REVIEW

PDGF receptor mutations in human diseases

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Abstract

PDGFRA and *PDGFRB* are classical proto-oncogenes that encode receptor tyrosine kinases responding to platelet-derived growth factor (PDGF). *PDGFRA* mutations are found in gastrointestinal stromal tumors (GISTs), inflammatory fibroid polyps and gliomas, and *PDGFRB* mutations drive myofibroma development. In addition, chromosomal rearrangement of either gene causes myeloid neoplasms associated with hypereosinophilia. Recently, mutations in *PDGFRB* were linked to several noncancerous diseases. Germline heterozygous variants that reduce receptor activity have been identified in primary familial brain calcification, whereas gain-of-function mutants are present in patients with fusiform aneurysms, Kosaki overgrowth syndrome or Penttinen premature aging syndrome. Functional analysis of these variants has led to the preclinical validation of tyrosine kinase inhibitors targeting PDGF receptors, such as imatinib, as a treatment for some of these conditions. This review summarizes the rapidly expanding knowledge in this field.

Keywords Infantile myofibromatosis · Fahr disease · Unicentric Castleman disease · Hereditary progressive mucinous histiocytosis

Introduction

Platelet-derived growth factor (PDGF) receptors (PDGFRs) belong to the family of receptor tyrosine kinases (RTKs) [1–4]. There are two isoforms of PDGF receptors, PDGFRα and PDGFRβ, which are encoded by two different genes, *PDGFRA* and *PDGFRB*, respectively. Five distinct ligands (PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC and PDGF-DD) can bind to one or both PDGFRs in a dimeric state. PDGF was initially purified from platelets in the seventies and can be produced by numerous other cell types, including epithelial and endothelial cells. PDGF receptors are mainly expressed by cells of mesenchymal origin, such as fibroblasts, pericytes and vascular smooth muscle cells, and stimulate their proliferation and motility [1, 2]. Early studies suggested that PDGF ligands and receptors may play a role in cancer development, and genetic alterations in both receptor genes were subsequently identified in hematopoietic, glial and soft-tissue cancers. Recently, mutations in

noncancerous disorders have also been found, including skeletal defects, brain calcification, and vascular anomalies. This review focuses on mutations in *PDGFRA* and *PDGFRB* that cause human diseases.

Receptor structure and signal transduction

PDGF receptors are members of the RTK class III family, along with c-KIT, colony stimulating factor 1 receptor (CSF1R) and Fms-like tyrosine kinase 3 receptor (FLT3). These receptors are characterized by a glycosylated extracellular domain composed of five immunoglobulin-like modules that bind the ligand, a helical transmembrane domain and an intracellular region with tyrosine kinase activity. More precisely, the cytosolic region contains (1) the juxtamembrane (JM) domain, (2) the highly conserved tyrosine kinase domain composed of the N-lobe, the insert region and the C-lobe containing the activation loop, and (3) a variable C-terminal tail (Fig. 1) [5–7].

PDGF binding induces receptor dimerization. The dimer is further stabilized by conformational changes in the extracellular region, which favor homotypic interactions between Ig-like domains 4 and 5. The transmembrane helix may also contribute to the formation of receptor dimers [6].

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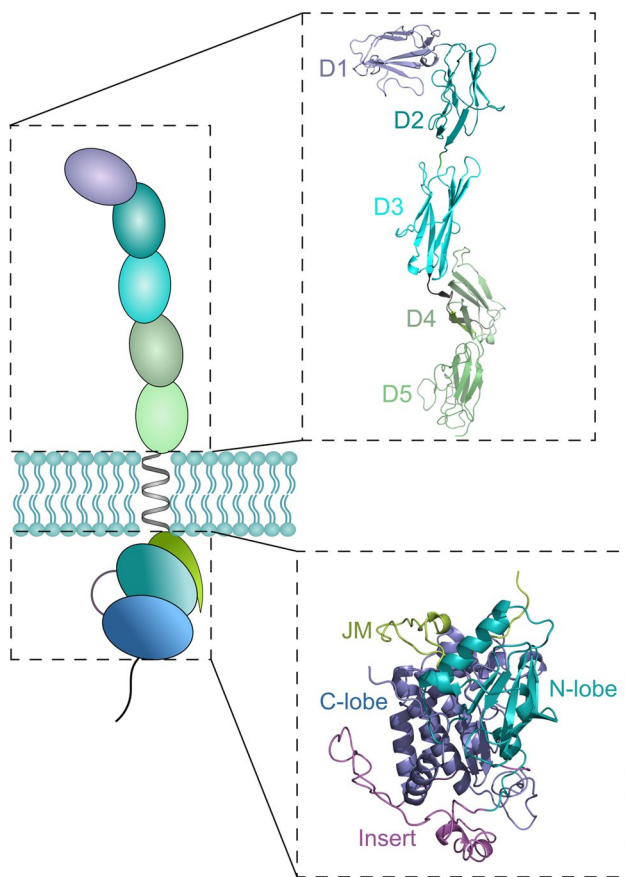
Fig. 1 PDGFR Structure. The receptor consists of an extracellular part composed of five immunoglobulin-like modules (D1-D5) that bind the ligand, a helical transmembrane domain, and an intracellular part containing the juxtamembrane (JM) regulatory region, the kinase domain made of a N- and C-lobe separated by the kinase insert. Adapted in PyMol from the crystal structure of human PDGFRA (PDB 5K5X) [6] and PDGFRB (PDB 3MJG) [7]

This process disrupts the inhibitory juxtamembrane domain. According to recent cryo-electron microscopy data, the active kinase domain adopts an asymmetric dimer conformation [8, 9]. The tyrosine-kinase domain of PDGF receptors transfers a phosphoryl group (PO_3^{2-}) from adenosine-5′-triphosphate to a tyrosine residue of the substrate [10]. ATP binds to the cleft between the N- and C-lobes of the kinase domain. The adenine moiety binds in a hydrophobic pocket through hydrogen bonds, while the ribose and triphosphate groups contact a hydrophilic channel that extends to the substrate binding site [11]. This leads to the trans-phosphorylation of receptor tyrosine residues. Phosphorylation of the juxtamembrane domain and the activation loop further stabilizes the active conformation of the kinase domain. In addition, multiple phospho-tyrosine residues act as docking sites for signaling molecules, which can themselves be phosphorylated. Phospholipase Cγ (PLCγ), phosphatidylinosit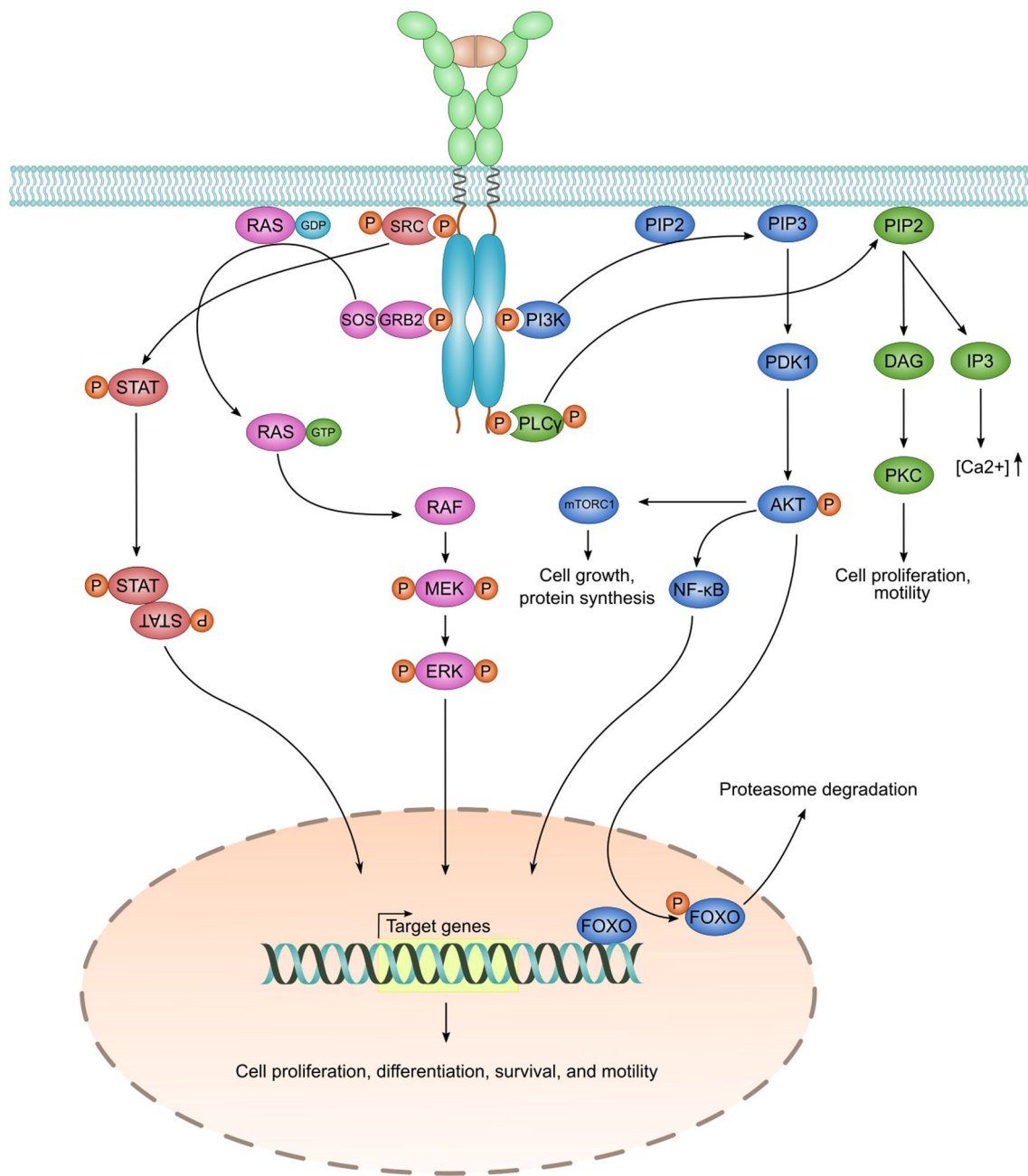ol- 3-kinase (PI3K), SRC family kinases and signal transducers and activators of transcription (STATs) are the main signaling mediators activated by PDGF receptors [5, 12, 13]. Adaptor molecules are also recruited to PDGFR and regulate multiple pathways, including the MAP kinase cascade (Fig. 2).

Physiological roles

Analysis of knockout mice has revealed the crucial role of PDGFRs and their ligands in embryonic development. This has been the subject of several excellent reviews [1–3]. PDGFRα has early developmental functions in gastrulation and formation of neural crest. It is also essential for organogenesis, particularly by driving the migration and proliferation of mesenchymal cells. Mice lacking PDGFRα are not viable and present multiple defects in the gastrointestinal tract, central nervous system, lungs, skeleton, testis, and kidneys [2]. This phenotype combines the defects observed in PDGF-A and PDGF-C knockout mice [2, 14, 15].

PDGFRβ is mainly implicated in blood vessels formation and kidney development [2]. Mice lacking PDGFRβ or PDGF-B exhibit defects in the development of both systems and die around birth. This is due to the lack of vascular smooth muscle cells, pericytes, and mesangial cells of kidney glomeruli, causing hemorrhages and altering glomerular filtration [16, 17]. In contrast, mice deficient in PDGF-D only present a mild vascular phenotype, with disorganized pericytes in the cardiac vasculature and a slight increase in blood pressure [18].

In adults, PDGF receptors contribute to wound healing and soft-tissue homeostasis. PDGF is released by platelets at the site of injury and promotes chemotaxis and proliferation of fibroblasts and vascular mural cells, as well as the synthesis of extracellular matrix components, all being key steps to initiate wound repair. Although PDGF effectively stimulates healing of difficult wound in patients, it is mostly redundant with other growth factors [19, 20]. In addition, mouse studies suggested new functions for PDGFRβ in bone regeneration, heart regeneration, and adipose tissue homeostasis [21–23]. Finally, PDGFRβ signaling is involved in interstitial fluid pressure homeostasis, by counteracting the decrease of interstitial fluid pressure observed during acute inflammatory events. This mechanism implicates the PI3K pathway as well as the $\alpha_2\beta_1$ integrin system to modulate tension between cells and extracellular matrix structures [24, 25]. The importance of PDGFRβ as a regulator of interstitial fluid pressure is further strengthen by the frequent observation of edema in patients receiving a PDGFR inhibitor, such as imatinib (see below for details). Interestingly, imatinib also induces growth deceleration in children treated for chronic myeloid leukemia, suggesting a role for PDGF receptors in bone formation after birth [26].

Fig. 2 Overview of signaling pathways downstream of PDGF receptors. PDGF binding induces receptor dimerization and trans-phosphorylation. The recruitment of signaling and adaptor molecules to the phosphorylated receptor triggers several signaling cascades: phospholipase C γ (PLCγ), phosphatidylinositol-3-kinase (PI3K), mitogen-activated protein (MAP) kinases and signal transducers and activators of transcription (STATs). P, phosphorylation site

Hematopoietic neoplasms

The first PDGF receptor gene alterations were described in hematologic malignancies. In myeloid neoplasms associated with hypereosinophilia, chromosomal rearrangements in hematopoietic progenitors produce fusion genes, such as *FIP1L1-PDGFRA* and *ETV6-PDGFRB*, which have been reviewed extensively [27–30]. These fusion proteins are comparable to BCR-ABL1 and consist of an N-terminal domain that originates from the fusion partner and a C-terminal part that contains the kinase domain of PDGFR [29, 30]. These fusion proteins are activated by either disruption of the autoinhibitory juxta-membrane domain (in the case of FIP1L1-PDGFRA for instance) or by constitutive oligomerization driven by the partner protein. Expression of these constitutively activated PDGFR

hybrid proteins is controlled by the promoter sequence of the partner gene, explaining why PDGFR fusion proteins accumulate in hematopoietic cells, which do not express wild-type PDGFR [31]. Similar *PDGFRB* fusions genes (such as *EBF1-PDGFRB)* have been reported in B-cell acute lymphoblastic leukemia [32].

Beside fusion genes, gain-of-function point mutations in *PDGFRA* have been described in myeloid neoplasms associated with hypereosinophilia [33]. These mutations are located in the N-lobe of the kinase domain, the insert or the activation loop (Fig. 3). However, this observation awaits confirmation in another cohort of patients.

A recurrent somatic p.N666S mutation in *PDGFRB* has also been found in stromal cells of patients affected with a rare lymphoproliferative disorder called unicentric Castleman disease (UCD). This mutation is located in the N-lobe of the kinase domain and triggers PDGFRβ constitutive activation [34].

Finally, a recent study identified a germline activating *PDGFRB* p.R853W variant in hereditary progressive mucinous histiocytosis, a rare type of histiocytosis transmitted in an autosomal-dominant mode [35].

Tumors of the gastrointestinal tract

Gastrointestinal stromal tumors (GISTs) are soft-tissue tumors of the gastrointestinal tract. Most cases harbor a mutation in *KIT*, which belongs to the same RTK class as PDGFR. A low proportion of sporadic cases (5–10%) present somatic mutations in *PDGFRA*. These mutations are mainly located in the activation loop (exon 18) and, to a lesser extent, in the juxtamembrane domain (exon 12) or in the N-lobe of the kinase domain (exon 14) (Fig. 3) [2, 36, 37].

In contrast to GIST, inflammatory fibroid polyps (IFPs) are benign lesions caused by excessive tissue proliferation and inflammatory cell infiltration into the lumen of the gastrointestinal tract. The PDGFRA regions affected by somatic mutations in IFP are the same as those in GIST (exons 12, 14 and 18) (Fig. 3), but they occur more frequently (at a rate of approximately 55%) [38, 39].

Germline *PDGFRA* mutations have been described in the so-called "PDGFRA-mutant syndrome" in three families with an autosomal-dominant mode of inheritance and in two unrelated individuals [40–43]. The presence of at least two IFPs (including fibrous tumors) and/or GISTs in one individual or in a family characterize this syndrome.
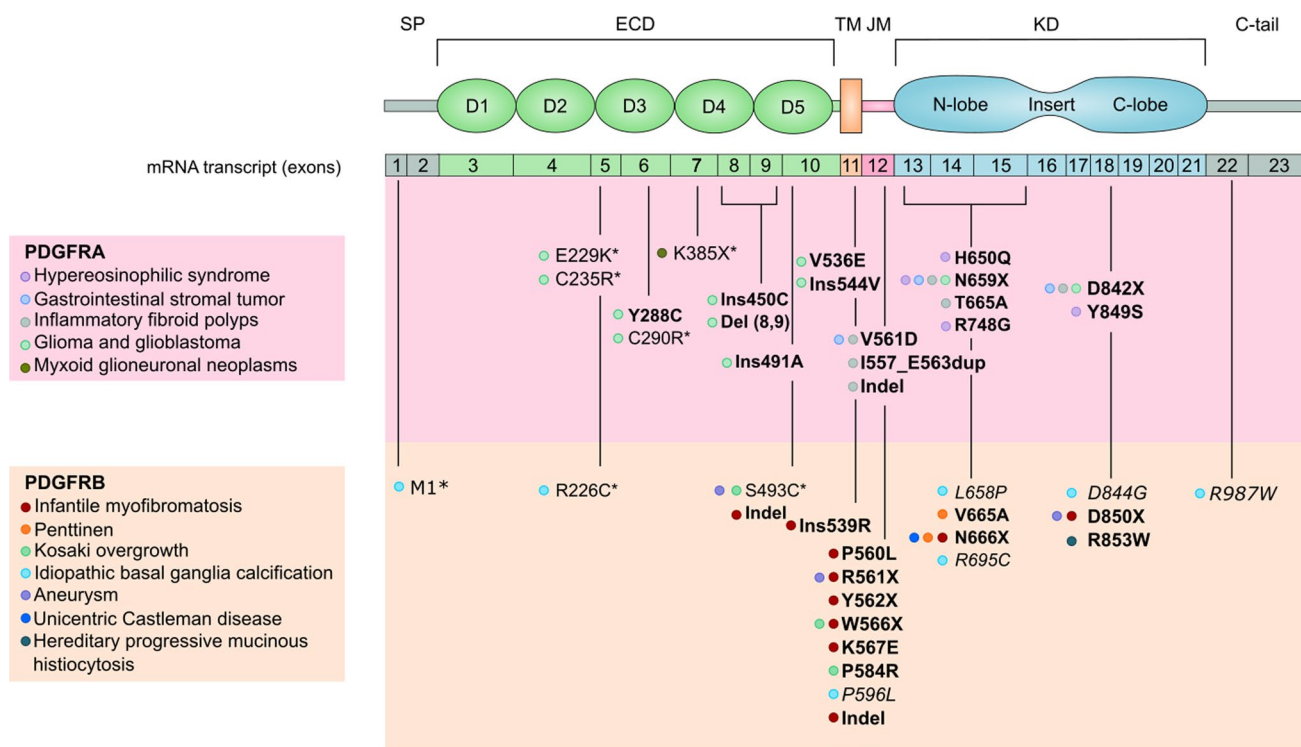
Fig. 3 Localization of *PDGFR* mutations associated with human diseases. Gain-of-function mutations are marked in bold, and loss-of-function mutations are marked in italics. Uncharacterized variants are indicated with an asterisk (*). Signal peptide (SP); extracellular domain (ECD); transmembrane (TM); juxtamembrane (JM); kinase domain (KD)

Some patients also have gastrointestinal lipomas and large hands [41]. Mutations in exon 12 (p.Y555C, p.V561D), exon 14 (p.P653L) and exon 18 (p.D846Y) have been identified. To date, this is the only disease associated with germline *PDGFRA* mutation.

Brain tumors

Both adult and pediatric forms of glioblastoma are associated with somatic alterations in *PDGFRA* [44, 45]. These variants include missense mutations, in-frame insertions or deletions, as well as gene amplification. Point mutations are located within the extracellular domain, the transmembrane and the kinase domains of the receptor (Fig. 3) [46, 47]. In children, *PDGFRA* mutations are found in approximately 37% of diffuse intrinsic pontine glioma cases, constituting a particularly aggressive subtype of glioblastoma [48]. In adults, most *PDGFRA*-amplified tumors harbor a genomic deletion of exons 8 and 9, the region coding for D4 and D5 in the extracellular part of the receptor (Fig. 3) [45]. One adult case with a gene fusion between *PDGFRA* and *VEGFR2* has also been reported [44]. In vitro and in vivo analyses have demonstrated that these oncogenic mutations constitutively activate PDGFRα [44, 45, 47].

More recently, recurrent *PDGFRA* mutations have been identified in low-grade neural tumors associated with intractable seizures, named septal dysembryoplastic neuroepithelial tumors or myxoid glioneuronal neoplasms [49–51]. These *PDGFRA* variants mostly consist of dinucleotide substitutions at codon K385 in the immunoglobulin-like module D4 of PDGFRα, which is responsible for receptor-receptor interaction and dimerization after ligand binding.

Finally, a subset of gliomas, called *IDH*-mutant gliomas, are associated with strong PDGFRα expression, in the absence of *PDGFRA* locus alteration. *IDH* mutations are responsible for epigenetic alterations and DNA hypermethylation, impairing proper gene regulation by insulators and leading to aberrant *PDGFRA* activation [52]. This may drive glioma tumorigenesis by the activation of oncogenic signaling pathways in the absence of canonical kinase mutations.

Myofibromas and infantile myofibromatosis

Myofibromas are the most common fibrous tumors in children. They consist of firm, nontender, flesh-colored nodules that may develop in any organ of the body but without metastasis or invasion of adjacent anatomical structures. The presence of multiple myofibromas defines infantile myofibromatosis (IM). Generalized IM refers to visceral involvement and has a poor outcome [53]. Most IM cases are sporadic, but several familial cases have been reported with an autosomal-dominant mode of inheritance (MIM #228550).

Whole-exome sequencing has identified germline heterozygous mutations in *PDGFRB* cosegregating with the disease in 18 out of 19 unrelated families [54–59]. The p.R561C mutation, reported in 14 of the 19 families, is the most commonly reported variant. To date, all identified germline mutations in IM affect the JM domain (Fig. 3) [54]. Functional assays confirmed that these variants confer constitutive activation of PDGFRβ [54, 60]. Furthermore, the ability of several of these variants to transform cells has been demonstrated both in vitro and in vivo [60, 61].

The p.R561C variant seems to be a weak activator of PDGFRβ in vitro compared to other described mutants [60]. Furthermore, a second somatic mutation (p.N666K), identified in a few patient lesions, shows that the presence of two variants in the same allele considerably increases receptor activity [54, 61, 62]. A "two-hit model" for familial IM was proposed, where a weak germline gain-of-function *PDGFRB* mutation affecting the JM domain needs a somatic second hit to initiate myofibroma development [61]. Furthermore, this two-hit model may explain the suspected incomplete penetrance of familial IM, as reported in three studies [57–59], in which the transmission of p.R561C, or any other weakly activated variant, would be necessary but not sufficient for disease development.

Sporadic cases of IM are more frequent. Recently, tumor sequencing analyses identified a broad catalog of gain-of-function mutations in *PDGFRB* [61–65]. Most of these variants are located in the JM and kinase domains, the classical hotspots for oncogenic mutations in RTK [61–63]. These mutations include single-nucleotide variants (SNV) as well as more complex in-frame indels and duplications in the JM domain, which are highly reminiscent of the internal tandem duplications in *FLT3* described in acute myeloid leukemia [30, 62]. Interestingly, oncogenic variants in the D5 and transmembrane domains have also been reported [62].

Kosaki overgrowth syndrome

Kosaki syndrome (MIM #616737) is a rare overgrowth syndrome described in 2015 by Takenouchi and Kosaki in two young female patients [66]. To date, a total of nine cases have been reported in the literature [66–70]. The spectrum of symptoms commonly found in patients includes postnatal and somatic overgrowth, distinctive facial features, hyperelastic and fragile skin, white matter lesions, neurologic deterioration, and myofibroma. Vascular lesions, specifically aneurysms, have also been reported in four individuals [67, 69, 70].

Sequencing analyses led to the identification of three de novo germline heterozygous mutations in *PDGFRB*. The p.P584R and p.W566R variants, reported in five and three individuals, respectively, affect the juxtamembrane part of the receptor [66, 67, 69, 70]. In vitro experiments demonstrate that both mutations confer constitutive signaling as well as transforming capacity to PDGFRβ.

Foster and colleagues [67] identified a third variant, namely, p.S493C, in one patient. Interestingly, this mutation is located in the extracellular part of the receptor within the Ig-like domain 5. Further functional investigations are necessary to confirm the impact of this mutant on receptor activity.

Penttinen premature aging syndrome

Penttinen and colleagues reported for the first time a distinctive progeroid disorder (MIM #601812) in a 10-year-old Finnish boy. The disorder is characterized by a prematurely aged appearance with lipoatrophy, epidermal and dermal atrophy along with hypertrophic lesions that include scars, thin hair, proptosis, underdeveloped cheekbones, and marked acro-osteolysis [71]. Johnston and colleagues linked Penttinen syndrome to the heterozygous *PDGFRB* p.V665A de novo mutation [72]. Functional explorations of the variant have revealed that p.V665A induces STAT3 and PLCγ phosphorylation, resulting in constitutive activation of PDGFRβ. Nevertheless, the signaling of this mutant appears to be slightly perturbed, as no phosphorylation of other classical PDGFR signaling mediator, such as SRC, AKT, and ERK, was detected. Additionally, He and colleagues observed that this mutant is a particularly strong activator of STAT1 signaling, leading to an interferon-like inflammatory response [73].

Another gain-of-function variant, p.N666S, was found in two patients affected with a severe form of Penttinen syndrome [74]. Similar to the p.V665A mutant, PDGFRβ p.N666S seems to be a particularly potent activator of STAT1 phosphorylation.

Aneurysms

Aneurysms are vascular lesions that have been reported in several patients affected with *PDGFRB*-related disorders.

The first reported case was a young girl initially diagnosed with generalized IM who had aneurysmal dilatations of the renal and iliac arteries reminiscent of fibromuscular dysplasia (FMD) [61, 75]. The tumors and the vascular wall were later shown to harbor a p.D850V somatic mutation in *PDGFRB* [61, 62]. One additional similar case was reported by Wright et al. [76].

In 2019, Karasozen and colleagues identified different somatic and activating mutations in *PDGFRB* in 4 of 6 analyzed fusiform cerebral aneurysms [77]. They suggested that the presence of these somatic variants in the cerebral vasculature disrupts proper formation of the media layer surrounding arteries and acts as a driver in the development of aneurysms. Most reported mutations are identical to those found in IM. These findings are consistent with the recent report of a fatal stroke in a patient with Kosaki syndrome as a consequence of a ruptured fusiform cerebral aneurysm [67].

Finally, aneurysms and cardiovascular lesions have been reported in a 13-year-old individual previously diagnosed with Kosaki overgrowth syndrome. In this case, echocardiogram and head and neck angiography revealed an abnormal coronary artery system with saccular aneurysms, as well as tortuosity of the cervical vertebral arteries. The patient suddenly died 6 years later, but no autopsy was performed to confirm aneurysm rupture as the cause of death [70].

In conclusion, these findings clearly establish a link between *PDGFRB* variants and aneurysms. However, further investigation is needed to determine the exact prevalence of *PDGFRB* mutations in vascular anomalies. These observations are consistent with the expression and physiological role of PDGFRβ in vascular smooth muscle cells, which migrate and proliferate upon activation of the receptor.

Definition of a mixed PDGFRB syndrome?

To date, distinct entities have been used to classify diseases related to germline *PDGFRB* gain-of-function mutations. However, many patients present symptoms overlapping between the different syndromes described above. For instance, some patients initially diagnosed with Kosaki syndrome also develop myofibroma, and a few individuals with Penttinen syndrome present overgrowth similar to Kosaki syndrome [66, 69, 78]. Among other examples, one patient harboring the variant p.N666H presented features overlapping between Kosaki and Penttinen syndromes, and the p.Arg561_Tyr562delinsH indel reported in one case of sporadic IM was also found in another individual presenting severe clinical features of IM, Kosaki, and Penttinen syndromes [62, 79, 80].

These observations suggest that a set of features might be shared by patients harboring germline *PDGFRB* gain-of-function mutations, which could be grouped in a single entity, the *PDGFRB* mutant syndrome (by analogy with the *PDGFRA*-mutant syndrome defined above). A recent study [81] has proposed redefining the spectrum of diseases associated with activating *PDGFRB* variants into two distinct but still overlapping groups: *PDGFRB*-activating variant spectrum disorder 1 and 2 (PAVS1 and PAVS2). Patients

diagnosed with IM and whose nodules regress over time are classified within the PAVS1 group. More complex syndromes involving multisystemic and progressive abnormalities are included in the second PAVS2 group. Nevertheless, the two categories are not mutually exclusive, and patients in the PAVS1 group remain at risk of developing potentially fatal comorbidities and especially aneurysms over time. Similarly, the appearance of myofibroma in patients within the PAVS2 entity cannot be ruled out. PAVS1 is associated with the weakly activated p.R561C germline variant and a range of somatic mutations, while more potent germline variants cause PAVS2. The molecular mechanism explaining the phenotypic heterogeneity among patients carrying a *PDGFRB* gain-of-function mutations remains to be fully understood.

Primary familial brain calcification

In contrast to the diseases described above, loss-of-function germline *PDGFRB* mutations have been identified in some patients with primary familial brain calcification (PFBC), previously called idiopathic basal ganglia calcification (IBGC) or Fahr disease (although this latter term should not be used in the context of *PDGFRB* variants) [82–85]. Patients with PFBC show symmetric and bilateral calcifications of hydroxyapatite in the basal ganglia and other areas of the brain, which are best diagnosed by cerebral computed tomography. These patients are often asymptomatic during childhood and young adulthood. Heterogeneous clinical symptoms appear between the ages of 30 and 50 years, including psychiatric manifestations, parkinsonism, movement and speech disorders, cognitive impairment, and seizures, among others. Movement disorder and cognitive impairment seem to be the most common clinical features. Some patients may remain asymptomatic [83, 86, 87].

Germline heterozygous *PDGFRB* mutations were found in three different families (p.L658P, p.D737N and p.M1?) [83, 85] and in apparently sporadic cases (p.R987W, p.R695C) (Fig. 3) [82–84]. Three of these mutations (p.L658P, p.R987W and p.R695C) lead to impaired PDGF-B/PDGFRβ signaling in cell culture assays [84, 88]. The p.E1071V substitution does not have a negative impact on the receptor activity, suggesting that it is not related to the disease [88].

Loss-of-function mutations can also be found in several other genes associated with PFBC. *PDGF-B* is mutated in several patients [89–94]. Two genes encoding phosphate transporters are also related to PFBC: *SLC20A2* [95–103], which encodes a sodium-dependent phosphate transporter, and *XPR1* [104, 105], encoding a transporter controlling phosphate efflux. Although *SLC20A2* mutations explain approximately 50% of PFBC cases (IBGC type 1, MIM #213600), *PDGF-B* and *PDGFRB* appear to be involved in 20% of cases (classified as IBGC4, MIM #615007, and IBGC5, MIM #615483, respectively) [86].

The link between impaired PDGF signaling and PFBC is still unclear. First, defective PDGF-B/PDGFRβ signaling might result in reduced expression of SLC20A2, leading to accumulation of phosphate in the extracellular compartment and the formation of calcification [106], a mechanism explained by the direct regulation of SLC20A2 expression by PDGF [107, 108]. Second, since PDGF-B is very important for the recruitment of pericytes during vessel formation and because pericytes are a major component of the blood–brain barrier (BBB), disruption of the BBB, allowing the formation of calcium phosphate precipitates, is a possible explanation for PFBC development [16, 86, 109, 110]. Finally, other BBB cell types may be involved, such as astrocytes [86, 111].

Interestingly, PFBC kinase domain mutations cluster with IM, Kosaki and Penttinen syndrome variants in the structure of the PDGFRβ kinase domain, as deduced from the crystal structure of the PDGFRα intracellular part [6]. This region is very close to the ATP-binding pocket.

Mouse models of impaired PDGFR signaling

Different mouse models have been generated to study in vivo the functional impact of mutations within PDGFRα or PDGFRβ.

Olson and colleagues [112] have established two models of PDGFRα conditional knock-in mice harboring either the p.D842V variant within the activation loop of the kinase or the p.V561D mutation in the juxtamembrane part of the receptor. In the embryo, these mutations promote the proliferation and migration of mesenchymal progenitor cells in the gastrointestinal tract, leading to stromal hyperplasia and polyps. A similar phenotype is observed in adult mice with mosaic activation of PDGFRα: animals develop widespread organ fibrotic lesions due to fibroblast proliferation and extracellular matrix deposition, revealing the important role of PDGFRα in the activation of signaling pathways responsible for connective tissue formation. These animals rarely develop tumors unless they are crossed with Ink4a/Arf-deficient mice, leading to sarcoma [112]. GISTs have not been documented in these mice.

Similarly, the effects of increased PDGFRβ signaling have been investigated using different knock-in mouse models. The first one consisted of a weakly activated p.D849N (corresponding to D850N in the human sequence) knock-in mutation, producing a mild phenotype [113]. Mice expressing the *PDGFRB* p.D849V mutant present growth deficiency during the second week after birth and usually die by day 14 [114]. Constitutive PDGFRβ signaling leads to vascular

smooth muscle cell proliferation while inhibiting their differentiation, and to pericyte activation with increased coverage around blood vessels. These changes in pericyte differentiation correlate with an immune response, autoinflammation, and lipoatrophy, a set of phenomena that seem to occur via PDGFRβ-dependent STAT1 activation [114, 115]. Nevertheless, this vascular phenotype does not reflect the human phenotype associated with germline *PDGFRB* mutant syndromes. These mice do not develop tumors.

The mechanism of autoinflammation through PDGFRβ-STAT1 signaling was further studied by He and colleagues [73] in several mouse models. *STAT1* knockout rescues the autoinflammatory phenotype observed in mice harboring the p.D849V variant. These animals show increased lifespan but progressively develop fibrosis and skeletal overgrowth. Although these results are reminiscent of some of the features observed in Penttinen or Kosaki syndromes, these animals do not constitute convincing models of the human diseases caused by activated *PDGFRB* mutations. Nevertheless, these findings are in line with the observation that variants associated with Penttinen syndrome (*i.e.,* p.V665A and p.N666S) are potent activators of STAT1 in vitro [73, 74]. It is important to note that the exact germline mutations identified in humans have not yet been tested in mice.

Mouse models indicate that both PDGFRα and PDGFRβ signaling act as negative regulators of adipogenesis and adipocyte differentiation. Conditional knock-in mice with a *PDGFRA* p.D842V activating mutation in adipocyte progenitors promotes the transition of these cells toward a profibrotic phenotype, causing adipose fibrosis and inhibiting their differentiation in adipocytes [116]. A similar phenotype is observed in mice harboring the equivalent *PDGFRB* p.D849V variant [73, 114]. In contrast, mice harboring a mosaic deletion of *PDGFRA* or *PDGFRB* are marked by a significant increase in adipose tissue formation [117]. The mechanism that regulates PDGFR signaling during adipogenesis remains unclear. However, this property is reminiscent of the lipoatrophy observed in some patients with Kosaki and Penttinen syndromes, which may be due to the switch of adipocyte progenitor cells toward their pro-fibrotic phenotype while inhibiting their differentiation.

A role for PDGFRβ was also suggested in myocardium regeneration through a signaling pathway involving the phosphorylation of Akt followed by EZH2-mediated *Ink4a/Arf* repression. This function was further studied using an AAV9 gene therapy vector to introduce the *PDGFRB* p.D849V variant in cardiomyocytes, to analyze heart regeneration and systolic function in mice [23]. This study provides an elegant model to evaluate the impact of PDGFR mutations in various systems.

PDGFRβ signaling in renal mesenchymal cells is essential for kidney development. In mice, specific deletion of *Pdgfrb* in these cells is responsible for impaired glomerulogenesis and death one month after birth [10]. In adults, the role of renal mesenchymal PDGFRβ signaling is assumed to be minor under physiological conditions; however, receptor activation increases in kidney diseases [118]. Mice harboring specific activation of PDGFRβ in renal mesenchymal cells progressively develop primary fibrosis but without any sign of inflammation or STAT1 activation [10]. Additionally, inhibition strategies using either specific antibodies or selective tyrosine-kinase inhibitors improve kidney lesions in various renal disease models [119–122]. Altogether, these results suggest that patients with a *PDGFRB* mutation may be at risk of developing renal disease. Interestingly, kidney failure and transplantation were reported in a complex case with generalized IM, severe hypertension and a renal artery aneurysm [123].

In conclusion, gain-of-function mutations in PDGFRα/PDGFRβ in mice seem to greatly impair the differentiation of cells of mesenchymal origin, such as adipocyte progenitors, vascular smooth muscle cells, pericytes, and renal mesenchymal cells. This promotes tissue fibrosis and organ failure, but tumors do not develop in these mice.

As described above, heterozygous loss-of-function variants have been identified in primary familial brain calcification. However, this is not observed in heterozygous *Pdgfrb* knockout mice, and the homozygous deletion of the receptor is lethal. Nevertheless, Keller et al. studied mice harboring hypomorphic mutations in the gene encoding PDGF-B. The mutant mice progressively develop brain calcifications and phenotypic features highly similar to those described in humans with PFBC [90]. These results provide strong evidence for a causative role of the loss of PDGFRβ signaling in the development of brain calcifications.

Clinical implications

Several types of drugs target PDGF receptors, including tyrosine kinase inhibitors (TKIs), antibodies and aptamers. TKIs have been approved for the treatment of various PDGFR-driven cancers.

Imatinib is a type II TKI and the first molecule described to inhibit KIT, ABL, and PDGFRs. The compound was initially developed to treat patients with BCR-ABL1-positive leukemia and, later, KIT-mutated GIST. Moreover, good response and long-term remission have been achieved in patients affected with myeloid neoplasms associated with hypereosinophilia and PDGFR gene rearrangement, such as *ETV6-PDGFRB* and *FIP1L1-PDGFRA* [29, 124–127]. Of interest, one 36-year-old man and two children diagnosed with a multicentric form of myofibroma and harboring gain-of-function variants in PDGFRβ received imatinib monotherapy, which considerably improved their quality of life [65, 80, 81]. Finally, imatinib was administered to one boy

affected with a complex syndrome related to the PDGFRB p.N666H variant [80] and in one individual diagnosed with Penttinen syndrome linked to the p.V665A variant [81]. In both cases, the treatment ameliorated several of the symptoms related to the disease. These are examples of successful application of targeted therapy using imatinib in both adults and children affected with a rare disease.

In vitro, the activity of most gain-of-function PDGFR variants is blocked when exposed to imatinib, except for *PDGFRA* p.D842V and its equivalent p.D850V mutation in *PDGFRB*, as well as p.D816V mutant in *KIT*. These mutations, which are located in the activation loop of the kinase domain, shift and stabilize the kinase in its active conformation. As a result, they decrease the affinity of type II TKIs, which act by occupying the ATP-binding pocket of the kinase in its inactive state.

Type I TKIs bind to the ATP-binding pocket of the kinase in the active conformation and are potentially able to counteract the resistance of mutations located within the activation loop. For example, crenolanib was able to inhibit the *PDGFRA* p.D842V mutation in imatinib-resistant GIST [128]. However, high activity across the human kinome associated with an increased risk of toxicity limits the routine use of this drug [129]. Avapritinib is another compound able to inhibit *PDGFRA* p.D842V activation loop mutants [129]. The drug was approved by the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) for patients with GIST harboring the *PDGFRA* p.D842V mutation.

Neutralizing antibodies such as olarutumab and rinucumab target PDGFRα or PDGFRβ, respectively [130, 131]. Phase Ib and II clinical trials initially showed promising results for olarutumab in combination with doxorubicin to treat patients with soft-tissue sarcoma [132]. However, a recent phase III study did not confirm any patient benefit [133]. An anti-PDGFRβ antibody was tested in combination with an anti-VEGF in the treatment of neovascular age-related macular degeneration. Despite promising results in vitro and in vivo, recent clinical trials failed to provide visual and anatomical improvements [130, 134]. Taken together, using anti-PDGFR antibodies in therapy as a single agent or in combination did not lead to significant improvement in clinical outcome.

PDR3 and Gint4.T are nuclease-resistant RNA aptamers designed to inhibit PDGFRα and PDGFRβ, respectively [135, 136]. These molecules act by binding the ectodomain of the receptor, preventing ligand-dependent receptor activation and signaling. Both aptamers show antitumor effects in glioblastoma cell culture. Moreover, in vitro assays show that when coupled to the receptor, Gint4.T-PDGFRB and PDR3-PDGFRA complexes are rapidly internalized and targeted to the endolysosomal system. This feature makes these two aptamers good carriers to deliver small therapeutic

molecules in specific cells [137]. However, these molecules have not yet reached the clinic.

Conclusions

Different types of cancers are driven by somatic gain-of-function mutations in *PDGFRA* and *PDGFRB*, which act as classical proto-oncogenes. In addition, *PDGFRB* variants were associated with a number of rare noncancerous diseases. Advances in deep sequencing have considerably increased the catalog of variants identified within *PDGFRB*. Germline loss-of-function mutations in *PDGFRB* have been reported in patients with primary familial brain calcification, while *PDGFRB*-activating mutations are associated with several disorders, namely, infantile myofibromatosis, Kosaki and Penttinen syndromes. More recent findings also suggest a role of somatic *PDGFRB* gain-of-function mutations in fusiform aneurysms. Some patients show a mixed phenotype overlapping with different conditions. These clinical observations shed light on the precise role of *PDGFRB* in human pathophysiology and highlight a number of differences with data collected from animal models. Most *PDGFRB* gain-of-function mutations remain sensitive to TKIs, such as imatinib, which was successfully administered to patients affected with IM or syndromic disease. However, novel therapeutic strategies are needed for several conditions described in this review, such as PFBC or glioblastoma. Many questions remain regarding the mechanisms whereby *PDGFRB* mutations cause such a variety of symptoms. Future experiments should focus on the identification of activated signaling pathways specific to some variants and the cell lineage-specific effects of those mutants.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

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