells	INHBB expression status	Role in cancer (promoting or inhibiting cancer)	Mechanism	Effects on cancer	References
Oral squamous cell carcinoma	Activin B-positive oral squamous cell carcinoma is significantly associated with regional lymph node metastasis.	Promoting	Activin B- decreased levels of E-cadherin and Zo-1 and increased levels of Snail-EMT	Enable oral squamous cell carcinoma cells to acquire characteristics that are easy to invade and metastasize.	[52]

cell maturation, islet plasticity, and the progression of insulinoma through its involvement in  $\beta$ -cell dedifferentiation [90]. Yang et al. reported that INHBB was upregulated in GBM (glioblastoma) and predicted poor survival. INHBB was a potential upstream molecule of the EGFR/ERK/AKT signaling pathway in GBM, and it promoted the growth, migration and stemness of GBM cells [126].

Considering that INHBB is associated with tumor stage and prognosis in a variety of tumors, INHBB has the potential to become a tumor biomarker. In addition, it is not difficult to find that the research on INHBB in tumors mainly focuses on proliferation, apoptosis, invasion, and metastasis, but some studies also suggest the possible role of INHBB in immunity [130], cell stem [126], and cachexia [139].

Due to extensive involvement of INHBB in the development, maturation, and normal physiological functions of the reproductive system, and its association with various hormonal pathways that play critical roles in regulating endocrine balance, the influence of INHBB on reproductive system tumors is governed by a complex regulatory network. While  $\beta$ -subunits are expressed, the expression of  $\alpha$ -subunits directly means the opposite effect, and endocrine factors are also involved, which led to the possibility that circulating activin and inhibin were once considered to be tumor markers of the reproductive system [16, 42, 69, 75, 108]. In addition, estrogen can cause a decrease in activin B in breast cancer cells [15]. Androgen deprivation therapy in prostate cancer leads to an increase of activin B [85]. So it may be a promising research direction to link the role of INHBB in the reproductive system with the hormone disorders often seen in reproductive system diseases. This indicates that in organs significantly influenced by hormonal fluctuations, such as the reproductive system, variations in hormonal levels can critically modulate functions of INHBB. Specifically, hormonal changes may alter the expression or activation of INHBB, thereby affecting its role in processes like tumor progression or normal reproductive activities.

Understanding these interactions is crucial for elucidating diverse functions of INHBB in hormone-responsive tissues.

In breast cancer cells, activin B suppressed the growth of breast cancer cells. The inhibitory effect is related to the normal expression and function of the receptors ALK 4 and ALK 7 [2]. Cripto is involved, which indicates that different expression patterns of receptors and co-receptors will also affect the role of INHBB. Currently, there are limited studies on INHBB and its receptors in tumors. We conducted a search in The Human Protein Atlas (HPA) (<https://www.proteinatlas.org/>) for the type II receptors ACVR2A and ACVR2B, as well as the type I receptor ALK4 (also known as ACVR1B) of INHBB. The HPA is a comprehensive human protein database that provides information on the expression of these receptors in various cancers. For ACVR2A, most cancer tissues showed moderate to strong cytoplasmic and membranous immunoreactivity, while several cases of gliomas were weakly stained or negative. For ACVR2B, the majority of cancer tissues showed weak to moderate cytoplasmic staining, with additional membranous staining in a few cases. Lymphomas, gliomas, and skin cancers were negative. For ALK4, hepatocellular carcinoma, colorectal cancer and stomach cancer showed moderate to strong positivity. Thyroid cancer, pancreatic cancer, breast cancer, lung cancer, urothelial cancer and ovarian cancer showed weak positivity. The remaining cancer tissues were generally negative. This suggests that the distribution of INHBB-associated receptors varies among different tumor types, which may offer new insights into mechanisms by which INHBB plays different roles in different tumors.

INHBB, as a member of the TGF- $\beta$  family, has homology with family members, shares receptors, and regulates each other. In nasopharyngeal carcinoma, INHBB reduction is through the activation of TGF- $\beta$  to mediate the anoikis resistance characteristics of nasopharyngeal carcinoma cells [140]. In non-small cell lung carcinomas, TGF- $\beta$  can inhibit the expression of INHBB [54]. That is to say, INHBB has

different effects, which may also be regulated by homologous ligands.

The regulation of the INHBB function is summarized in Fig. 3. In tumors, the expression and role of different regulators are different. External stimuli such as TGF- $\beta$  and LPS affect the expression of INHBB. Internal factors such as Sox9 and EZH2 regulate the expression of INHBB. Inhibitors such as follistatin and inhibin hinder the binding of activin and receptor, and co-receptors hinder the transmission of activin signals. These factors may constitute the functional differences of INHBB in different types of tumors.

### INHBB and immune modulation in cancer

As a critical member of the TGF- $\beta$  family, TGF- $\beta$  plays a crucial role in maintaining immune homeostasis and tolerance, significantly impacting both innate and adaptive immunity. It directly promotes the proliferation of regulatory T cells (Tregs) and inhibits the activity of effector T cells, dendritic cells, and natural killer (NK) cells, thereby establishing a complex network of immune suppression [7]. Within the context of cancer, TGF- $\beta$  helps to create an immunosuppressive tumor microenvironment, facilitating tumor immune evasion and affecting the efficacy of cancer immunotherapies. The dual role of TGF- $\beta$  as a tumor suppressor in early-stage cancer and as a promoter of tumor progression and metastasis in advanced stages highlights its complex nature.

Overall, the signaling transduction of TGF- $\beta$  family members is overlapping. Similar to INHBB signaling, TGF- $\beta$  signaling initiates a cascade of SMAD signaling upon binding to its receptors. TGFBR2 first phosphorylates and activates TGFBR1, which then phosphorylates SMAD2 and SMAD3. These receptor-phosphorylated SMADs subsequently form heterotrimeric complexes with SMAD4 and enter the nucleus. Within the nucleus, the activated SMAD complexes interact with other transcription factors to regulate the expression of hundreds of genes.

In the immune system, TGF- $\beta$ -activated SMAD signaling can promote the expression of FOXP3 in immature CD4+T cells, driving their differentiation towards a regulatory T cell phenotype, inducing a T helper 17 (TH17) phenotype, regulating immunoglobulin class switching in B cells, and suppressing several cytotoxic genes in CD8+T cells [7]. These actions highlight the key role of TGF- $\beta$  in modulating the immune system, particularly through regulating the differentiation and function of immune cells with significant involvement of SMADs, suggesting a similar regulatory potential for INHBB through these pathways. Although current studies have not definitively demonstrated regulatory effects of INHBB on the immune system, some

research still provides insights. For instance, a bioinformatics analysis in gastric cancer indicated that INHBB regulates immune cell infiltration, particularly macrophage infiltration, and that patients with high INHBB expression and high macrophage infiltration have poorer prognoses. Moreover, a positive correlation between INHBB and TGF- $\beta$ 1 expression suggests that INHBB may facilitate immune cell infiltration, thereby promoting the progression of gastric cancer [130]. In colorectal cancer, increased expression of INHBB is associated with trends of resistance to immunotherapy [127], poorer patient survival rates, and increased lymph node metastasis [43]. Furthermore, INHBB is significantly linked to the infiltration of immune cells such as macrophages, and inhibits the infiltration of memory T cells, mast cells, and dendritic cells [131]. These findings imply that INHBB could play a role analogous to TGF- $\beta$  in mediating cancer-related immunosuppression, a hypothesis that requires further validation through more comprehensive studies.

### Discussion and conclusion

After analyzing the role of INHBB in various types of cancer, it has been observed that INHBB acts as a tumor suppressor gene in breast cancer, nasopharyngeal carcinoma, and prostate cancer. In these cancers, it primarily functions by inhibiting cell proliferation and promoting apoptosis. Conversely, in cancers such as endometrial cancer, renal clear cell carcinoma, hepatocellular carcinoma, and oral squamous cell carcinoma, INHBB appears to enhance the malignant potential of tumor cells, mainly by promoting cell invasion, metastasis, and dedifferentiation [56, 89, 90, 121]. However, whether INHBB promotes or inhibits tumor growth depends not only on the type of tumor but also on its subtypes and various stages of progression [22, 34, 125].

Considering that INHBB is the key subunit in the formation of inhibin B ( $\alpha/\beta$ B) and activin B ( $\beta$ B/ $\beta$ B), the various dimeric forms of INHBB may play distinct roles within the organism [128, 129]. Just as INHBB in follicular development, the expression of activin and inhibin changes with time [76], reaching the balance of development. In addition, the single nucleotide polymorphism and epigenetic regulation of INHBB make people suspect that the variation of INHBB in the process of tumor progression leads to a change in its function [48, 66, 114]. Finally, INHBB acts as a member of the TGF- $\beta$  family, which has a high degree of homology with family members [128, 129], and the corresponding receptor and effector proteins also cross react [25]. This makes the pathway of INHBB not specific, and the change of receptor may also lead to the opposite effect in the tumor. Moreover, the activation of INHBB is affected

by many components, including the same family members, antagonists, hormones, inflammatory stimulants, and so on. The changes in these regulatory factors may change the expression of INHBB, resulting in a different expression of INHBB and achieving the opposite effect. In normal development and cancer, INHBB has a complex mechanism of action, in addition to the SMAD signaling pathway, there are many non-SMAD pathways [8, 51, 59, 102], but so far no research can clarify how different mechanisms are selected. The aforementioned mechanisms provide a preliminary explanation for why INHBB may exert completely opposing effects in tumors, yet the details therein necessitate further investigation.

The role of INHBB in tumors remains incompletely understood, yet its expression during tumor progression exhibits certain regularity, thus suggesting the potential for INHBB to serve as a novel tumor biomarker. INHBB primarily functions through the common pathways of type I and type II receptors, offering avenues for intervening in tumor progression by targeting INHBB [2]. However, the variability in signaling pathways of INHBB complicates efforts to target INHBB for intervention in tumor progression.

INHBB assumes an emerging role in tumors, potentially exhibiting both pro- and anti-carcinogenic effects that may vary temporally and spatially. Despite the increasing recognition of its significance across various tumors, further research is warranted to elucidate the underlying mechanisms involved. Investigating the mechanisms underlying actions of INHBB in tumors can aid in unraveling the intricate network regulating tumor progression.

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## Declarations

**Competing Interests** The authors declare that they have no competing interests.

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