Korean J Physiol Pharmacol 2025;29(2):139-155
https://doi.org/10.4196/kjpp.24.309

KJPP

Review Article

Roles of PDGF/PDGFR signaling in various organs

Sung-Cherl Jung[1], Dawon Kang[2,*], and Eun-A Ko[1,*]

[1]Department of Physiology, College of Medicine, Jeju National University, Jeju 63243, [2]Department of Physiology, College of Medicine and Institute of Medical Sciences, Gyeongsang National University, Jinju 52727, Korea

ARTICLE INFO

Received September 20, 2024
Revised October 3, 2024
Accepted October 7, 2024
Published online October 31, 2024

***Correspondence**
Eun-A Ko
E-mail: koeuna@jejunu.ac.kr
Dawon Kang
E-mail: dawon@gnu.ac.kr

Key Words
Cancer
Fibrosis
Growth factor
Platelet-derived growth factor

ABSTRACT Platelet-derived growth factors (PDGFs) ligands and their corresponding receptors, PDGF receptor (PDGFR)α and PDGFRβ, play a crucial role in controlling diverse biological functions, including cell growth, viability and migration. These growth factors bind to PDGFRs, which are receptor tyrosine kinases present on the surface of target cells. The interaction between PDGFs and PDGFRs induces receptor dimerization and subsequent activation through auto-phosphorylation, which in turn triggers a cascade of intracellular signaling pathways. PDGF/PDGFR signaling is essential for maintaining normal physiological functions, including tissue regeneration and growth. However, dysregulation of this signaling pathway leads to pathological conditions, including fibrosis, atherosclerosis, and cancer development in various organs. The pathological impact of PDGF/PDGFR signaling primarily stems from its capacity to promote excessive cell proliferation, enhanced migration, and increased extracellular matrix deposition, resulting in tissue overgrowth, scarring, and abnormal vessel formation. These processes are integral to the pathogenesis of fibrotic, neoplastic, and vascular disorders. Therefore, understanding these pathways is crucial for developing targeted treatments designed to inhibit PDGF/PDGFR signaling in these diseases. This review delves into the dual role of PDGF/PDGFR signaling in both physiological and pathophysiological contexts across different organs and provides insights into current pharmacological therapies designed to target the PDGF signaling pathway.

INTRODUCTION

Platelet-derived growth factors (PDGFs) are key signaling molecules that interact with specific cell to modulate various cellular responses. Upon binding to their receptors (PDGFRs), PDGFs initiate dimerization and tyrosine phosphorylation, which activates downstream signaling pathways. The PDGF signaling network comprises four ligands—PDGF-A, PDGF-B, PDGF-C, and PDGF-D, that interact with two receptors, PDGFRα and PDGFRβ [1-6]. PDGFRα exhibits broader ligand specificity, binding to PDGF-A, PDGF-B, PDGF-C homodimers, and PDGF-AB heterodimers, whereas PDGFRβ specifically binds to PDGF-B and PDGF-D homodimers. Under both physiological and pathological conditions, the critical functions of PDGFRs have been studied in various cell types, including neuronal cells, corneal epithelial cells, dermal fibroblasts, endothelial cells, smooth muscle cells, platelets, and pericytes [7-13]. PDGFRs are crucial for wound healing, tissue repair, and embryonic development because they stimulate the proliferation and migration of fibroblasts or pericytes, which are essential for tissue regeneration and the maintenance of homeostasis after injury [14-19].

Dysregulation of the PDGF/PDGFR signaling pathway is pivotal in tumor angiogenesis, as it drives blood vessel formation, upregulates vascular endothelial growth factor (VEGF) expression, and promotes tumor cell proliferation, ultimately facilitating tumor growth and metastasis [20-22]. Consequently, aberrant

Author contributions: S.C.J., D.K., and E.A.K. conceived the idea and wrote manuscript. All authors read and approved the final manuscript.

PDGFR activity is linked to various pathological conditions, including fibrotic diseases, atherosclerosis, and cancer [11,23-25]. In fibrotic diseases, which are characterized by excessive extracellular matrix (ECM) deposition following injury, the PDGF/PDGFR pathway is essential for transforming fibroblasts into myofibroblasts, thus promoting cell proliferation and migration. Consequently, understanding the PDGF/PDGFR pathway has become a crucial therapeutic approach for the treatment of cancer and fibrosis [26-29]. This review discusses the distinctive features of PDGF signaling that contribute to the pathogenesis in various organs.

This review provides a comprehensive understanding of the pathophysiological role of PDGF/PDGFR signaling in various diseases by integrating findings across organ systems. Given the widespread impact of PDGFR expression and function on all organs, we emphasize emerging therapeutic approaches and their potential systemic effects. We expand on our previous research on ion channel expression in PDGFRα-positive Leydig cells, extending the analysis transcriptome to include significant K^+ ion channel expression in PDGFRα cells within the gastrointestinal (GI) tract. Notably, we observed PDGFRα cell expression across various organs. This review will offer insights into systemic PDGF/PDGFR signaling impacts across multiple organ systems, its therapeutic implications, and the significant ion channel expression particularly in PDGFRα cells.

MAIN BODY

Brain

Extensive studies have deepened our understanding of the intricate relationship between PDGFs expression and neurodegenerative diseases. Both PDGFRα and PDGFRβ receptors, expressed by various neuronal cell types, are crucial for brain development and function [30-32]. PDGFs are crucial for the development and specialization of oligodendrocyte progenitor cells, which are essential for myelination in the central nervous system [33-37]. PDGFs are vital for maintaining the integrity of the blood-brain barrier (BBB) and supporting neurovascular unit stability. Studies have shown that mice with disrupted meningeal PDGF-C signaling exhibit severe vascular abnormalities and impaired brain development [38,39].

Ischemic stroke prompts the formation of new blood vessels in damaged tissues to support repair and recovery. Brain pericytes, which interact closely with endothelial cells, regulate BBB formation, angiogenesis, and vascular functions [40-44]. During ischemic stroke, pericytes are rapidly lost in the infarct core and detach from the endothelial cells in the adjacent region, leading to vascular destabilization and secondary injury [45,46]. Following ischemic stroke, PDGFRβ expression in pericytes is upregulated, playing a vital role in regulating their survival, migration, and interactions with endothelial cells in the brain. PDGF-B, produced by endothelial cells involved in blood vessel formation, activates PDGFRβ signaling to recruit pericytes and ensure the stability of newly formed blood vessels [32,47-49]. Additionally, PDGF-D, another ligand of PDGFRβ, supports pericyte function and promotes angiogenesis, thereby enhancing neurovascular integrity, promoting neuronal survival, facilitating neovascularization, and improving neurological recovery post-stroke [50,51]. Pericyte activation has been found to be associated with neurorestorative effects and vascular stabilization observed in the striatum of Parkinson's disease lesions [52,53]. PDGF-BB, which activates pericytes, has emerged as a potential therapeutic option for Parkinson's disease, a debilitating neurodegenerative disorder characterized by deterioration of the nigrostriatal pathway and resulting motor dysfunction [54,55].

Glioblastoma multiforms (GBM) requires new treatments to enhance patient survival and quality of life. One promising strategy is CP-673451, an inhibitor of tyrosine kinase receptors that specifically targets PDGFRα/β [56-60]. This potent inhibitor induces the differentiation of GBM cells by downregulating phosphorylated p38 mitogen-activated protein kinase (MAPK), thereby reducing the proliferative and invasive properties of tumor cells [59,61]. The occurrence of PDGFRA abnormalities is more frequently observed in pediatric high-grade gliomas than in adults and is associated with enhanced pro-tumorigenic potential and less favorable prognosis [62-65]. However, when considering effective GBM treatments, monotherapies targeting a single receptor tyrosine kinase (RTK) may prove insufficient because of the presence of multiple RTK subpopulations in GBM. Considering the heterogeneity of tumors and enhanced treatment outcomes, it may be necessary to employ combinations or alternative therapies that target multiple pathways [66-69]. Studies suggest that PDGFRα and epidermal growth factor receptor (EGFR) amplications likely arise from common parental cells but can evolve independently, resulting in distinct subpopulations. In GBM, PDGFRα-amplified cells constitute a minor population interspersed within the EGFR-amplified regions [67-70]. An autophagy, a crucial cellular degradation process, plays a significant role in cancer, particularly glioblastoma, an aggressive and deadly brain tumor [71-73]. Despite the complexities arising from tumor heterogeneity and mutations, targeting autophagy may offer promising anti-cancer strategies. It regulates PDGF-A signaling, which is a key factor in uncontrolled tumor growth. Once activated, PDGF-A is degraded *via* autophagy, which involves SQSTM1/p62. Inhibiting autophagy has been observed to dramatically alter PDGFRα levels and activity, with reducing PDGFRα levels, thereby affecting tumor formation [72,74].

Neurodegenerative disorders are defined by the gradual loss of neurons and subsequent decline in nervous system function. Studies have identified the involvement of the PDGF/PDGFR signaling in several neurodegenerative conditions, notably Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis

[55,75-77]. PDGF-BB plays a complex role in these diseases, particularly in Alzheimer's disease. In this condition, PDGFRβ signaling deficiency leads to pericyte loss and BBB disruption. The observed correlation between reduced plasma PDGF-BB levels and mild cognitive impairments indicates that PDGF-BB could serve as both a diagnostic indicator and potential treatment strategy [55,76]. PDGF-BB exhibits neurorestorative effects by enhancing tyrosine hydroxylase fiber intensity, increasing tyrosine hydroxylase expression in dopaminergic neurons, and restoring dopamine transporter binding. These actions contribute to the alleviation of behavioral impairments associated with neurodegenerative diseases [55,78]. In contrast, PDGF-CC plays a different role in amyotrophic lateral sclerosis. It contributes to vascular abnormalities by disrupting the blood-spinal cord barrier. This finding suggests that inhibiting PDGF-CC may have therapeutic potential in experimental models of amyotrophic lateral sclerosis [77,79].

In our previous study, we analyzed large-scale gene expression data to identify genes that may be influenced by PDGFRα in gliomas. We compared the gene expression profiles across the entire genome between PDGFRα-positive and PDGFRα-negative cells originating from human oligodendrocyte progenitors [80]. Dysregulated genes in PDGFRα-positive cells, deemed PDGFRα-influenced, are strongly associated with cancer-related pathways. From this set of genes, we developed a prognostic gene signature capable of predicting clinical outcomes in two independent glioma cohorts, irrespective of conventional predictive indicators. Our results suggest that PDGFRα-regulated genes may function as valuable biomarkers and potential therapeutic targets in both clinical and therapeutic contexts. Understanding the diverse roles of PDGFs in nervous system development and cancer, particularly glioblastoma, offers significant insights into potential therapeutic strategies.

Lung

Rapid proliferation and migration of pulmonary arterial smooth muscle cells (PASMCs) are crucial contributors to the onset of pulmonary arterial hypertension (PAH) and right ventricular failure [81,82]. This vascular remodeling is induced by growth factors such as VEGF, transforming growth factor-beta (TGF-β), and PDGF [83-86]. Studies have emphasized the importance of targeting PDGF signaling in the lungs, because PDGF and its receptors are crucial for regulating cellular growth, differentiation, migration, survival, and metabolic processes [87-94]. Gene knockout experiments have elucidated the essential role of PDGF-A and PDGFRα signaling in the development of lung alveoli [14,95]. PDGF-B signaling *via* PDGFRβ is primarily produced and secreted by endothelial and circulating inflammatory cells [85,96].

Increased activity of the PDGF pathway has been observed in pulmonary vascular lesions of patients with PAH [85,97]. Idiopathic pulmonary fibrosis (IPF), a fatal lung disorder characterized by advancing tissue scarring, is primarily mediated by the activation and transformation of fibroblasts into myofibroblasts *via* TGF-β1 and PDGF signaling [98-100]. Several novel targeted pathways are currently under investigation to improve the treatment of lung disorders, and preclinical and clinical studies have demonstrated increased expression and activation of PDGFRα and PDGFRβ in IPF PASMCs. Inhibition of PDGFR has been demonstrated to be effective in animal models of PAH [101,102], and blocking PDGFRα/β signaling has shown potential in attenuating the progression of IPF, fibrosis, and lung cancer, highlighting the importance of understanding this pathway for effective treatment [29,92,103,104]. For instance, olaratumab, a monoclonal antibody targeting PDGFRα, has been utilized in cancer therapy and has potential applications in lung diseases by neutralizing PDGFRα-mediated signaling pathways, thereby reducing lung cancer growth [92,105].

TGF-β interacts synergistically with other growth factors, such as fibroblast growth factor 2 and epidermal growth factor, providing additional opportunities for combination therapies targeting TGF-β. This indicates the inhibition of multiple kinases, including PDGFR, VEGRF, and FGFR, which can produce broader therapeutic effects [106-108]. Concurrently, targeting the TGF-β and PDGF-BB pathways has demonstrated synergistic effects in reducing the hyperproliferation and remodeling of PASMCs in PAH. Notably, dual inhibition of TGF-β and PDGF exhibited promising results in mitigating radiation-induced pulmonary fibrosis, suggesting the potential of this combination therapy [109,110]. Targeting the PDGFR, CSF1R, and KIT kinases may also offer a novel therapeutic approach, as these kinases are highly expressed and upregulated in cells characteristic of pulmonary arteriolar lesions in PAH [88]. These kinases induce inflammation and abnormal cell proliferation through autocrine and paracrine signaling pathways. Interests in the use of tyrosine kinase inhibitors (TKIs) for PAH has emerged from promising preclinical and clinical efficacy data, demonstrating that orally administered imatinib reduces pulmonary vascular resistance and improves exercise capacity [111]. However, its systemic side effects limit its use [112]. Seralutinib, a PDGFR/CSF1R/c-KIT inhibitor, has demonstrated higher potency and fewer systemic side effects than imatinib and, exhibits greater efficacy against PDGFRβ and CSF1R [88,113,114].

PDGF plays a crucial role in asthma pathogenesis by promoting several key processes involved in airway remodeling. It stimulates airway smooth muscle cell proliferation and migration, while also enhancing collagen production by lung fibroblasts. These effects contribute significantly to the structural changes observed in asthmatic airways [115-118]. Studies in mouse models have provided strong evidence for PDGF's involvement in asthma. Overexpression of PDGF-BB in mouse airway epithelium resulted in increased airway smooth muscle and altered gene expression. Furthermore, chronic allergen exposure in mice led to elevated

PDGF-BB levels in broncho-alveolar fluid, supporting its role in airway smooth muscle remodeling [115,117,118]. Given the importance of airway remodeling in asthma progression, researchers are exploring new therapeutic approaches targeting PDGF signaling. TKIs such as nilotinib, imatinib, and mastinib are being explored to evaluate their potential in modulating PDGF pathways and improving asthma management [118-121]. Beyond asthma, PDGF also plays a significant role in other lung pathologies, including non-small cell lung cancer. Studies have shown that PDGF-AA acts as a crucial autocrine regulator of VEGF expression in these tumors, influencing tumor size and patient prognosis [122]. Our knowledge of PDGF's functions in multiple lung diseases emphasizes its significance as a potential treatment strategy, offering new possibilities for developing therapies for asthma and lung cancer.

Liver

Liver fibrosis is a pathological wound healing response triggered by chronic liver injury. This condition is characterized by excessive accumulation of ECM and abnormal connective tissue growth, leading to severe complications, such as liver failure, cirrhosis, or cancer [123-126]. Chronic liver diseases associated with fibrosis have increased global morbidity and mortality rates, which continue to rise. In the case of short-term liver injury, fibrosis is typically avoided because of the balance between profibrosis and anti-fibrosis mechanisms. However, prolonged or chronic liver damage compromises the hepatocyte membranes, leading to hepatocyte necrosis and apoptosis [127-130]. Damaged hepatocytes release molecular signals that activate hepatic stellate cells (HSCs). These cells respond to chemotactic signals such as PDGFs, TGF-β1, epidermal growth factor, and type I collagen by migrating to inflamed regions, thus driving the progression of hepatic fibrosis [131-134]. Upon activation, the HSCs migrate to the site of liver injury, where they enhance contractility, upregulate alpha smooth muscle actin expression, and secrete a range of cytokines such as TGF-β1, PDGF, and connective tissue growth factor. Although this response initially aids wound healing, prolonged fibrosis ultimately alters the liver sinusoid structure, compromising liver function and potentially progressing to cirrhosis [132,135-138]. Emerging evidence has suggested that HSCs are the primary targets for liver fibrosis treatment, with dysregulated PDGF-B/PDGFRβ signaling playing a crucial role in the pathological trans-differentiation of HSC and the progression of liver fibrosis [139-141]. PDGF-BB is a potent mitogen for HSCs that, promotes the synthesis of various ECM components. Therefore, inhibiting the formation of the PDGF-BB/PDGFR-ββ complex is essential for anti-fibrosis therapies.

In addition to PDGFRβ, PDGFRα is also expressed in HSCs and myofibroblasts within the murine liver, indicating its involvement in cell proliferation and migration in human primary HSCs [142-144]. PDGF-C binds to and activates PDGFR; however, unlike PDGF-A and PDGF-B, it requires extracellular proteolytic cleavage to form the complete precursor [145,146]. PDGF-CC specifically interacts with PDGF-α/α homodimers and PDGFR-α/β heterodimers, but does not bind to PDGFR-β/β homodimers, ensures that its effects are dependent on the expression of PDGFRα [146-148]. It promotes DNA replication in various mesenchymal cells, including stellate cells, indicating its potential involvement in fibrogenesis [149-151]. Studies using transgenic mice expressing PDGF-C (PDGF-C Tg) have reported HSC activation, chronic inflammation, and liver injury [150,152,153].

Given the critical role of PDGF/PDGFR signaling in liver fibrosis, targeting this pathway offers a promising therapeutic strategy. Several TKIs that block PDGFR activity have been developed and evaluated in preclinical and clinical studies. These inhibitors are effective in reducing HSC proliferation and ECM production by inhibiting PDGFR signaling [154,155]. Olaratumab, a monoclonal antibody against PDGFRα, has shown to decrease cell proliferation and exhibit notable anti-tumor effects [28,144,156]. Kikuchi *et al*. [142] observed that HSCs and myofibroblasts exhibited elevated PDGFRα expression in chronic liver injury models. They found that olaratumab effectively inhibited HSCs proliferation and migration, while the fibrosis-promoting gene expression remained unaltered. These effects are mediated by various signaling pathways, such as Erk1/2, p38, Elk-1, AKT, mTOR, and CrkII/CrkL [144]. Although TKIs provide essential benefits, clinical cases have reported hepatotoxicity associated with various TKIs. For example, sorafenib demonstrates significant individual variability in pharmacokinetics and efficacy [157]. More concerning, severe hepatotoxicity and liver failure have been documented in patients receiving treatment with sorafenib and imatinib [158-160].

PDGFRα not only plays a profibrotic role in HSCs during chronic liver injury but also enhances the immune response by assisting macrophages in clearing dying hepatocytes, thereby improving liver health despite ongoing damage [142]. It has also been demonstrated that pharmacological intervention of PDGF-BB/PDGFRβ signaling migrates hepatocyte injury and cholestatic fibrosis caused by bile duct ligation [139]. Traditional Chinese medicine targets PDGFRβ, modulates the PDGF-BB/PDGFRβ signaling pathway, inhibits HSC activation and migration, promotes HSC apoptosis, and reduces CCl_4-induced liver fibrosis [161,162]. The combination of PDGFR inhibitors with other anti-fibrotic agents has exhibited synergistic effects in reducing liver fibrosis. For instance, combining PDGFR inhibitors with TGF-β signaling inhibitors, another crucial pathway in fibrosis, has demonstrated enhanced anti-fibrotic outcomes [163,164].

GI tract

GI tract development relies on complex signaling between epithelial and mesenchymal cells, resulting in the formation of organized villi and crypt structures, characterized by rapid cell renewal and differentiation [165,166]. This process is influenced

by PDGF-A and its receptor, PDGFRα [167-171]. In the absence of these factors, the GI mucosal lining becomes abnormal, the villi are reduced in number, and the pericryptal mesenchyme is lost owing to disrupted villus morphogenesis and mesenchymal cell signaling. Mesenchymal cells expressing PDGFRα support intestinal stem cells, with distinct subpopulations found in the gastric corpus and antrum [169]. In the colon, mucosal subepithelial PDGFRα cells, located in the basement membrane beneath the epithelial layer, contribute to the formation of contractile cellular networks *via* gap junctions. These cells develop intricate subepithelial reticular networks around the crypts encompassing the lamina propria [172]. Within this region, PDGFRα cells are closely associated with neural and capillary networks, as well as myofibroblasts, epithelial cells, and immune cells. Furthermore, PDGF-A mesenchymal cells use myosin II forces to shape the intestinal lining into villi, aided by enzymes that increase tissue fluidity and create variations in surface tension [173]. These cellular dynamics highlight the critical role of PDGFRα signaling in maintaining the structural and physiological function of the GI tract.

In the normal GI tract, the interstitial cells of Cajal (ICCs), which are Kit-positive, function as pacemaker cells that regulate gut motility [174,175]. Gastrointestinal stromal tumors (GISTs) can arise in any part of the GI tract and are frequently occur because of mutations in KIT or PDGF-A in ICCs [176-180]. These advancements are crucial for the development of precision therapies that employ low-molecular-weight TKIs. Medications such as imatinib, sunitinib, regorafenib, and ripretinib have been approved for the treatment of advanced GIST, and imatinib has been approved as an adjuvant therapy for high-risk patients [181-185]. Mutations in either KIT or PDGF-A result in conformational changes in the ATP-binding domain, triggering the activation of downstream signaling pathways such as MAPK, AKT, STAT1, and STAT3, which drive unregulated cell proliferation and tumor growth [186-188]. TKIs such as imatinib typically function by competitively binding to the ATP site, thereby blocking these signaling pathways and improving patient survival [189]. Although mutations in KIT and PDGF-A drive the majority of GISTs, some GISTs (10%–15%) lack these mutations and are termed KIT/PDGF-A-wild-type GISTs, which are generally resistant to TKI treatment [190-193]. These subgroups often exhibit primary resistance to imatinib, which poses a significant challenge for treatment.

Based on RNA-sequencing data obtained from the small intestine of Pdgfratm11(EGFP)Sor/J mice [194], we investigated the expression profiles of K^+ channels within PDGFRα cells. Our analysis demonstrated differential expression patterns in the smooth muscles of the jejunum and colon, as well as in the colonic mucosa. Among the various K^+ channel subtypes, Kcnj8 exhibited predominant expression in PDGFRα cells located in both the smooth muscle of the jejunum and the smooth muscle and mucosa of the colon (Fig. 1). Notably, Kcnj8 showed the highest expression levels in the smooth muscle of the jejunum, whereas Kcng 4 was the most abundantly expressed in the smooth muscle

A

Smooth muscle		Mucosa
Jejunum	Colon	Colon
Kcnj8	Kcng4	Kcnj8
Kcnh2	Kcnj8	Kcnk1
Kcnk3	Kcnk2	Kcnq1
Kcng4	Kcnh2	Kcns3
Kcnq4	Kcnj5	Kcnk2
Kcnb1	Kcnb1	Kcng4
Kcnf1	Kcng1	Kcnh2
Kcna6	Kcng2	Kcnk3
Kcna2	Kcnk3	Kcnf1
Kcna5	Kcnf1	Kcng1
Kcng2	Kcnq4	Kcnq4
Kcnk2	Kcna6	Kcng2
Kcns3	Kcna2	Kcnb1
Kcnj5	Kcna5	Kcna2
Kcng1	Kcns3	Kcna6
Kcnk1	Kcnk1	Kcna5
Kcnq1	Kcnq1	Kcnj5

B

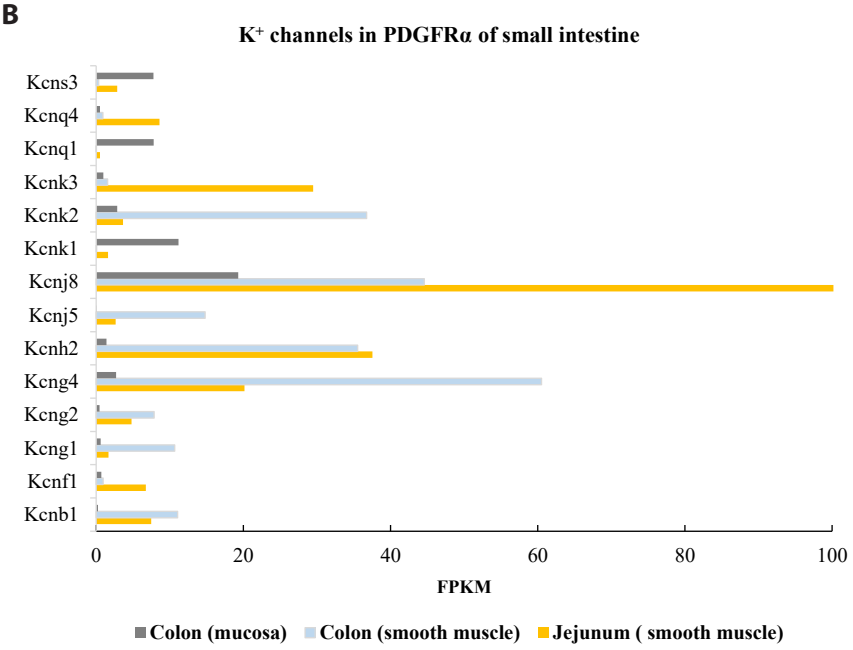

Fig. 1. Expression of various K^+ channel subtypes in the small intestine, including the smooth muscle of the jejunum and mucosa/smooth muscle of the colon. Table (A) shows the subtypes with the highest expression levels. The bar graph (B) illustrates the differential expression across these tissues. The unit the expression is Fragments Per Kilobase of transcript per Million mapped reads (FPKM). PDGFRα, platelet-derived growth factor receptor α.

of the colon, and Kcnj8 was significantly expressed in the colonic mucosa. Kcnj8 encodes the inwardly rectifying K^+ channel subtype Kir6.1, a key component of ATP-sensitive K^+ channels that plays a critical role in regulating smooth muscle contractility. Additionally, Kir6.1 is present in epithelial cells of the small intestine and directly influences intestinal permeability [195,196]. Kcng4 encodes a subunit of voltage-gated K^+ channels that is involved in modulating the membrane potential of various cell types within the small intestine, including enteric neurons, smooth muscle cells, ICCs, and epithelial cells. Through this modulation, Kcng4 contributes to the regulation of motility and absorption [197-201].

Testis

Testes are essential for the development of the male reproductive system, primarily because of the function of interstitial Leydig cells, which produce testosterone necessary for spermatogenesis [202-204]. Several studies have reported that PDGF-A and PDGF-B are present in the testis, including the Leydig, peritubular myoid, and Sertoli cells, which form homodimers PDGF-AA and PDGF-BB, respectively [205-210]. In Leydig cells, the PDGF signaling, particularly through its receptors PDGFRα or PDGFRβ, is crucial for the proliferation, differentiation, and survival of cells [206,211-215]. PDGF signaling also affects stem cell differentiation, depending on the inducing factors. Peritubular stem cells in seminiferous tubules, also known as stem Leydig cells, can differentiate into both Leydig and myoid cells [214]. For instance, exposure to PDGF-AA and luteinizing hormone promotes the development of these stem cells into Leydig cells, while exposure to PDGF-BB and TGF-β promotes their differentiation into both Leydig and myoid cells. Additionally, PDGF-AA is involved in primary cilia function in the development of the male reproductive system, which is mediated by the AKT and ERK signaling pathways [207,216].

In our previous study using PDGFRα^{EGFP} mice, we investigated PDGFRα expression in testicular tissues. We observed that PDGFRα cells are primarily located in the interstitial spaces of the testis, specifically within Leydig cells and peritubular myoid cells, but not in germ cells, Sertoli cells, or vascular endothelial cells in adult mice [217]. Furthermore, we observed co-localization of PDGFRα cells with c-Kit, calcium-activated chloride channel, ANO-1, and TASK-1 in both Leydig and peritubular myoid cells in adult testicular tissues [218,219]. KIT functions through tyrosine kinase activity [220] and, along with its ligand, is crucial for postnatal testicular development. Sertoli cells secrete the Kit ligand, commonly referred to as the stem cell factor, along with its receptor, c-Kit, which is present in spermatogonia and Leydig cells [221]. Signaling pathways involving c-Kit and Kit ligands are crucial for primordial germ cell development and spermatogonial stem cell formation during embryogenesis [222-225]. Stem Leydig cells respond to the concentration of the Kit ligand, which stimulates differentiation at lower levels and also promotes proliferation at higher levels [223].

ANO1 plays a critical role in the regulation of spontaneous activity in various smooth muscle organs. It functions as a source of depolarization of smooth muscle cells, propagates slow waves, and modulates smooth muscle motility [226-229]. Activation of ANO1 channels influences cellular excitability by controlling the membrane potential. Chloride efflux through ANO1 can induce membrane depolarization, leading to the opening of voltage-gated Ca^{2+} channels, which facilitates increased Ca^{2+} entry into the cell and amplifies the initial Ca^{2+} signal [230-232]. This mechanism is essential for several physiological processes. Previous studies have demonstrated that increased intracellular Ca^{2+} levels are crucial for stimulating steroidogenesis in Leydig cells [233-235]. Therefore, ANO1 channels may regulate cell signaling pathways that are essential for steroidogenesis by increasing intracellular Ca^{2+} levels. This regulation affects testosterone production, which is essential for male reproductive health. Additionally, we identified the expression of the acid-sensitive potassium channel TASK-1 (encoded by the *KCNK3* gene), a member of the K^+ channel family, in PDGFRα-expressing cells located in Leydig cells. The TASK-1 channel is a member of the two-pore domain K^+ channel family. This channel controls the resting membrane potential by facilitating the constant efflux of K^+ ions, thereby maintaining the negative membrane potential essential for cellular stability and excitability [236-238]. A previous study showed that TASK-1 channels were expressed in both human and rodent α-cells in islets, and played a critical role in modulating the glucose-regulated suppression of glucagon release by pancreatic α-cells [239]. TASK-1 channels hyperpolarize the membrane potential, reducing excitability and Ca^{2+} influx during glucose stimulation, resulting in lowered glucagon secretion. In Leydig cells, TASK-1 may contribute to their proper functioning and the overall hormonal balance within the testis by influencing membrane potential and Ca^{2+} dynamics.

SUMMARY

In our study, we found that PDGFRα exhibited differential expression across various organs, including the brain, lung, liver, intestine, and testis, as observed in PDGFRα^{EGFP} mice (Fig. 2). In the brain, PDGFRα expression was specifically localized to the hippocampus. In the lungs, it is associated with the blood vessels. In the liver, it was observed around the central vein. In the intestine, PDGFRα was present in the villi of the ileum, and in the testis, it was detected in the interstitial space around the peritubular myoid and Leydig cells. PDGFRs are integral to normal cellular function and development; however, their dysregulation can contribute to diseases pathogenesis in various organs, which requires further investigation. Advanced targeted therapies have markedly improved patient outcomes. Nonetheless, additional research is essential to overcome treatment resistance and tumor heterogeneity and to enhance management strategies targeting

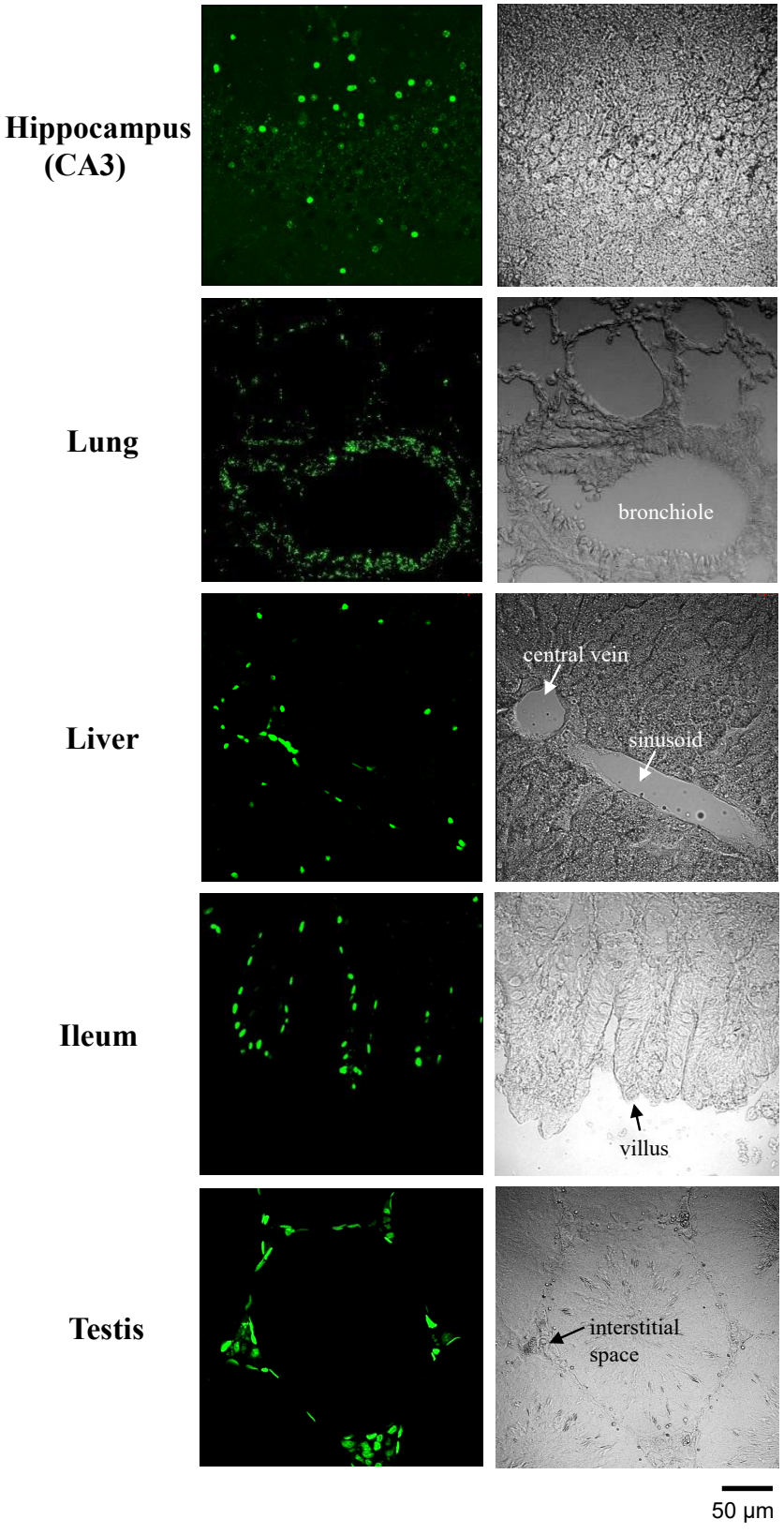

Fig. 2. The expression pattern of platelet-derived growth factor receptor α (PDGFRα) was analyzed in various organs of 8-week-old Pdgfratm11(EGFP)Sor/J mice. Immunofluorescence imaging revealed PDGFRα expression (green) in the brain, lung, liver, ileum, and testis.

PDGF signaling. This includes the exploration of the molecular mechanisms and complexities of PDGFR-mediated pathways to facilitate the development of new clinical applications.

FUNDING

EAK was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (NRF-2022R1F1A1062897). DK was supported by the NRF grant funded by the Korea government (RS-2023-00219399). SCJ was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (2022R111A3063177).

ACKNOWLEDGEMENTS

None.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Bergsten E, Uutela M, Li X, Pietras K, Ostman A, Heldin CH, Alitalo K, Eriksson U. PDGF-D is a specific, protease-activated ligand for the PDGF beta-receptor. *Nat Cell Biol*. 2001;3:512-516.
2. Fredriksson L, Li H, Eriksson U. The PDGF family: four gene products form five dimeric isoforms. *Cytokine Growth Factor Rev*. 2004;15:197-204.
3. Keating MT, Escobedo JA, Fantl WJ, Williams LT. Ligand activation causes a phosphorylation-dependent change in platelet-derived growth factor receptor conformation. *Trans Assoc Am Physicians*. 1988;101:24-32.
4. Donovan J, Abraham D, Norman J. Platelet-derived growth factor signaling in mesenchymal cells. *Front Biosci (Landmark Ed)*. 2013;18:106-119.
5. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. *Genes Dev*. 2008;22:1276-1312.
6. Beckmann MP, Betsholtz C, Heldin CH, Westermark B, Di Marco E, Di Fiore PP, Robbins KC, Aaronson SA. Comparison of biological properties and transforming potential of human PDGF-A and PDGF-B chains. *Science*. 1988;241:1346-1349.
7. Bi Q, Wang C, Cheng G, Chen N, Wei B, Liu X, Li L, Lu C, He J, Weng Y, Yin C, Lin Y, Wan S, Zhao L, Xu J, Wang Y, Gu Y, Shen XZ, Shi P. Microglia-derived PDGFB promotes neuronal potassium currents to suppress basal sympathetic tonicity and limit hypertension. *Immunity*. 2022;55:1466-1482.e9.
8. Wei J, Tang H, Xu ZQ, Li B, Xie LQ, Xu GX. Expression and function of PDGF-α in columnar epithelial cells of age-related cataracts patients. *Genet Mol Res*. 2015;14:13320-13327.
9. Takamura N, Renaud L, da Silveira WA, Feghali-Bostwick C. PDGF promotes dermal fibroblast activation *via* a novel mechanism mediated by signaling through MCHR1. *Front Immunol*. 2021;12:745308.
10. Battegay EJ, Rupp J, Iruela-Arispe L, Sage EH, Pech M. PDGF-BB modulates endothelial proliferation and angiogenesis in vitro via PDGF beta-receptors. *J Cell Biol*. 1994;125:917-928.
11. Xu F, Chen H, Zhou C, Zang T, Wang R, Shen S, Li C, Yu Y, Pei Z, Shen L, Qian J, Ge J. Targeting deubiquitinase OTUB1 protects vascular smooth muscle cells in atherosclerosis by modulating PDGFRβ. *Front Med*. 2024;18:465-483.
12. Vassbotn FS, Havnen OK, Heldin CH, Holmsen H. Negative feedback regulation of human platelets via autocrine activation of the platelet-derived growth factor alpha-receptor. *J Biol Chem*. 1994;269:13874-13879.
13. Su W, Liu G, Liu X, Zhou Y, Sun Q, Zhen G, Wang X, Hu Y, Gao P, Demehri S, Cao X, Wan M. Angiogenesis stimulated by elevated PDGF-BB in subchondral bone contributes to osteoarthritis development. *JCI Insight*. 2020;5:e135446.
14. Gouveia L, Betsholtz C, Andrae J. PDGF-A signaling is required for secondary alveolar septation and controls epithelial proliferation in the developing lung. *Development*. 2018;145:dev161976.
15. Pierce GF, Tarpley JE, Allman RM, Goode PS, Serdar CM, Morris B, Mustoe TA, Vande Berg J. Tissue repair processes in healing chronic pressure ulcers treated with recombinant platelet-derived growth factor BB. *Am J Pathol*. 1994;145:1399-1410.
16. Deptuła M, Sawicka J, Sass P, Sosnowski P, Karpowicz P, Zawrzykraj M, Wardowska A, Tymińska A, Dzierżyńska M, Pietralik-Molińska Z, Peplińska B, Zieliński J, Kondej K, Kozak M, Sachadyn P, Rodziewicz-Motowidło S, Pikuła M. Development and evaluation of RADA-PDGF2 self-assembling peptide hydrogel for enhanced skin wound healing. *Front Pharmacol*. 2023;14:1293647.
17. Deptuła M, Karpowicz P, Wardowska A, Sass P, Sosnowski P, Mieczkowska A, Filipowicz N, Dzierżyńska M, Sawicka J, Nowicka E, Langa P, Schumacher A, Cichorek M, Zieliński J, Kondej K, Kasprzykowski F, Czupryn A, Janus Ł, Mucha P, Skowron P, *et al*. Development of a peptide derived from platelet-derived growth factor (PDGF-BB) into a potential drug candidate for the treatment of wounds. *Adv Wound Care (New Rochelle)*. 2020;9:657-675.
18. Yao L, Rathnakar BH, Kwon HR, Sakashita H, Kim JH, Rackley A, Tomasek JJ, Berry WL, Olson LE. Temporal control of PDGFRα regulates the fibroblast-to-myofibroblast transition in wound healing. *Cell Rep*. 2022;40:111192.
19. Shibahara T, Ago T, Tachibana M, Nakamura K, Yamanaka K, Kuroda J, Wakisaka Y, Kitazono T. Reciprocal interaction between pericytes and macrophage in poststroke tissue repair and functional recovery. *Stroke*. 2020;51:3095-3106.
20. Sang BT, Wang CD, Liu X, Guo JQ, Lai JY, Wu XM. PDGF-BB/PDGFRβ induces tumour angiogenesis via enhancing PKM2 mediated by the PI3K/AKT pathway in Wilms' tumour. *Med Oncol*. 2023;40:240.
21. Zhang K, Wang L, Wei A, Jia X, Liu X. CM082, a novel angiogenesis inhibitor, enhances the antitumor activity of gefitinib on epidermal growth factor receptor mutant non-small cell lung cancer in vitro and in vivo. *Thorac Cancer*. 2020;11:1566-1577.
22. Pfister C, Pfrommer H, Tatagiba MS, Roser F. Vascular endothelial growth factor signals through platelet-derived growth factor recep-

tor β in meningiomas in vitro. *Br J Cancer*. 2012;107:1702-1713.
23. Szebeni B, Veres-Székely A, Pap D, Bokrossy P, Varga Z, Gaál A, Mihály J, Pállinger É, Takács IM, Pajtók C, Bernáth M, Reusz GS, Szabó AJ, Vannay Á. Extracellular vesicles of patients on peritoneal dialysis inhibit the TGF-β- and PDGF-B-mediated fibrotic processes. *Cells*. 2024;13:605.
24. Liu Y, Sun B, Lin Y, Deng H, Wang X, Xu C, Wang K, Yu N, Liu R, Han M. Lysyl oxidase promotes the formation of vasculogenic mimicry in gastric cancer through PDGF-PDGFR pathway. *J Cancer*. 2024;15:1816-1825.
25. Zou X, Tang XY, Qu ZY, Sun ZW, Ji CF, Li YJ, Guo SD. Targeting the PDGF/PDGFR signaling pathway for cancer therapy: a review. *Int J Biol Macromol*. 2022;202:539-557.
26. Ai JY, Liu CF, Zhang W, Rao GW. Current status of drugs targeting PDGF/PDGFR. *Drug Discov Today*. 2024;29:103989.
27. Roh JW, Huang J, Hu W, Yang X, Jennings NB, Sehgal V, Sohn BH, Han HD, Lee SJ, Thanapprapasr D, Bottsford-Miller J, Zand B, Dalton HJ, Previs RA, Davis AN, Matsuo K, Lee JS, Ram P, Coleman RL, Sood AK. Biologic effects of platelet-derived growth factor receptor α blockade in uterine cancer. *Clin Cancer Res*. 2014;20:2740-2750.
28. Shah GD, Loizos N, Youssoufian H, Schwartz JD, Rowinsky EK. Rationale for the development of IMC-3G3, a fully human immunoglobulin G subclass 1 monoclonal antibody targeting the platelet-derived growth factor receptor alpha. *Cancer.* 2010;116:1018-1026.
29. Wang Y, Chen D, Xie H, Zhou S, Jia M, He X, Guo F, Lai Y, Tang XX. LncRNA GAS5 suppresses TGF-β1-induced transformation of pulmonary pericytes into myofibroblasts by recruiting KDM5B and promoting H3K4me2/3 demethylation of the PDGFRα/β promoter. *Mol Med*. 2023;29:32.
30. Zhu Q, Zhao X, Zheng K, Li H, Huang H, Zhang Z, Mastracci T, Wegner M, Chen Y, Sussel L, Qiu M. Genetic evidence that Nkx2.2 and Pdgfra are major determinants of the timing of oligodendrocyte differentiation in the developing CNS. *Development*. 2014;141:548-555.
31. Hattori Y, Itoh H, Tsugawa Y, Nishida Y, Kurata K, Uemura A, Miyata T. Embryonic pericytes promote microglial homeostasis and their effects on neural progenitors in the developing cerebral cortex. *J Neurosci*. 2022;42:362-376.
32. Shen J, Xu G, Zhu R, Yuan J, Ishii Y, Hamashima T, Matsushima T, Yamamoto S, Takatsuru Y, Nabekura J, Sasahara M. PDGFR-β restores blood-brain barrier functions in a mouse model of focal cerebral ischemia. *J Cereb Blood Flow Metab*. 2019;39:1501-1515.
33. Cardona HJ, Somasundaram A, Crabtree DM, Gadd SL, Becher OJ. Prenatal overexpression of platelet-derived growth factor receptor A results in central nervous system hypomyelination. *Brain Behav*. 2021;11:e2332.
34. Zhou L, Shao CY, Xie YJ, Wang N, Xu SM, Luo BY, Wu ZY, Ke YH, Qiu M, Shen Y. Gab1 mediates PDGF signaling and is essential to oligodendrocyte differentiation and CNS myelination. *Elife*. 2020;9:e52056.
35. Vora P, Pillai PP, Zhu W, Mustapha J, Namaka MP, Frost EE. Differential effects of growth factors on oligodendrocyte progenitor migration. *Eur J Cell Biol*. 2011;90:649-656.
36. McKinnon RD, Waldron S, Kiel ME. PDGF alpha-receptor signal strength controls an RTK rheostat that integrates phosphoinositol 3'-kinase and phospholipase Cgamma pathways during oligodendrocyte maturation. *J Neurosci*. 2005;25:3499-3508.
37. Hamashima T, Ishii Y, Nguyen LQ, Okuno N, Sang Y, Matsushima T, Kurashige Y, Takebayashi H, Mori H, Fujimori T, Yamamoto S, Sasahara M. Oligodendrogenesis and myelin formation in the forebrain require platelet-derived growth factor receptor-alpha. *Neuroscience*. 2020;436:11-26.
38. Andrae J, Gouveia L, Gallini R, He L, Fredriksson L, Nilsson I, Johansson BR, Eriksson U, Betsholtz C. A role for PDGF-C/PDGFRα signaling in the formation of the meningeal basement membranes surrounding the cerebral cortex. *Biol Open*. 2016;5:461-474.
39. Fredriksson L, Nilsson I, Su EJ, Andrae J, Ding H, Betsholtz C, Eriksson U, Lawrence DA. Platelet-derived growth factor C deficiency in C57BL/6 mice leads to abnormal cerebral vascularization, loss of neuroependymal integrity, and ventricular abnormalities. *Am J Pathol*. 2012;180:1136-1144.
40. Bennett HC, Zhang Q, Wu YT, Manjila SB, Chon U, Shin D, Vanselow DJ, Pi HJ, Drew PJ, Kim Y. Aging drives cerebrovascular network remodeling and functional changes in the mouse brain. *Nat Commun*. 2024;15:6398.
41. Ren SY, Xia Y, Yu B, Lei QJ, Hou PF, Guo S, Wu SL, Liu W, Yang SF, Jiang YB, Chen JF, Shen KF, Zhang CQ, Wang F, Yan M, Ren H, Yang N, Zhang J, Zhang K, Lin S, *et al*. Growth hormone promotes myelin repair after chronic hypoxia via triggering pericyte-dependent angiogenesis. *Neuron*. 2024;112:2177-2196.e6.
42. Bell RD, Winkler EA, Sagare AP, Singh I, LaRue B, Deane R, Zlokovic BV. Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. *Neuron*. 2010;68:409-427. Erratum in: *Neuron*. 2023;111:3131-3132.
43. Shi LJ, Ge H, Ye F, Li X, Jiang Q. The role of pericyte in ocular vascular diseases. *J Biomed Res*. 2024:1-10.
44. Chen J, Luo Y, Hui H, Cai T, Huang H, Yang F, Feng J, Zhang J, Yan X. CD146 coordinates brain endothelial cell-pericyte communication for blood-brain barrier development. *Proc Natl Acad Sci U S A*. 2017;114:E7622-E7631.
45. Roth M, Carlsson R, Buizza C, Enström A, Paul G. Pericyte response to ischemic stroke precedes endothelial cell death and blood-brain barrier breakdown. *J Cereb Blood Flow Metab*. 2024:271678X241261946.
46. Gaceb A, Roupé L, Enström A, Almasoudi W, Carlsson R, Lindgren AG, Paul G. Pericyte microvesicles as plasma biomarkers reflecting brain microvascular signaling in patients with acute ischemic stroke. *Stroke*. 2024;55:558-568.
47. Arimura K, Ago T, Kamouchi M, Nakamura K, Ishitsuka K, Kuroda J, Sugimori H, Ooboshi H, Sasaki T, Kitazono T. PDGF receptor β signaling in pericytes following ischemic brain injury. *Curr Neurovasc Res*. 2012;9:1-9.
48. Kim Y, Kim M, Kim SD, Yoon N, Wang X, Bae GU, Song YS. Distribution of neuroglobin in pericytes is associated with blood-brain barrier leakage against cerebral ischemia in mice. *Exp Neurobiol*. 2022;31:289-298.
49. Lindahl P, Johansson BR, Levéen P, Betsholtz C. Pericyte loss and microaneurysm formation in PDGF-B-deficient mice. *Science*. 1997;277:242-245.
50. Bernard M, Menet R, Lecordier S, ElAli A. Endothelial PDGF-D contributes to neurovascular protection after ischemic stroke by rescuing pericyte functions. *Cell Mol Life Sci*. 2024;81:225.

51. Krenzlin H, Behera P, Lorenz V, Passaro C, Zdioruk M, Nowicki MO, Grauwet K, Zhang H, Skubal M, Ito H, Zane R, Gutknecht M, Griessl MB, Ricklefs F, Ding L, Peled S, Rooj A, James CD, Cobbs CS, Cook CH, *et al*. Cytomegalovirus promotes murine glioblastoma growth via pericyte recruitment and angiogenesis. *J Clin Invest*. 2019;129:1671-1683.
52. Elabi O, Gaceb A, Carlsson R, Padel T, Soylu-Kucharz R, Cortijo I, Li W, Li JY, Paul G. Human α-synuclein overexpression in a mouse model of Parkinson's disease leads to vascular pathology, blood brain barrier leakage and pericyte activation. *Sci Rep*. 2021;11:1120.
53. Elabi OF, Cunha JPMCM, Gaceb A, Fex M, Paul G. High-fat diet-induced diabetes leads to vascular alterations, pericyte reduction, and perivascular depletion of microglia in a 6-OHDA toxin model of Parkinson disease. *J Neuroinflammation*. 2021;18:175.
54. Padel T, Özen I, Boix J, Barbariga M, Gaceb A, Roth M, Paul G. Platelet-derived growth factor-BB has neurorestorative effects and modulates the pericyte response in a partial 6-hydroxydopamine lesion mouse model of Parkinson's disease. *Neurobiol Dis*. 2016;94:95-105.
55. Chen H, Teng Y, Chen X, Liu Z, Geng F, Liu Y, Jiang H, Wang Z, Yang L. Platelet-derived growth factor (PDGF)-BB protects dopaminergic neurons via activation of Akt/ERK/CREB pathways to upregulate tyrosine hydroxylase. *CNS Neurosci Ther*. 2021;27:1300-1312.
56. Frumento D, Grossi G, Falesiedi M, Musumeci F, Carbone A, Schenone S. Small molecule tyrosine kinase inhibitors (TKIs) for glioblastoma treatment. *Int J Mol Sci*. 2024;25:1398.
57. Duangdara J, Boonsri B, Sayinta A, Supradit K, Thintharua P, Kumkate S, Suriyonplengsaeng C, Larbcharoensub N, Mingphruedhi S, Rungsakulkij N, Muangkaew P, Tangtawee P, Vassanasiri W, Suragul W, Janvilisri T, Tohtong R, Bates DO, Wongprasert K. CP-673451, a selective platelet-derived growth factor receptor tyrosine kinase inhibitor, induces apoptosis in *Opisthorchis viverrini*-associated cholangiocarcinoma via Nrf2 suppression and enhanced ROS. *Pharmaceuticals (Basel)*. 2023;17:9.
58. De Coninck S, De Smedt R, Lintermans B, Reunes L, Kosasih HJ, Reekmans A, Brown LM, Van Roy N, Palhais B, Roels J, Van der Linden M, Van Dorpe J, Ntziachristos P, Van Delft FW, Mansour MR, Pieters T, Lammens T, De Moerloose B, De Bock CE, Goossens S, *et al*. Targeting hyperactive platelet-derived growth factor receptor-β signaling in T-cell acute lymphoblastic leukemia and lymphoma. *Haematologica*. 2024;109:1373-1384.
59. Lane R, Cilibrasi C, Chen J, Shah K, Messuti E, Mazarakis NK, Stebbing J, Critchley G, Song E, Simon T, Giamas G. PDGF-R inhibition induces glioblastoma cell differentiation via DUSP1/$p38^{MAPK}$ signalling. *Oncogene*. 2022;41:2749-2763.
60. Wan X, Zhou M, Huang F, Zhao N, Chen X, Wu Y, Zhu W, Ni Z, Jin F, Wang Y, Hu Z, Chen X, Ren M, Zhang H, Zha X. AKT1-CREB stimulation of PDGFRα expression is pivotal for PTEN deficient tumor development. *Cell Death Dis*. 2021;12:172.
61. Roberts WG, Whalen PM, Soderstrom E, Moraski G, Lyssikatos JP, Wang HF, Cooper B, Baker DA, Savage D, Dalvie D, Atherton JA, Ralston S, Szewc R, Kath JC, Lin J, Soderstrom C, Tkalcevic G, Cohen BD, Pollack V, Barth W, *et al*. Antiangiogenic and antitumor activity of a selective PDGFR tyrosine kinase inhibitor, CP-673,451. *Cancer Res*. 2005;65:957-966.
62. Schwark K, Messinger D, Cummings JR, Bradin J, Kawakibi A, Babila CM, Lyons S, Ji S, Cartaxo RT, Kong S, Cantor E, Koschmann C, Yadav VN. Receptor tyrosine kinase (RTK) targeting in pediatric high-grade glioma and diffuse midline glioma: pre-clinical models and precision medicine. *Front Oncol*. 2022;12:922928.
63. Koschmann C, Zamler D, MacKay A, Robinson D, Wu YM, Doherty R, Marini B, Tran D, Garton H, Muraszko K, Robertson P, Leonard M, Zhao L, Bixby D, Peterson L, Camelo-Piragua S, Jones C, Mody R, Lowenstein PR, Castro MG. Characterizing and targeting PDGFRA alterations in pediatric high-grade glioma. *Oncotarget*. 2016;7:65696-65706.
64. Paugh BS, Zhu X, Qu C, Endersby R, Diaz AK, Zhang J, Bax DA, Carvalho D, Reis RM, Onar-Thomas A, Broniscer A, Wetmore C, Zhang J, Jones C, Ellison DW, Baker SJ. Novel oncogenic PDGFRA mutations in pediatric high-grade gliomas. *Cancer Res*. 2013;73:6219-6229.
65. Paugh BS, Qu C, Jones C, Liu Z, Adamowicz-Brice M, Zhang J, Bax DA, Coyle B, Barrow J, Hargrave D, Lowe J, Gajjar A, Zhao W, Broniscer A, Ellison DW, Grundy RG, Baker SJ. Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. *J Clin Oncol*. 2010;28:3061-3068.
66. Cenciarelli C, Marei HE, Zonfrillo M, Pierimarchi P, Paldino E, Casalbore P, Felsani A, Vescovi AL, Maira G, Mangiola A. PDGF receptor alpha inhibition induces apoptosis in glioblastoma cancer stem cells refractory to anti-Notch and anti-EGFR treatment. *Mol Cancer*. 2014;13:247.
67. Szerlip NJ, Pedraza A, Chakravarty D, Azim M, McGuire J, Fang Y, Ozawa T, Holland EC, Huse JT, Jhanwar S, Leversha MA, Mikkelsen T, Brennan CW. Intratumoral heterogeneity of receptor tyrosine kinases EGFR and PDGFRA amplification in glioblastoma defines subpopulations with distinct growth factor response. *Proc Natl Acad Sci U S A*. 2012;109:3041-3046.
68. Yeo AT, Jun HJ, Appleman VA, Zhang P, Varma H, Sarkaria JN, Charest A. EGFRvIII tumorigenicity requires PDGFRA co-signaling and reveals therapeutic vulnerabilities in glioblastoma. *Oncogene*. 2021;40:2682-2696.
69. Ohkawa Y, Wade A, Lindberg OR, Chen KY, Tran VM, Brown SJ, Kumar A, Kalita M, James CD, Phillips JJ. Heparan sulfate synthesized by *Ext1* regulates receptor tyrosine kinase signaling and promotes resistance to EGFR inhibitors in GBM. *Mol Cancer Res*. 2021;19:150-161.
70. Chakravarty D, Pedraza AM, Cotari J, Liu AH, Punko D, Kokroo A, Huse JT, Altan-Bonnet G, Brennan CW. EGFR and PDGFRA co-expression and heterodimerization in glioblastoma tumor sphere lines. *Sci Rep*. 2017;7:9043.
71. Simpson JE, Gammoh N. The impact of autophagy during the development and survival of glioblastoma. *Open Biol*. 2020;10:200184.
72. Simpson JE, Muir MT, Lee M, Naughton C, Gilbert N, Pollard SM, Gammoh N. Autophagy supports PDGFRA-dependent brain tumor development by enhancing oncogenic signaling. *Dev Cell*. 2024;59:228-243.e7.
73. Calis S, Dogan B, Durdagi S, Celebi A, Yapicier O, Kilic T, Turanli ET, Avsar T. A novel BH3 mimetic Bcl-2 inhibitor promotes autophagic cell death and reduces in vivo Glioblastoma tumor growth. *Cell Death Discov*. 2022;8:433.
74. Simpson JE, Gammoh N. Autophagy cooperates with PDGFRA to support oncogenic growth signaling. *Autophagy*. 2024;20:1901-1902.

75. Sil S, Periyasamy P, Thangaraj A, Chivero ET, Buch S. PDGF/PDGFR axis in the neural systems. *Mol Aspects Med*. 2018;62:63-74.
76. Smyth LCD, Highet B, Jansson D, Wu J, Rustenhoven J, Aalderink M, Tan A, Li S, Johnson R, Coppieters N, Handley R, Narayan P, Singh-Bains MK, Schweder P, Turner C, Mee EW, Heppner P, Correia J, Park TI, Curtis MA, *et al*. Characterisation of PDGF-BB:PDGFRβ signalling pathways in human brain pericytes: evidence of disruption in Alzheimer's disease. *Commun Biol*. 2022;5:235.
77. Lewandowski SA, Nilsson I, Fredriksson L, Lönnerberg P, Muhl L, Zeitelhofer M, Adzemovic MZ, Nichterwitz S, Lawrence DA, Hedlund E, Eriksson U. Presymptomatic activation of the PDGF-CC pathway accelerates onset of ALS neurodegeneration. *Acta Neuropathol*. 2016;131:453-464.
78. Paul G, Zachrisson O, Varrone A, Almqvist P, Jerling M, Lind G, Rehncrona S, Linderoth B, Bjartmarz H, Shafer LL, Coffey R, Svensson M, Mercer KJ, Forsberg A, Halldin C, Svenningsson P, Widner H, Frisén J, Pålhagen S, Haegerstrand A. Safety and tolerability of intracerebroventricular PDGF-BB in Parkinson's disease patients. *J Clin Invest*. 2015;125:1339-1346.
79. Lewandowski SA, Fredriksson L, Lawrence DA, Eriksson U. Pharmacological targeting of the PDGF-CC signaling pathway for blood-brain barrier restoration in neurological disorders. *Pharmacol Ther*. 2016;167:108-119.
80. Ko EA, Lee H, Sanders KM, Koh SD, Zhou T. Expression of alpha-type platelet-derived growth factor receptor-influenced genes predicts clinical outcome in glioma. *Transl Oncol*. 2020;13:233-240.
81. Shen H, Gao Y, Ge D, Tan M, Yin Q, Wei TW, He F, Lee TY, Li Z, Chen Y, Yang Q, Liu Z, Li X, Chen Z, Yang Y, Zhang Z, Thistlethwaite PA, Wang J, Malhotra A, Yuan JX, *et al*. BRCC3 regulation of ALK2 in vascular smooth muscle cells: implication in pulmonary hypertension. *Circulation*. 2024;150:132-150.
82. Knight H, Abis G, Kaur M, Green HLH, Krasemann S, Hartmann K, Lynham S, Clark J, Zhao L, Ruppert C, Weiss A, Schermuly RT, Eaton P, Rudyk O. Cyclin D-CDK4 disulfide bond attenuates pulmonary vascular cell proliferation. *Circ Res*. 2023;133:966-988.
83. Shen QY, Wu L, Wei CS, Zhou YN, Wu HM. Sevoflurane prevents airway remodeling via downregulation of VEGF and TGF-β1 in mice with OVA-induced chronic airway inflammation. *Inflammation*. 2019;42:1015-1022.
84. Westergren-Thorsson G, Bagher M, Andersson-Sjöland A, Thiman L, Löfdahl CG, Hallgren O, Bjermer L, Larsson-Callerfelt AK. VEGF synthesis is induced by prostacyclin and TGF-β in distal lung fibroblasts from COPD patients and control subjects: implications for pulmonary vascular remodelling. *Respirology*. 2018;23:68-75.
85. Saddouk FZ, Kuzemczak A, Saito J, Greif DM. Endothelial HIFα/PDGF-B to smooth muscle Beclin1 signaling sustains pathological muscularization in pulmonary hypertension. *JCI Insight*. 2024;9:e162449.
86. Zhang W, Lin W, Zeng X, Zhang M, Chen Q, Tang Y, Sun J, Liang B, Zha L, Yu Z. FUT8-mediated core fucosylation promotes the pulmonary vascular remodeling in pulmonary arterial hypertension. *Aging Dis*. 2023;14:1927-1944.
87. Perros F, Montani D, Dorfmüller P, Durand-Gasselin I, Tcherakian C, Le Pavec J, Mazmanian M, Fadel E, Mussot S, Mercier O, Hervé P, Emilie D, Eddahibi S, Simonneau G, Souza R, Humbert M. Platelet-derived growth factor expression and function in idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2008;178:81-88.
88. Galkin A, Sitapara R, Clemons B, Garcia E, Kennedy M, Guimond D, Carter LL, Douthitt A, Osterhout R, Gandjeva A, Slee D, Salter-Cid L, Tuder RM, Zisman LS. Inhaled seralutinib exhibits potent efficacy in models of pulmonary arterial hypertension. *Eur Respir J*. 2022;60:2102356.
89. Yamamura A, Fujiwara M, Kawade A, Amano T, Hossain A, Nayeem MJ, Kondo R, Suzuki Y, Inoue Y, Hayashi H, Suzuki S, Sato M, Yamamura H. Corosolic acid attenuates platelet-derived growth factor signaling in macrophages and smooth muscle cells of pulmonary arterial hypertension. *Eur J Pharmacol*. 2024;973:176564.
90. Yamamura A, Nayeem MJ, Al Mamun A, Takahashi R, Hayashi H, Sato M. Platelet-derived growth factor up-regulates Ca^{2+}-sensing receptors in idiopathic pulmonary arterial hypertension. *FASEB J*. 2019;33:7363-7374.
91. Cantoni S, Galletti M, Zambelli F, Valente S, Ponti F, Tassinari R, Pasquinelli G, Galiè N, Ventura C. Sodium butyrate inhibits platelet-derived growth factor-induced proliferation and migration in pulmonary artery smooth muscle cells through Akt inhibition. *FEBS J*. 2013;280:2042-2055.
92. Gerber DE, Gupta P, Dellinger MT, Toombs JE, Peyton M, Duignan I, Malaby J, Bailey T, Burns C, Brekken RA, Loizos N. Stromal platelet-derived growth factor receptor α (PDGFRα) provides a therapeutic target independent of tumor cell PDGFRα expression in lung cancer xenografts. *Mol Cancer Ther*. 2012;11:2473-2482.
93. McGowan SE, McCoy DM. Neuropilin-1 and platelet-derived growth factor receptors cooperatively regulate intermediate filaments and mesenchymal cell migration during alveolar septation. *Am J Physiol Lung Cell Mol Physiol*. 2018;315:L102-L115.
94. Gouveia L, Betsholtz C, Andrae J. Expression analysis of platelet-derived growth factor receptor alpha and its ligands in the developing mouse lung. *Physiol Rep*. 2017;5:e13092.
95. McGowan SE, McCoy DM. Regulation of fibroblast lipid storage and myofibroblast phenotypes during alveolar septation in mice. *Am J Physiol Lung Cell Mol Physiol*. 2014;307:L618-L631.
96. Ntokou A, Dave JM, Kauffman AC, Sauler M, Ryu C, Hwa J, Herzog EL, Singh I, Saltzman WM, Greif DM. Macrophage-derived PDGF-B induces muscularization in murine and human pulmonary hypertension. *JCI Insight*. 2021;6:e139067.
97. Saygin D, Tabib T, Bittar HET, Valenzi E, Sembrat J, Chan SY, Rojas M, Lafyatis R. Transcriptional profiling of lung cell populations in idiopathic pulmonary arterial hypertension. *Pulm Circ*. 2020;10.
98. Mohammed OA, Abdel-Reheim MA, Saleh LA, Alamri MMS, Alfaifi J, Adam MIE, Farrag AA, AlQahtani AAJ, BinAfif WF, Hashish AA, Abdel-Ghany S, Elmorsy EA, El-Wakeel HS, Doghish AS, Hamad RS, Saber S. Alvespimycin exhibits potential anti-TGF-β signaling in the setting of a proteasome activator in rats with bleomycin-induced pulmonary fibrosis: a promising novel approach. *Pharmaceuticals (Basel)*. 2023;16:1123.
99. Abdelhady R, Cavalu S, Saber S, Elmowafy R, Morsy NE, Ibrahim S, Abdeldaiem MSI, Samy M, Abd-Eldayem MA, Shata A, Elgharabawy RM. Mirtazapine, an atypical antidepressant, mitigates lung fibrosis by suppressing NLPR3 inflammasome and fibrosis-related mediators in endotracheal bleomycin rat model. *Biomed Pharmacother*. 2023;161:114553.

100. Montero P, Milara J, Roger I, Cortijo J. Role of JAK/STAT in interstitial lung diseases; molecular and cellular mechanisms. *Int J Mol Sci*. 2021;22:6211.
101. Medarametla V, Festin S, Sugarragchaa C, Eng A, Naqwi A, Wiedmann T, Zisman LS. PK10453, a nonselective platelet-derived growth factor receptor inhibitor, prevents the progression of pulmonary arterial hypertension. *Pulm Circ*. 2014;4:82-102.
102. Schermuly RT, Dony E, Ghofrani HA, Pullamsetti S, Savai R, Roth M, Sydykov A, Lai YJ, Weissmann N, Seeger W, Grimminger F. Reversal of experimental pulmonary hypertension by PDGF inhibition. *J Clin Invest*. 2005;115:2811-2821.
103. Lebel M, Cliche DO, Charbonneau M, Adam D, Brochiero E, Dubois CM, Cantin AM. Invadosome formation by lung fibroblasts in idiopathic pulmonary fibrosis. *Int J Mol Sci*. 2022;24:499.
104. Aono Y, Kishi M, Yokota Y, Azuma M, Kinoshita K, Takezaki A, Sato S, Kawano H, Kishi J, Goto H, Uehara H, Izumi K, Nishioka Y. Role of platelet-derived growth factor/platelet-derived growth factor receptor axis in the trafficking of circulating fibrocytes in pulmonary fibrosis. *Am J Respir Cell Mol Biol*. 2014;51:793-801.
105. Mo G, Baldwin JR, Luffer-Atlas D, Ilaria RL Jr, Conti I, Heathman M, Cronier DM. Population pharmacokinetic modeling of olaratumab, an anti-PDGFRα human monoclonal antibody, in patients with advanced and/or metastatic cancer. *Clin Pharmacokinet*. 2018;57:355-365.
106. Morrell NW, Yang X, Upton PD, Jourdan KB, Morgan N, Sheares KK, Trembath RC. Altered growth responses of pulmonary artery smooth muscle cells from patients with primary pulmonary hypertension to transforming growth factor-beta(1) and bone morphogenetic proteins. *Circulation*. 2001;104:790-795.
107. Abdollahi A, Li M, Ping G, Plathow C, Domhan S, Kiessling F, Lee LB, McMahon G, Gröne HJ, Lipson KE, Huber PE. Inhibition of platelet-derived growth factor signaling attenuates pulmonary fibrosis. *J Exp Med*. 2005;201:925-935.
108. Roskoski R Jr. The role of small molecule platelet-derived growth factor receptor (PDGFR) inhibitors in the treatment of neoplastic disorders. *Pharmacol Res*. 2018;129:65-83.
109. Dadrich M, Nicolay NH, Flechsig P, Bickelhaupt S, Hoeltgen L, Roeder F, Hauser K, Tietz A, Jenne J, Lopez R, Roehrich M, Wirkner U, Lahn M, Huber PE. Combined inhibition of TGFβ and PDGF signaling attenuates radiation-induced pulmonary fibrosis. *Oncoimmunology*. 2015;5:e1123366.
110. Elkiki SM, Mansour HH, Anis LM, Gabr HM, Kamal MM. Evaluation of aromatase inhibitor on radiation induced pulmonary fibrosis via TGF-β/Smad 3 and TGF-β/PDGF pathways in rats. *Toxicol Mech Methods*. 2021;31:538-545.
111. Ogawa A, Miyaji K, Matsubara H. Efficacy and safety of long-term imatinib therapy for patients with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. *Respir Med*. 2017;131:215-219.
112. Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galié N, Gómez-Sánchez MA, Grimminger F, Grünig E, Hassoun PM, Morrell NW, Peacock AJ, Satoh T, Simonneau G, Tapson VF, Torres F, Lawrence D, Quinn DA, Ghofrani HA. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. *Circulation*. 2013;127:1128-1138.
113. Frantz RP, McLaughlin VV, Sahay S, Escribano Subías P, Zolty RL, Benza RL, Channick RN, Chin KM, Hemnes AR, Howard LS, Sitbon O, Vachiéry JL, Zamanian RT, Cravets M, Roscigno RF, Mottola D, Osterhout R, Bruey JM, Elman E, Tompkins CA, *et al*; TORREY Study Investigators. Seralutinib in adults with pulmonary arterial hypertension (TORREY): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Respir Med*. 2024;12:523-534.
114. Novara ME, Di Martino E, Stephens B, Nayrouz M, Vitulo P, Carollo A, Provenzani A. Future perspectives of pulmonary arterial hypertension: a review of novel pipeline treatments and indications. *Drugs R D*. 2024;24:13-28.
115. Hirota JA, Ask K, Farkas L, Smith JA, Ellis R, Rodriguez-Lecompte JC, Kolb M, Inman MD. In vivo role of platelet-derived growth factor-BB in airway smooth muscle proliferation in mouse lung. *Am J Respir Cell Mol Biol*. 2011;45:566-572.
116. Liang X, Wang J, Chen W, Ma X, Wang Y, Nagao N, Weng W, Huang J, Liu J. Inhibition of airway remodeling and inflammation by isoforskolin in PDGF-induced rat ASMCs and OVA-induced rat asthma model. *Biomed Pharmacother*. 2017;95:275-286.
117. Lewis CC, Chu HW, Westcott JY, Tucker A, Langmack EL, Sutherland ER, Kraft M. Airway fibroblasts exhibit a synthetic phenotype in severe asthma. *J Allergy Clin Immunol*. 2005;115:534-540.
118. Kardas G, Daszyńska-Kardas A, Marynowski M, Brząkalska O, Kuna P, Panek M. Role of platelet-derived growth factor (PDGF) in asthma as an immunoregulatory factor mediating airway remodeling and possible pharmacological target. *Front Pharmacol*. 2020;11:47.
119. Kang HS, Rhee CK, Lee HY, Yoon HK, Kwon SS, Lee SY. Different anti-remodeling effect of nilotinib and fluticasone in a chronic asthma model. *Korean J Intern Med*. 2016;31:1150-1158.
120. Rhee CK, Kim JW, Park CK, Kim JS, Kang JY, Kim SJ, Kim SC, Kwon SS, Kim YK, Park SH, Lee SY. Effect of imatinib on airway smooth muscle thickening in a murine model of chronic asthma. *Int Arch Allergy Immunol*. 2011;155:243-251.
121. Lee-Fowler TM, Guntur V, Dodam J, Cohn LA, DeClue AE, Reinero CR. The tyrosine kinase inhibitor masitinib blunts airway inflammation and improves associated lung mechanics in a feline model of chronic allergic asthma. *Int Arch Allergy Immunol*. 2012;158:369-374.
122. Shikada Y, Yonemitsu Y, Koga T, Onimaru M, Nakano T, Okano S, Sata S, Nakagawa K, Yoshino I, Maehara Y, Sueishi K. Platelet-derived growth factor-AA is an essential and autocrine regulator of vascular endothelial growth factor expression in non-small cell lung carcinomas. *Cancer Res*. 2005;65:7241-7248.
123. Kisseleva T, Brenner D. Molecular and cellular mechanisms of liver fibrosis and its regression. *Nat Rev Gastroenterol Hepatol*. 2021;18:151-166.
124. Hu D, Lai J, Chen Q, Bai L. New advances of NG2-expressing cell subset in marrow mesenchymal stem cells as novel therapeutic tools for liver fibrosis/cirrhosis. *Stem Cell Res Ther*. 2024;15:199.
125. Tashiro H, Onoe T, Tanimine N, Tazuma S, Shibata Y, Sudo T, Sada H, Shimada N, Tazawa H, Suzuki T, Shimizu Y. Utility of machine learning in the prediction of post-hepatectomy liver failure in liver cancer. *J Hepatocell Carcinoma*. 2024;11:1323-1330.
126. Zhang J, Zhang L, Yang X, Zheng Y, Xu H, Du S, Mao Y, Sang X, Zhao H, Xu Y, Lu X. Liver fibrosis as a predictor of liver failure and outcome following ALPPS among patients with primary liver cancer. *Sci Rep*. 2024;14:15827.

127. Tan Z, Sun H, Xue T, Gan C, Liu H, Xie Y, Yao Y, Ye T. Liver fibrosis: therapeutic targets and advances in drug therapy. *Front Cell Dev Biol*. 2021;9:730176.
128. Thompson MD, Wickline ED, Bowen WB, Lu A, Singh S, Misse A, Monga SP. Spontaneous repopulation of β-catenin null livers with β-catenin-positive hepatocytes after chronic murine liver injury. *Hepatology*. 2011;54:1333-1343.
129. Jin X, Zimmers TA, Perez EA, Pierce RH, Zhang Z, Koniaris LG. Paradoxical effects of short- and long-term interleukin-6 exposure on liver injury and repair. *Hepatology*. 2006;43:474-484.
130. Mavila N, Siraganahalli Eshwaraiah M, Kennedy J. Ductular reactions in liver injury, regeneration, and disease progression-an overview. *Cells*. 2024;13:579.
131. Yang C, Zeisberg M, Mosterman B, Sudhakar A, Yerramalla U, Holthaus K, Xu L, Eng F, Afdhal N, Kalluri R. Liver fibrosis: insights into migration of hepatic stellate cells in response to extracellular matrix and growth factors. *Gastroenterology*. 2003;124:147-159.
132. Zhao J, Bai J, Peng F, Qiu C, Li Y, Zhong L. USP9X-mediated NRP1 deubiquitination promotes liver fibrosis by activating hepatic stellate cells. *Cell Death Dis*. 2023;14:40.
133. Yoshiji H, Kuriyama S, Noguchi R, Ikenaka Y, Yoshii J, Yanase K, Namisaki T, Kitade M, Yamazaki M, Asada K, Akahane T, Tsujimoto T, Uemura M, Fukui H. Amelioration of liver fibrogenesis by dual inhibition of PDGF and TGF-beta with a combination of imatinib mesylate and ACE inhibitor in rats. *Int J Mol Med*. 2006;17:899-904.
134. Gao J, Wei B, de Assuncao TM, Liu Z, Hu X, Ibrahim S, Cooper SA, Cao S, Shah VH, Kostallari E. Hepatic stellate cell autophagy inhibits extracellular vesicle release to attenuate liver fibrosis. *J Hepatol*. 2020;73:1144-1154.
135. Wang J, Zhang Y, Ma Y, Zhao S, Wang J, Chen H, Zhang J, Liu J. TET1 inhibits liver fibrosis by blocking hepatic stellate cell activation. *J Gastroenterol Hepatol*. 2024;39:1403-1412.
136. Zhu Y, Kang A, Kuai Y, Guo Y, Miao X, Zhu L, Kong M, Li N. The chromatin remodeling protein BRG1 regulates HSC-myofibroblast differentiation and liver fibrosis. *Cell Death Dis*. 2023;14:826.
137. Yan M, Xie Y, Yao J, Li X. The dual-mode transition of myofibroblasts derived from hepatic stellate cells in liver fibrosis. *Int J Mol Sci*. 2023;24:15460.
138. Qi J, Li L, Yan X, Hua W, Zhou Z. Sappanone A alleviates the severity of carbon tetrachloride-induced liver fibrosis in mice. *Antioxidants (Basel)*. 2023;12:1718.
139. Wang X, Gao Y, Li Y, Huang Y, Zhu Y, Lv W, Wang R, Gou L, Cheng C, Feng Z, Xie J, Tian J, Yao R. Roseotoxin B alleviates cholestatic liver fibrosis through inhibiting PDGF-B/PDGFR-β pathway in hepatic stellate cells. *Cell Death Dis*. 2020;11:458.
140. Wang X, Wu X, Zhang A, Wang S, Hu C, Chen W, Shen Y, Tan R, Sun Y, Xu Q. Targeting the PDGF-B/PDGFR-β interface with destruxin A5 to selectively block PDGF-BB/PDGFR-ββ signaling and attenuate liver fibrosis. *EBioMedicine*. 2016;7:146-156.
141. Bai Q, An J, Wu X, You H, Ma H, Liu T, Gao N, Jia J. HBV promotes the proliferation of hepatic stellate cells via the PDGF-B/PDGFR-β signaling pathway in vitro. *Int J Mol Med*. 2012;30:1443-1450.
142. Kikuchi A, Singh S, Poddar M, Nakao T, Schmidt HM, Gayden JD, Sato T, Arteel GE, Monga SP. Hepatic stellate cell-specific platelet-derived growth factor receptor-α loss reduces fibrosis and promotes repair after hepatocellular injury. *Am J Pathol*. 2020;190:2080-2094.
143. Kostallari E, Hirsova P, Prasnicka A, Verma VK, Yaqoob U, Wongjarupong N, Roberts LR, Shah VH. Hepatic stellate cell-derived platelet-derived growth factor receptor-alpha-enriched extracellular vesicles promote liver fibrosis in mice through SHP2. *Hepatology*. 2018;68:333-348.
144. Kikuchi A, Pradhan-Sundd T, Singh S, Nagarajan S, Loizos N, Monga SP. Platelet-derived growth factor receptor α contributes to human hepatic stellate cell proliferation and migration. *Am J Pathol*. 2017;187:2273-2287.
145. Chen PH, Chen X, He X. Platelet-derived growth factors and their receptors: structural and functional perspectives. *Biochim Biophys Acta*. 2013;1834:2176-2186.
146. Li X, Pontén A, Aase K, Karlsson L, Abramsson A, Uutela M, Bäckström G, Hellström M, Boström H, Li H, Soriano P, Betsholtz C, Heldin CH, Alitalo K, Ostman A, Eriksson U. PDGF-C is a new protease-activated ligand for the PDGF alpha-receptor. *Nat Cell Biol*. 2000;2:302-309.
147. Gillnäs S, Gallini R, He L, Betsholtz C, Andrae J. Severe cerebellar malformations in mutant mice demonstrate a role for PDGF-C/PDGFRα signalling in cerebellar development. *Biol Open*. 2022;11:bio059431.
148. Cao R, Bråkenhielm E, Li X, Pietras K, Widenfalk J, Ostman A, Eriksson U, Cao Y. Angiogenesis stimulated by PDGF-CC, a novel member in the PDGF family, involves activation of PDGFR-alphaalpha and -alphabeta receptors. *FASEB J*. 2002;16:1575-1583.
149. Seo W, Jeong WI. Novel insight into a platelet-derived growth factor-C/Smad3 axis in liver fibrosis. Focus on "Role of Smad3 in platelet-derived growth factor-C-induced liver fibrosis". *Am J Physiol Cell Physiol*. 2016;310:C434-C435.
150. Lee JI, Wright JH, Johnson MM, Bauer RL, Sorg K, Yuen S, Hayes BJ, Nguyen L, Riehle KJ, Campbell JS. Role of Smad3 in platelet-derived growth factor-C-induced liver fibrosis. *Am J Physiol Cell Physiol*. 2016;310:C436-C445.
151. Campbell JS, Hughes SD, Gilbertson DG, Palmer TE, Holdren MS, Haran AC, Odell MM, Bauer RL, Ren HP, Haugen HS, Yeh MM, Fausto N. Platelet-derived growth factor C induces liver fibrosis, steatosis, and hepatocellular carcinoma. *Proc Natl Acad Sci U S A*. 2005;102:3389-3394.
152. Wright JH, Johnson MM, Shimizu-Albergine M, Bauer RL, Hayes BJ, Surapisitchat J, Hudkins KL, Riehle KJ, Johnson SC, Yeh MM, Bammler TK, Beyer RP, Gilbertson DG, Alpers CE, Fausto N, Campbell JS. Paracrine activation of hepatic stellate cells in platelet-derived growth factor C transgenic mice: evidence for stromal induction of hepatocellular carcinoma. *Int J Cancer*. 2014;134:778-788.
153. Okada H, Honda M, Campbell JS, Takegoshi K, Sakai Y, Yamashita T, Shirasaki T, Takabatake R, Nakamura M, Tanaka T, Kaneko S. Inhibition of microRNA-214 ameliorates hepatic fibrosis and tumor incidence in platelet-derived growth factor C transgenic mice. *Cancer Sci*. 2015;106:1143-1152.
154. Buttell A, Qiu W. The action and resistance mechanisms of Lenvatinib in liver cancer. *Mol Carcinog*. 2023;62:1918-1934.
155. Capozzi M, De Divitiis C, Ottaiano A, von Arx C, Scala S, Tatangelo F, Delrio P, Tafuto S. Lenvatinib, a molecule with versatile ap-

plication: from preclinical evidence to future development in anticancer treatment. *Cancer Manag Res*. 2019;11:3847-3860.
156. Loizos N, Xu Y, Huber J, Liu M, Lu D, Finnerty B, Rolser R, Malikzay A, Persaud A, Corcoran E, Deevi DS, Balderes P, Bassi R, Jimenez X, Joynes CJ, Mangalampalli VR, Steiner P, Tonra JR, Wu Y, Pereira DS, *et al*. Targeting the platelet-derived growth factor receptor alpha with a neutralizing human monoclonal antibody inhibits the growth of tumor xenografts: implications as a potential therapeutic target. *Mol Cancer Ther*. 2005;4:369-379.
157. Strumberg D, Clark JW, Awada A, Moore MJ, Richly H, Hendlisz A, Hirte HW, Eder JP, Lenz HJ, Schwartz B. Safety, pharmacokinetics, and preliminary antitumor activity of sorafenib: a review of four phase I trials in patients with advanced refractory solid tumors. *Oncologist*. 2007;12:426-437.
158. Qu K, Huang Z, Lin T, Liu S, Chang H, Yan Z, Zhang H, Liu C. New insight into the anti-liver fibrosis effect of multitargeted tyrosine kinase inhibitors: from molecular target to clinical trials. *Front Pharmacol*. 2016;6:300.
159. Haq MI, Nixon J, Stanley AJ. Imatinib and liver toxicity. *BMJ Case Rep*. 2018;11:e226740.
160. Cross TJ, Bagot C, Portmann B, Wendon J, Gillett D. Imatinib mesylate as a cause of acute liver failure. *Am J Hematol*. 2006;81:189-192.
161. Liu F, Li S, Chen P, Gu Y, Wang S, Wang L, Chen C, Wang R, Yuan Y. Salvianolic acid B inhibits hepatic stellate cell activation and liver fibrosis by targeting PDGFRβ. *Int Immunopharmacol*. 2023;122:110550. Erratum in: *Int Immunopharmacol*. 2023;123:110790.
162. Wang R, Liu F, Chen P, Li S, Gu Y, Wang L, Chen C, Yuan Y. Gomisin D alleviates liver fibrosis through targeting PDGFRβ in hepatic stellate cells. *Int J Biol Macromol*. 2023;235:123639.
163. Karimi J, Mohammadalipour A, Sheikh N, Khodadadi I, Hashemnia M, Goudarzi F, Khanjarsim V, Solgi G, Hajilooi M, Bahabadi M, Kheiripour N, Hedayatyanfard K. Protective effects of combined Losartan and Nilotinib on carbon tetrachloride (CCl_4)-induced liver fibrosis in rats. *Drug Chem Toxicol*. 2020;43:468-478.
164. Huang Z, Ding M, Dong Y, Ma M, Song X, Liu Y, Gao Z, Guan H, Chu Y, Feng H, Wang X, Liu H. Targeted truncated TGF-β receptor type II delivery to fibrotic liver by PDGFβ receptor-binding peptide modification for improving the anti-fibrotic activity against hepatic fibrosis in vitro and in vivo. *Int J Biol Macromol*. 2021;188:941-949.
165. Xiang J, Guo J, Zhang S, Wu H, Chen YG, Wang J, Li B, Liu H. A stromal lineage maintains crypt structure and villus homeostasis in the intestinal stem cell niche. *BMC Biol*. 2023;21:169.
166. Lin M, Hartl K, Heuberger J, Beccaceci G, Berger H, Li H, Liu L, Müllerke S, Conrad T, Heymann F, Woehler A, Tacke F, Rajewsky N, Sigal M. Establishment of gastrointestinal assembloids to study the interplay between epithelial crypts and their mesenchymal niche. *Nat Commun*. 2023;14:3025.
167. Chen J, Horiuchi S, Kuramochi S, Kawasaki T, Kawasumi H, Akiyama S, Arai T, Morinaga K, Kimura T, Kiyono T, Akutsu H, Ishida S, Umezawa A. Human intestinal organoid-derived PDGFRα+mesenchymal stroma enables proliferation and maintenance of LGR4+epithelial stem cells. *Stem Cell Res Ther*. 2024;15:16.
168. Greicius G, Kabiri Z, Sigmundsson K, Liang C, Bunte R, Singh MK, Virshup DM. *PDGFRα*$^{+}$ pericryptal stromal cells are the critical source of Wnts and RSPO3 for murine intestinal stem cells in vivo. *Proc Natl Acad Sci U S A*. 2018;115:E3173-E3181.
169. Manieri E, Tie G, Malagola E, Seruggia D, Madha S, Maglieri A, Huang K, Fujiwara Y, Zhang K, Orkin SH, Wang TC, He R, McCarthy N, Shivdasani RA. Role of PDGFRA^{+} cells and a CD55^{+} PDGFRA^{Lo} fraction in the gastric mesenchymal niche. *Nat Commun*. 2023;14:7978.
170. Yang Y, Gomez M, Marsh T, Poillet-Perez L, Sawant A, Chen L, Park NR, Jackson SR, Hu Z, Alon N, Liu C, Debnath J, Guan JL, Davidson S, Verzi M, White E. Autophagy in PDGFRα+ mesenchymal cells is essential for intestinal stem cell survival. *Proc Natl Acad Sci U S A*. 2022;119:e2202016119.
171. Karlsson L, Lindahl P, Heath JK, Betsholtz C. Abnormal gastrointestinal development in PDGF-A and PDGFR-(alpha) deficient mice implicates a novel mesenchymal structure with putative instructive properties in villus morphogenesis. *Development*. 2000;127:3457-3466.
172. Tamura S, Mantani Y, Nakanishi S, Ohno N, Yokoyama T, Hoshi N. Region specificity of fibroblast-like cells in the mucosa of the rat large intestine. *Cell Tissue Res*. 2022;389:427-441.
173. Huycke TR, Häkkinen TJ, Miyazaki H, Srivastava V, Barruet E, McGinnis CS, Kalantari A, Cornwall-Scoones J, Vaka D, Zhu Q, Jo H, Oria R, Weaver VM, DeGrado WF, Thomson M, Garikipati K, Boffelli D, Klein OD, Gartner ZJ. Patterning and folding of intestinal villi by active mesenchymal dewetting. *Cell*. 2024;187:3072-3089.e20.
174. Thomsen L, Robinson TL, Lee JC, Farraway LA, Hughes MJ, Andrews DW, Huizinga JD. Interstitial cells of Cajal generate a rhythmic pacemaker current. *Nat Med*. 1998;4:848-851.
175. Iino S, Ward SM, Sanders KM. Interstitial cells of Cajal are functionally innervated by excitatory motor neurones in the murine intestine. *J Physiol*. 2004;556:521-530.
176. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B, Eisenberg B, Roberts PJ, Singer S, Fletcher CDM, Silberman S, Dimitrijevic S, Fletcher JA. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol*. 2023;41:4829-4836.
177. Tieniber AD, Rossi F, Hanna AN, Liu M, Etherington MS, Loo JK, Param N, Zeng S, Do K, Wang L, DeMatteo RP. Multiple intratumoral sources of kit ligand promote gastrointestinal stromal tumor. *Oncogene*. 2023;42:2578-2588.
178. Incorvaia L, De Biase D, Nannini M, Fumagalli E, Vincenzi B, De Luca I, Brando C, Perez A, Pantaleo MA, Gasperoni S, D'Ambrosio L, Grignani G, Maloberti T, Pedone E, Bazan Russo TD, Mazzocca A, Algeri L, Dimino A, Barraco N, Serino R, *et al*. KIT/PDGFRA variant allele frequency as prognostic factor in gastrointestinal stromal tumors (GISTs): results from a multi-institutional cohort study. *Oncologist*. 2024;29:e141-e151.
179. Yamaguchi U, Nakayama R, Honda K, Ichikawa H, Hasegawa T, Shitashige M, Ono M, Shoji A, Sakuma T, Kuwabara H, Shimada Y, Sasako M, Shimoda T, Kawai A, Hirohashi S, Yamada T. Distinct gene expression-defined classes of gastrointestinal stromal tumor. *J Clin Oncol*. 2008;26:4100-4108.
180. Kondo J, Huh WJ, Franklin JL, Heinrich MC, Rubin BP, Coffey RJ. A smooth muscle-derived, Braf-driven mouse model of gastrointestinal stromal tumor (GIST): evidence for an alternative GIST cell-of-origin. *J Pathol*. 2020;252:441-450.
181. Zhang X, Ren X, Zhu T, Zheng W, Shen C, Lu C. A real-world

pharmacovigilance study of FDA adverse event reporting system (FAERS) events for sunitinib. *Front Pharmacol*. 2024;15:1407709.
182. Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, *et al*; GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:295-302.
183. Martin-Broto J, Valverde C, Hindi N, Vincenzi B, Martinez-Trufero J, Grignani G, Italiano A, Lavernia J, Vallejo A, Tos PD, Le Loarer F, Gonzalez-Campora R, Ramos R, Hernández-Jover D, Gutierrez A, Serrano C, Monteagudo M, Letón R, Robledo M, Moura DS, *et al*. REGISTRI: Regorafenib in first-line of KIT/PDGFRA wild type metastatic GIST: a collaborative Spanish (GEIS), Italian (ISG) and French Sarcoma Group (FSG) phase II trial. *Mol Cancer*. 2023;22:127.
184. Serrano C, Martín-Broto J, Asencio-Pascual JM, López-Guerrero JA, Rubió-Casadevall J, Bagué S, García-Del-Muro X, Fernández-Hernández JÁ, Herrero L, López-Pousa A, Poveda A, Martínez-Marín V. 2023 GEIS Guidelines for gastrointestinal stromal tumors. *Ther Adv Med Oncol*. 2023;15:17588359231192388.
185. Di Vito A, Ravegnini G, Gorini F, Aasen T, Serrano C, Benuzzi E, Coschina E, Monesmith S, Morroni F, Angelini S, Hrelia P. The multifaceted landscape behind imatinib resistance in gastrointestinal stromal tumors (GISTs): a lesson from ripretinib. *Pharmacol Ther*. 2023;248:108475.
186. Negri T, Bozzi F, Conca E, Brich S, Gronchi A, Bertulli R, Fumagalli E, Pierotti MA, Tamborini E, Pilotti S. Oncogenic and ligand-dependent activation of KIT/PDGFRA in surgical samples of imatinib-treated gastrointestinal stromal tumours (GISTs). *J Pathol*. 2009;217:103-112.
187. Kang HJ, Nam SW, Kim H, Rhee H, Kim NG, Kim H, Hyung WJ, Noh SH, Kim JH, Yun CO, Liu ET, Kim H. Correlation of KIT and platelet-derived growth factor receptor alpha mutations with gene activation and expression profiles in gastrointestinal stromal tumors. *Oncogene*. 2005;24:1066-1074.
188. Niinuma T, Suzuki H, Sugai T. Molecular characterization and pathogenesis of gastrointestinal stromal tumor. *Transl Gastroenterol Hepatol*. 2018;3:2.
189. Marcucci G, Perrotti D, Caligiuri MA. Understanding the molecular basis of imatinib mesylate therapy in chronic myelogenous leukemia and the related mechanisms of resistance. Commentary re: A. N. Mohamed et al., The effect of imatinib mesylate on patients with Philadelphia chromosome-positive chronic myeloid leukemia with secondary chromosomal aberrations. Clin. Cancer Res., 9: 1333-1337, 2003. *Clin Cancer Res*. 2003;9:1248-1252.
190. Ding H, Yu X, Yu Y, Lao X, Hang C, Gao K, Jia Y, Yan Z. Clinical significance of the molecular heterogeneity of gastrointestinal stromal tumors and related research: a systematic review. *Oncol Rep*. 2020;43:751-764.
191. Kang HJ, Koh KH, Yang E, You KT, Kim HJ, Paik YK, Kim H. Differentially expressed proteins in gastrointestinal stromal tumors with KIT and PDGFRA mutations. *Proteomics*. 2006;6:1151-1157.
192. Medeiros F, Corless CL, Duensing A, Hornick JL, Oliveira AM, Heinrich MC, Fletcher JA, Fletcher CD. KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. *Am J Surg Pathol*. 2004;28:889-894.
193. Lasota J, Miettinen M. KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs). *Semin Diagn Pathol*. 2006;23:91-102.
194. Ha SE, Lee MY, Kurahashi M, Wei L, Jorgensen BG, Park C, Park PJ, Redelman D, Sasse KC, Becker LS, Sanders KM, Ro S. Transcriptome analysis of PDGFRα+ cells identifies T-type Ca2+ channel CACNA1G as a new pathological marker for PDGFRα+ cell hyperplasia. *PLoS One*. 2017;12:e0182265.
195. Jöns T, Wittschieber D, Beyer A, Meier C, Brune A, Thomzig A, Ahnert-Hilger G, Veh RW. K+-ATP-channel-related protein complexes: potential transducers in the regulation of epithelial tight junction permeability. *J Cell Sci*. 2006;119:3087-3097.
196. Cosme D, Estevinho MM, Rieder F, Magro F. Potassium channels in intestinal epithelial cells and their pharmacological modulation: a systematic review. *Am J Physiol Cell Physiol*. 2021;320:C520-C546. Erratum in: *Am J Physiol Cell Physiol*. 2023;325:C1.
197. Lee MC, Nahorski MS, Hockley JRF, Lu VB, Ison G, Pattison LA, Callejo G, Stouffer K, Fletcher E, Brown C, Drissi I, Wheeler D, Ernfors P, Menon D, Reimann F, Smith ESJ, Woods CG. Human labor pain is influenced by the voltage-gated potassium channel K_V6.4 subunit. *Cell Rep*. 2020;32:107941.
198. Tewari D, Sattler C, Benndorf K. Functional properties of a disease mutation for migraine in Kv2.1/6.4 channels. *Biochem Biophys Res Commun*. 2024;738:150560.
199. Gutman GA, Chandy KG, Grissmer S, Lazdunski M, McKinnon D, Pardo LA, Robertson GA, Rudy B, Sanguinetti MC, Stühmer W, Wang X. International Union of Pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. *Pharmacol Rev*. 2005;57:473-508.
200. O'Donnell AM, Nakamura H, Tomuschat C, Marayati NF, Puri P. Altered expression of KCNG3 and KCNG4 in Hirschsprung's disease. *Pediatr Surg Int*. 2019;35:193-197.
201. Heitzmann D, Warth R. Physiology and pathophysiology of potassium channels in gastrointestinal epithelia. *Physiol Rev*. 2008;88:1119-1182.
202. Chung JY, Kim JY, Kim YJ, Jung SJ, Park JE, Lee SG, Kim JT, Oh S, Lee CJ, Yoon YD, Yoo YH, Kim JM. Cellular defense mechanisms against benzo[a]pyrene in testicular Leydig cells: implications of p53, aryl-hydrocarbon receptor, and cytochrome P450 1A1 status. *Endocrinology*. 2007;148:6134-6144.
203. Zirkin BR. Spermatogenesis: its regulation by testosterone and FSH. *Semin Cell Dev Biol*. 1998;9:417-421.
204. Ge RS, Li X, Wang Y. Leydig cell and spermatogenesis. *Adv Exp Med Biol*. 2021;1288:111-129.
205. Gnessi L, Emidi A, Jannini EA, Carosa E, Maroder M, Arizzi M, Ulisse S, Spera G. Testicular development involves the spatiotemporal control of PDGFs and PDGF receptors gene expression and action. *J Cell Biol*. 1995;131:1105-1121.
206. Li X, Quan H, He J, Li H, Zhu Q, Wang Y, Zhu Y, Ge RS. The role of platelet-derived growth factor BB signaling pathway in the regulation of stem and progenitor Leydig cell proliferation and steroidogenesis in male rats. *J Steroid Biochem Mol Biol*. 2023;233:106344.
207. Tsai YC, Kuo TN, Chao YY, Lee PR, Lin RC, Xiao XY, Huang BM, Wang CY. PDGF-AA activates AKT and ERK signaling for testicular interstitial Leydig cell growth via primary cilia. *J Cell Biochem*.

2023;124:89-102.
208. Bergeron F, Bagu ET, Tremblay JJ. Transcription of platelet-derived growth factor receptor α in Leydig cells involves specificity protein 1 and 3. *J Mol Endocrinol*. 2011;46:125-138.
209. Nurmio M, Kallio J, Adam M, Mayerhofer A, Toppari J, Jahnukainen K. Peritubular myoid cells have a role in postnatal testicular growth. *Spermatogenesis*. 2012;2:79-87.
210. Hashemnia SM, Atari-Hajipirloo S, Roshan-Milani S, Valizadeh N, Mahabadi S, Kheradmand F. Imatinib alters cell viability but not growth factors levels in TM4 Sertoli cells. *Int J Reprod Biomed*. 2016;14:577-582.
211. Eliveld J, van den Berg EA, Chikhovskaya JV, van Daalen SKM, de Winter-Korver CM, van der Veen F, Repping S, Teerds K, van Pelt AMM. Primary human testicular PDGFRα+ cells are multipotent and can be differentiated into cells with Leydig cell characteristics in vitro. *Hum Reprod*. 2019;34:1621-1631.
212. Eliveld J, van Daalen SKM, de Winter-Korver CM, van der Veen F, Repping S, Teerds K, van Pelt AMM. A comparative analysis of human adult testicular cells expressing stem Leydig cell markers in the interstitium, vasculature, and peritubular layer. *Andrology*. 2020;8:1265-1276.
213. Wang Y, Li X, Ge F, Yuan K, Su Z, Wang G, Lian Q, Ge RS. Platelet-derived growth factor BB stimulates differentiation of rat immature Leydig cells. *J Mol Endocrinol*. 2018;60:29-43.
214. Zhao X, Wen X, Ji M, Guan X, Chen P, Hao X, Chen F, Hu Y, Duan P, Ge RS, Chen H. Differentiation of seminiferous tubule-associated stem cells into leydig cell and myoid cell lineages. *Mol Cell Endocrinol*. 2021;525:111179.
215. Odeh HM, Kleinguetl C, Ge R, Zirkin BR, Chen H. Regulation of the proliferation and differentiation of Leydig stem cells in the adult testis. *Biol Reprod*. 2014;90:123.
216. Umberger NL, Caspary T. Ciliary transport regulates PDGF-AA/αα signaling via elevated mammalian target of rapamycin signaling and diminished PP2A activity. *Mol Biol Cell*. 2015;26(2):350-358.
217. Woo MS, Kim EJ, Lee DK, Lee CE, Ko EA, Kang D. Analysis of platelet-derived growth factor receptor alpha expression in adult mouse testis. *J Anim Reprod Biotechnol*. 2024;39:81-87.
218. Ko EA, Woo MS, Kang D. Testosterone secretion is affected by receptor tyrosine kinase c-Kit and anoctamin 1 activation in mouse Leydig cells. *J Anim Reprod Biotechnol*. 2022;37:87-95.
219. Woo MS, Kim EJ, Prayoga AH, Kim Y, Kang D. Expression of TASK-1 channel in mouse Leydig cells. *J Anim Reprod Biotechnol*. 2023;38:291-299.
220. Besmer P, Manova K, Duttlinger R, Huang EJ, Packer A, Gyssler C, Bachvarova RF. The kit-ligand (steel factor) and its receptor c-kit/W: pleiotropic roles in gametogenesis and melanogenesis. *Dev Suppl*. 1993:125-137.
221. Panahi S, Karamian A, Sajadi E, Aliaghaei A, Nazarian H, Abdi S, Danyali S, Paktinat S, Abdollahifar MA, Farahani RM. Sertoli cell-conditioned medium restores spermatogenesis in azoospermic mouse testis. *Cell Tissue Res*. 2020;379:577-587.
222. Jung H, Song H, Yoon M. The KIT is a putative marker for differentiating spermatogonia in stallions. *Anim Reprod Sci*. 2015;152:39-46.
223. Liu S, Chen X, Wang Y, Li L, Wang G, Li X, Chen H, Guo J, Lin H, Lian QQ, Ge RS. A role of KIT receptor signaling for proliferation and differentiation of rat stem Leydig cells in vitro. *Mol Cell Endocrinol*. 2017;444:1-8.
224. Rothschild G, Sottas CM, Kissel H, Agosti V, Manova K, Hardy MP, Besmer P. A role for kit receptor signaling in Leydig cell steroidogenesis. *Biol Reprod*. 2003;69:925-932.
225. Kissel H, Timokhina I, Hardy MP, Rothschild G, Tajima Y, Soares V, Angeles M, Whitlow SR, Manova K, Besmer P. Point mutation in kit receptor tyrosine kinase reveals essential roles for kit signaling in spermatogenesis and oogenesis without affecting other kit responses. *EMBO J*. 2000;19:1312-1326.
226. Chen D, Li H, Wang X, Zhang L, Ji Z, Zhang J. Hypertriglyceridemia impairs urethral spontaneous tone through down-regulation of ANO1 in mouse urethral smooth muscle cells. *Urology*. 2022;165:157-163.
227. Chen D, Meng W, Shu L, Liu S, Gu Y, Wang X, Feng M. ANO1 in urethral SMCs contributes to sex differences in urethral spontaneous tone. *Am J Physiol Renal Physiol*. 2020;319:F394-F402.
228. Brijs J, Hennig GW, Kellermann AM, Axelsson M, Olsson C. The presence and role of interstitial cells of Cajal in the proximal intestine of shorthorn sculpin (Myoxocephalus scorpius). *J Exp Biol*. 2017;220:347-357.
229. Iqbal J, Tonta MA, Mitsui R, Li Q, Kett M, Li J, Parkington HC, Hashitani H, Lang RJ. Potassium and ANO1/ TMEM16A chloride channel profiles distinguish atypical and typical smooth muscle cells from interstitial cells in the mouse renal pelvis. *Br J Pharmacol*. 2012;165:2389-2408.
230. Wray S, Prendergast C, Arrowsmith S. Calcium-activated chloride channels in myometrial and vascular smooth muscle. *Front Physiol*. 2021;12:751008.
231. Forrest AS, Angermann JE, Raghunathan R, Lachendro C, Greenwood IA, Leblanc N. Intricate interaction between store-operated calcium entry and calcium-activated chloride channels in pulmonary artery smooth muscle cells. *Adv Exp Med Biol*. 2010;661:31-55.
232. Akin EJ, Aoun J, Jimenez C, Mayne K, Baeck J, Young MD, Sullivan B, Sanders KM, Ward SM, Bulley S, Jaggar JH, Earley S, Greenwood IA, Leblanc N. ANO1, CaV1.2, and IP3R form a localized unit of EC-coupling in mouse pulmonary arterial smooth muscle. *J Gen Physiol*. 2023;155:e202213217.
233. Abdou HS, Villeneuve G, Tremblay JJ. The calcium signaling pathway regulates leydig cell steroidogenesis through a transcriptional cascade involving the nuclear receptor NR4A1 and the steroidogenic acute regulatory protein. *Endocrinology*. 2013;154:511-520.
234. Abdou HS, Robert NM, Tremblay JJ. Calcium-dependent Nr4a1 expression in mouse Leydig cells requires distinct AP1/CRE and MEF2 elements. *J Mol Endocrinol*. 2016;56:151-161.
235. Costa RR, Varanda WA, Franci CR. A calcium-induced calcium release mechanism supports luteinizing hormone-induced testosterone secretion in mouse Leydig cells. *Am J Physiol Cell Physiol*. 2010;299:C316-C323.
236. Saint-Martin Willer A, Santos-Gomes J, Adão R, Brás-Silva C, Eyries M, Pérez-Vizcaino F, Capuano V, Montani D, Antigny F. Physiological and pathophysiological roles of the KCNK3 potassium channel in the pulmonary circulation and the heart. *J Physiol*. 2023;601:3717-3737. Erratum in: *J Physiol*. 2024;602:2145-2146.
237. Duprat F, Lesage F, Fink M, Reyes R, Heurteaux C, Lazdunski M. TASK, a human background K+ channel to sense external pH

variations near physiological pH. *EMBO J*. 1997;16:5464-5471.
238. Schewe M, Nematian-Ardestani E, Sun H, Musinszki M, Cordeiro S, Bucci G, de Groot BL, Tucker SJ, Rapedius M, Baukrowitz T. A non-canonical voltage-sensing mechanism controls gating in K2P K(+) channels. *Cell*. 2016;164:937-949.
239. Dadi PK, Luo B, Vierra NC, Jacobson DA. TASK-1 potassium channels limit pancreatic α-cell calcium influx and glucagon secretion. *Mol Endocrinol*. 2015;29:777-787.