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Review

PIK3CA gene mutation induced rare vascular diseases

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ABSTRACT

The PIK3CA gene is the member of PI3K family. Although targeting the mutation of PIK3CA is a good treatment strategy for cancer, various other reasons can also worsen the cancer's progression and lead to the death of patients. However, PIK3CA can be treated as the main target that leads to the rare vascular diseases' progression. Therefore, this review will focus on the mutation of the PIK3CA gene in rare vascular diseases, including single-type vascular malformation and multiple-type combined vascular malformation. The specific mechanisms, treatment strategies of PIK3CA, and limitations of the current treatment methods for these rare vascular diseases will also be discussed in this review. Moreover, some rare conditions for the patients with rare vascular diseases will be discussed in this review.

Key words: PIK3CA gene mutation, rare vascular diseases, vascular malformation, surgical and drug therapies

1. Introduction

Rare diseases, also known as orphan diseases, represent an extensive range of disorders and conditions that are generally characterized by their low prevalence rates. According to the World Health Organization, rare disease can be defined as the condition affecting no more than one in 2,000 people (Schieppati et al., 2008). Although the individual rarity is low, rare diseases have already influenced a vast number of populations worldwide; around 263 to 446 million people are troubled by various rare diseases right now (Chung et al., 2022). There are the estimations suggesting that there are between 6,000 and 8,000 distinct types of rare diseases identified. For some of them, for example, cystic fibrosis, one famous rare disease that was distinguished in 1938, was researched until 1989 to figure out the specific gene mutation, which therefore provided more treatment methods for cystic fibrosis patients (Davis et al., 2006). However, there is still no specific and effective treatment method for rare vascular diseases right now. Rare vascular diseases is one of the major rare diseases, which include various branches. Unlike the normal pathogenic factors of vascular diseases such as oxidative stress (Madamanchi et al., 2005), inflammatory cytokines (NF-κB, JAK-STAT, and Smad) (Sprague et al., 2009), and the differentiation of vascular stem cells (Tang et al., 2012), the pathogenic factors of rare vascular diseases are mainly genetic mutation. For example, according to Lelievre et al., hereditary hemorrhagic telangiectasia (HHT) is a rare genetic disease caused by mutations affecting components of bonemorphogenetic protein (BMP)/transforming growth factor-β (TGF-β) signaling in endothelial cells (Lelievre et al., 2023); another example is the pathogenic sequence variants of COL3A1, which leads to the inheritance of vascular Ehlers–Danlos syndromes (vEDS) (Baderkhan et al., 2021).

Phosphatidylinositol 3-kinase (PI3K), the lipid kinases phosphorylate the 3' hydroxyl group of the inositol ring of phosphatidylinositol, is composited by a family of related enzymes that are encoded by a group of genes (Voutsadakis et al., 2021). Three classes are involved in the PI3K and the sub-units Class IA and Class IB were deeply studied. The genes encoding PI3K include PIK3CA, PIK3CB, PIK3CD, etc. Among them, PIK3CA is the famous gene that encodes p110α to enhance PI3K signaling and promote cell proliferation and survival. Different cancers and overgrowth syndromes are implicated with the mutation PIK3CA (Yuan et al., 2008). Somatic gain-of-function mutations in the PIK3CA gene cause PIK3CA-related overgrowth spectrum (PROS) by hyperactivating the PI3K/AKT/mTOR signaling pathway, leading to uncontrolled cell growth and

proliferation. This results in various clinical manifestations, including tissue overgrowth, vascular malformations, and neurological symptoms (Luks et al., 2015). In several cancers. such as colorectal cancer (Voutsadakis et al., 2021), breast cancer (Mosele et al., 2020), prostate cancer (Herberts et al., 2020), etc., can be found with the mutation of PIK3CA. Besides cancers, PIK3CA gene mutation can also be targeted as an important point for treatment of rare vascular diseases. Therefore, in this review, the PIK3CA gene mutation-induced rare vascular diseases will be described specifically. The treatment methods and the clinical data from research in recent years will also be expounded and discussed, as well the deficiency of the modern treatment methods in this article.

2. Single-type vascular malformation

2.1. Megalencephaly-capillary malformation syndrome (MCAP)

MCAP belongs to the PIK3CA-related overgrowth spectrum (PROS), which is a genetic disorder characterized by overgrowth of body tissues, prominently featuring an abnormally large brain (megalencephaly) and capillary malformations due to somatic mosaic gain-of-function variants in PIK3CA. According to Mirzaa et al., most individuals with MCAP syndrome experience some level of intellectual disability, with the severity varying from mild learning difficulties to profound impairments. While many patients exhibit mild to moderate developmental delays, they tend to make consistent progress, although at a slower pace than typical, and a small percentage face severe disabilities (Mirzaa et al., 2013). PIK3CA gene mutation is the pathogenic factor of MCAP. According to Tapper et al., the PIK3CA mutation at E726K would induce several major phenotypic criteria such as macrocephaly, capillary malformation (CM), and overgrowth/asymmetry; minor phenotypic criteria such as mid-line facial capillary malformation and neonatal hypotonia were also shown (Tapper et al., 2014). Moreover, a heterozygous mutation in *PIK3CA* at R115P was detected in 20% of buccal cells and 25% of skin cell in a patient that first came to the hospital at 19 weeks of gestation (Swarr et al., 2013). In addition, according to Chen et al., after being diagnosed by using the cerebrospinal fluid (CSF)-derived cell-free DNA, the high mosaic (a condition where an individual has cells with different genetic makeup due to mutations occurring after fertilization, leading to a mixture of normal and mutated cells) PIK3CA mutation at H1047T was detected (Chen et al., 2022). Atypical lymphocytes in pleural fluid with increased fluorodeoxyglucose (FDG) uptake in bilateral cervical, mediastinal, abdominal, and pelvic lymph nodes on the entire body were shown in this patient (Chen et al., 2022). Several other mutation spots of PIK3CA were reported by Davis et al. Mutations at N345I, C378Y, E726K, G1049S, G914R, and M1043I were detected by the genetic testing (Davis et al., 2019). Cardiac arrhythmia (CA), cutaneous capillary malformation (CCM), Chiari malformation (ChM), digit abnormalities (syndactyly or polydactyly) (DA), hydrocephalus without a shunt (H−), hydrocephalus with shunt (H+), hemihypertrophy, megalencephaly, and polymicrogyria were figured out as the main phenotype of 9 patients (Davis et al., 2019). According to Alamar et al., endoscopic third ventriculostomy (ETV) is an effective and safe treatment option for managing hydrocephalus associated with MCAP (Alamar et al., 2021). Surgical treatment is also a proper way for the MCAP treatment. According to Ariwodo et al., a patient with MCAP syndrome had the surgical intervention at both of the intractable hemispheric epilepsy and sagittal synostosis (Ariwodo et al., 2023). The unique case of MCAP was presented on a 7-month-old girl with MCAP linked to a PIK3CA somatic mosaic variant who developed pulmonary arterial hypertension (PAH), illustrating that PAH should be considered a severe potential complication in MCAP patients, irrespective of the absence of neonatal cardiac abnormalities (Yoh et al., 2023).

2.2. Fibro-adipose vascular anomaly (FAVA)

FAVA is a painful, rare vascular malformation primarily affecting children, characterized by fibrous tissue and immature blood vessels developing within the muscles and nerves, often leading to localized mass, severe pain, and limb contractures. According to Luks et al., as early as 2015, they figured out the common mutation at E545K, Q546K, E542K, and H1047R from 5 out of 8 FAVA patients. According to Driskill et al., a case study of a 23-year-old male with FAVA associated with a somatic activating PIK3CA mutation at the H1047R (Driskill et al., 2022). Surgical is one of the most common strategies for FAVA treatment. One case reported details about a 26-year-old woman with FAVA, whose diagnosis was confirmed through radiological and histopathological exams and who saw significant improvement in pain and mobility following an en-bloc resection of the thigh mass (Parmar et al., 2022). Moreover, endoscopic surgery was also a good strategy for FAVA treatment. According to Wang et al., endoscopic surgery is a minimally invasive, effective, and safe method for treating subcutaneous vascular malformations and intramuscular FAVA. This technique has the potential to become the new standard, as it minimized wound complications and reduced recovery time for patients undergoing resection of benign soft-tissue lesions. Oral drug treatment is also an essential strategy for FAVA treatment. According to Al-Huniti et al., after 11 children treated with sirolimus, the initial symptoms was improved and pain were dramatically reduced (Al-Huniti et al., 2023). In further research, Wang et al. declared that the sirolimus therapy to treat FAVA showed promising results in lesion shrinkage, symptom relief, and complete or partial responses in patients without serious adverse effects, suggesting sirolimus as an effective and safe treatment option for FAVA (Wang et al., 2023). The effect of sirolimus was

also confirmed by Chaudhary et al., in which there were no major adverse effects shown on three children patients (Chaudhary et al., 2023). Another team also declared that after the surgery-based comprehensive treatment, oral sirolimus or alpelisib helped patients deal with unresectable lesions and major nerve involvement (Wang et al., 2023). These studies highlighted the importance of an integrated approach incorporating radiology, histology, and genetic findings for accurate diagnosis and treatment of FAVA.

2.3. Others

Generalized lymphatic anomaly (GLA) is a rare and complex lymphatic disorder that was induced by the mutation of PIK3CA. Basing on the five tissue samples, four distinct somatic PIK3CA variants E542K, Q546K, H1047R, and H1047L were found, which further induce the hyperactivation of the PI3K–AKT–mTOR pathway; moreover, from the in vitro finding, sirolimus could be used to inhibit the active form of PIK3CA at H1047R (Rodriguez-Laguna et al., 2019). According to Khullar et al., a 7-year-old patient underwent diagnosis and treatment for GLA-induced dry cough, breathlessness, and knee pain, with imaging revealing a low-density soft tissue mass in the mediastinum and multiple lytic bone lesions. Treatments include surgery, medication, and chemotherapy, using sirolimus to inhibit lymphangiogenesis and reduce lymphatic endothelial cell growth (Khullar et al., 2022; Ramallo et al., 2023).

Diffuse capillary malformation with overgrowth (DCMO) is a single vascular malformation disease in which the skin, subcutaneous adipose, and endothelial cells are enriched with the variants; facial asymmetry, macrocephaly/megalencephaly, hypotonia, hydrocephalus, and developmental delay were also pretty common in DCMO patients (Goss et al., 2020). According to Goss et al., two PIK3CA mutation locations at G106V and D350G were found in two female patients with CM in their trunks and extremities, in which the D350G was not documented by any research; however, any hotspot variants of PIK3CA were not found (Goss et al., 2020). In addition, according to Chen et al., two cases with the PIK3CA mutation reported at M1043V and C378Y were reported in 2024 (Chen et al., 2024). Therefore, it's obvious the mutation of PIK3A in DCMO is shown at non-hotspot. A case reported by Fageeh et al. showed a one-year-old boy with no medical history presented with persistent birth-present skin lesions and widespread non-scaly reticulated erythematous patches and therefore led to a diagnosis of DCMO (Fageeh et al., 2023).

3. Multiple type combined vascular malformation

3.1. Klippel-Trenaunay syndrome (KTS)

KTS is the rare congenital vascular disease caused by capillary malformation, venous varicosities, bony or soft tissue hypertrophy, and other reasons (Permatananda et al., 2021). According to Anderson et al., almost half of 410 KTS patients had skin-related complications, which were induced by CM, venous malformation (VM), and/or lymphatic malformation (LM) (Anderson et al., 2021); Similarly, Larson et al. declared that after checking the spinal neuroimaging of 116 KTS patients, 19 patients were diagnosed as neurovascular anomalies, 5 patients were considered spinal cord cavernous malformations (CMs), 14 patients were diagnosed as paraspinal or epidural venous malformation, and 4 patients were defined as arteriovenous shunts (AVS) (Larson et al., 2021). PIK3CA mutation is the major reason that leads to KTS, which therefore diagnosis KTS as the PROS rather than a distinct diagnostic entity (Vahidnezhad et al., 2016). According to Luks and Kurek et al., the most common mutations of PIK3CA in KTS patients were E542K, E545K, H1047R, and H1047L (Luks et al., 2015; Kurek et al., 2012). This statement was confirmed by Sasaki in later research. After the NGS (next-generation sequence)-based sequencing of the PIK3CA gene acquired from the tissue samples of 9 female and 5 male patients, 12 out of 14 patients were detected with the PIK3CA missense mutation (Sasaki et al., 2023) with capillaro-venous malformation (CVM) or capillaro-lymphatico-venous malformation (CLVM). Among the 12 patients, 8 patients were found with the hotspot mutations at E542K, E545K, H1047R, and H1047L, and the non-hotspot variants C420R, Q546K, and Q546R were identified in the rest of 4 patients (Sasaki et al., 2023). Due to the mutation in PIK3CA, KTS could therefore develop with cancers, such as non-small-cell lung cancer (NSCLC) and keratinizing squamous cell carcinoma (Serio et al., 2023). Several treatment methods were developed by the researchers. Superficial and deep venous interventions such as endovenous laser therapy, ultrasound-guide sclerotherapy, endovenous stenting, popliteal vein release, and valvuloplasty were safe and significant in improving the condition in KTS patients; moreover, the lliofemoral venous stenting was also recommended to the KTS patient as a treatment strategy (Saleem et al., 2022). Outflow coil embolization with sclerotherapy, endovenous laser therapy (EVLT), radio-frequency ablation (RFA), and mechanochemical ablation were proved to be effective treatments for lateral marginal vein (LMV) in KTS as well (Fereydooni et al., 2019). According to Wen et al., 7 KTS patients were diagnosed with subclavian-jugular venous angel activity by lymphoscintigraphy, which led them to do thoracic duct decompression and helped them have symptomatic relief. Thus, lymphoscintigraphy is a good method for KTS diagnosis (Wen et al., 2021).

3.2. Congenital vascular malformations (CVMs)

CVMs are defects in the blood vessels present at birth, which have been increasingly linked to mutations in the PIK3CA gene. The PIK3CA gene encodes the catalytic subunit p110α of phosphoinositide 3-kinase (PI3K), a key regulator of various cellular functions, including growth,

proliferation, and survival. Mutations in PIK3CA lead to hyper-activation of the PI3K/AKT/mTOR pathway, which is crucial for vascular development and homeostasis. This hyperactivation results in abnormal blood vessel formation and maintenance, contributing to the development of CVMs. CM, LM, and combined malformations such as capillary-lymphatic-venous malformations were shown in CVM patients (Kim et al., 2017). According to Tuleja et al., although, among 457 patients, 79% of patients were diagnosed as simple CVMs or the simple CVMs combined with other anomalies, the ratio of multiple malformation CVMs is still 21% of the whole set. Bleeding and skin ulceration in arteriovenous malformations, localized intra-vascular coagulopathy in venous malformations, and infectious complications in lymphatic malformations were the main clinical problems for CVMs diagnosis, but for the CVMs patients with other anomalies, the limb length difference appeared (Tuleja et al., 2023).

3.3. Capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry of face and limbs, and partial/generalized overgrowth (CLAPO) syndrome

CLAPO is a part of PROS presented with congenital capillary malformation. Based on the research by Watson et al., lower lip CM and face/neck LM and lip and face or generalized overgrowth syndrome were always shown by CLAPO patients (Watson et al., 2022). Several gene mutation spots of PIK3CA were figured out by the Rodriguez-Laguna team. According to Rodriguez-Laguna et al., after analyzing the PIK3CA mutation in six patients (a total of nine), five distinct mutations in the PIK3CA gene were identified: one hotspot mutation E542K and two recurrent gain-of-function mutations H1047L and C420R. A mutation previously associated with macrodactyly A115P was also found (Rodriguez-Laguna et al., 2018). In addition, a novel somatic PIK3CA mutation at F83S that has not been previously described in developmental disorders was also found (Rodriguez-Laguna et al., 2018). Sirolimus was confirmed as one effective treatment method for CLAPO treatment. González-Hermosa et al. declared that after 13 months of sirolimus treatment, the size of the cervicofacial lymphatic malformation was reduced and no variations in shape or size in the lower lip's capillary malformation were observed; moreover, after 16 months of treatment, no side effects appeared (González-Hermosa et al., 2019). Cerejeira et al. declared that after using the pulsed dye laser strategy for CLAPO treatment, the remarkable erythema reduction was observed in the seven patients and the side effect was barely found in these patients (Cerejeira et al., 2022).

3.4. Capillary-lymphatic-venous malformation (CLVM)

CLVM is a complex type of vascular malformation that involves abnormalities in the capillaries, lymphatic vessels, and veins. This condition is part of the spectrum of combined vascular malformations, characterized by the presence of multiple types of malformed blood vessels. (Rodríguez-Laguna et al., 2022). According to Le Cras et al., after extracting the DNA from isolated endothelial cells (EC) of 7 CLVM patients, the somatic activating mutations at the hotspots at E542K, E545R, E545K, and H1047R were found, which suggested that the lesion presented in the vascular anomaly was induced by the PIK3CA mutation (Le Cras et al., 2020). The case reported about combined CLVM in a 12-month-old female with a lymphatic-venous malformation (LVM), classified as a CLVM by the International Society for the Study of Vascular Anomalies (ISSVA). The patient was treated with sirolimus and sclerotherapy instead of surgery, which revealed the importance of accurate vascular anomaly classification and imaging for guiding proper treatment and referrals (Castro et al., 2021).

3.5. Congenital lipomatous overgrowth with vascular, epidermal, skeletal, and spinal anomalies syndrome (CLOVE)

CLOVE is a recently identified overgrowth disorder. It is clinically marked by congenital lipomatous overgrowth (CLO), vascular anomalies (V), epidermal nevi (E), and skeletal deformities (S). This syndrome presents a distinct combination of tissue overgrowth and vascular abnormalities, often evident at birth (Alomar et al., 2019). According to Collins et al., a pathogenic somatic missense mutation in PIK3CA at E542K was detected in a 17-year-old boy diagnosed with CLOVE (Collins et al., 2021). The other PIK3CA mutation at H1047R was detected by Pagliazzi et al., in which the mosaic gain-of-function mutation of the PIK3CA gene at H1047R was detected (Pagliazzi et al., 2021). In 2022, after extracting the DNA from a 2-year-old patient, Garreta Fontelles et al. also found the mutation of the PIK3CA gene at H1047R (Garreta Fontelles et al. 2022). In the three cases, alpelisib was used for the treatment, and based on the result, the symptoms involved pain, inflammation, and vascular malformation, etc., were all relieved. Furthermore, according to De Grazia et al., sirolimus was used for the CLOVE treatment and showed good clinical response with better physical mobility, less pain, decreased number of hospitalizations, and disappearance of lymphorrhea (De Grazia et al., 2019). Miransertib was used for the CLOVE treatment as well. According to Forde et al., after 22 months of miransertib treatment, decreasing in volumes of fatty overgrowth, alleviation of respiratory compromise, and improvement in seating and lying posture were observed. In addition, novel mutation spots of PIK3CA caused CLOVE syndrome were kept figured out (Forde et al., 2021). According to Yan et al., a novel somatic frameshift mutation at c.3206_3207insG (p.X1069Trpfs*4) was identified in the genomic DNA extracted from the patient's vascular malformation sample (Yan et al., 2021).

This mutation alters the canonical stop codon of the PIK3CA gene and was predicted to result in an extended protein with four additional amino acid residues. On the other hand, the detection of CLOVE is also important. Rana et al. declared that the radiological characteristics of CLOVES syndrome, as well as the distinguishing ultrasound features of other similar syndromes, have been thoroughly detailed in the literature. These imaging findings help in accurately diagnosing and differentiating CLOVES from other overgrowth and vascular anomaly syndromes (Rana et al., 2022).

4. Treatment strategies

The treatments for the PIK3CA gene mutation-induced vascular malformation are relatively simple. Different surgical methods are the main choice for the rare vascular patients induced by the PIK3CA gene. Drug therapy was not always selected as the first choice but for post-operation. Here is the table listing the mutation spots of each disease described in the previous parts; treatment methods and phenotype are also listed in the table (Table 1).

Among all the cases presented in recent years, sirolimus was the most useful drug for the clinical treatment. Sirolimus (rapamycin) was first developed for renal transplantation patients to do long-term therapy (Kahan et al., 2001), which was found to inhibit the mTOR in the PIK3CA gene mutation-induced PROP and vascular malformation (Adams et al., 2019). In cells, sirolimus binds to the immunophilin FK binding protein 12 (FKBP-12), which in turn inhibits the activation of mTOR. This inhibition results in the obstruction of several signal transduction pathways, thereby inhibiting downstream protein biosynthesis, cell proliferation, and angiogenesis (Guertin et al., 2007). PIK3CA gene mutation-induced rare vascular disease is not the unique target of sirolimus treatment. According to Levan et al., after taking the sirolimus therapy, 12 patients had less pain and improvement in anemia and GI bleeding (Levan et al., 2022). Siolimus was the first choice for the FAVA, CLVM, GLA, and CLAPO treatment without bad side effects. Miransertib is the oral, allosteric inhibitor of AKT, which has the anti-proliferative activity in primary fibroblasts in the presence or absence of growth factors (Ranieri et al., 2018); alpelisib is the PI3Kα inhibitor, and it can reverse abnormal AKT phosphorylation, correct cell morphology, and normalize extracellular fibronectin levels (Singh et al., 2024). The two drugs were used in other PIK3CA gene mutation-induced diseases such as CLOVE syndrome (Martinez-Lopez et al., 2017), fbroadipose or facial infltrating lipomatosis (Canaud et al., 2021), and fbroadipose hyperplasia or overgrowth/ hemihyperplasia-multiple lipomatosis (Keppler-Noreuil et al., 2015), etc. Using the alpelisbi on FAVA treatment was also conducted by one of the recent study, but these two drugs were still not the first choice for the other PIK3CA mutation-induced rare vascular diseases, expect CLOVE. Here, Table 2 concludes the characteristics and differences of the three PIK3CA inhibitors.

Table 1. List of mutation spots, phenotype and the treatment methods for each of PIK3CA induced rare vascular diseases.

Diseases	Mutation Spots/type	Phenotype	Treatment Methods
MCAP	E726K, R115P, H1047T, N345I, C378Y, G1049S, G914R, and M1043I. Gain of function	CA, CCM, ChM, DA, H+, H–, macrocephaly, CM, and overgrowth/asymmetry, etc.	Surgical intervention such as endoscopic third ventriculostomy (ETV)
FAVA	E545K, Q546K, E542K, and H1047R Gain of function	Fibrous tissue and immature blood vessels developing within the muscles and nerves, localized mass, severe pain, and limb contractures.	Endoscopic surgery, Sirolimus (Rapamycin), Alpelisib
GLA	E542K, Q546K, H1047R, and H1047L Gain of function	Breathlessness, low-density soft tissue mass in the mediastinum and multiple lytic bone lesions	Surgery, Sirolimus
DCMO	G106V, D350G, M1043V, and C378Y Gain of function	CMs, facial asymmetry, macrocephaly/megalencephaly, hypotonia, hydrocephalus, and developmental delay.	Not discussed
KTS	E542K, E545K, H1047R, H1047L, C420R, Q546K, and Q546R Gain of function	CM, VM and/or LM, cord cavernous malformations, arteriovenous shunts	Endovenous laser therapy, ultrasound-guide sclerotherapy, popliteal vein release, and valvuloplasty, etc.
CVMs	Not discussed	CM, LM, and combined malformation (e.g. capillary-lymphatic-venous malformations)	Not discussed
CLAPO	E542K, H1047L and C420R, R115P, and F83S Gain of function	Capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry of face and limbs, and partial/generalized overgrowth	Sirolimus, Pulsed dye laser
CLVM	E542K, E545R, E545K, and H1047R Gain of function	Complex type of vascular malformation that involves abnormalities in the capillaries, lymphatic vessels, and veins	Sirolimus Sclerotherapy
CLOVE	E542K, H1047R, X1069T Gain of function	Congenital lipomatous overgrowth, vascular anomalies, epidermal nevi, and skeletal deformities	Alpelisib Sirolimus

Table 2. Characteristics and differences of the three PIK3CA inhibitors.

PIK3CA inhibitors	Characteristics
Sirolimus	mTOR inhibitor, for vascular malformations and overgrowth disorders.
Miransertib	Oral, allosteric inhibitor of AKT, anti-proliferative activity in primary fibroblasts in the presence or absence of growth factors. Only used in CLOVE but not in other PIK3CA gene mutation-induced rare vascular diseases.
Alpelisib	As the PI3Kα inhibitor, alpelisib could reverse abnormal AKT phosphorylation, correct cell morphology, and normalize extracellular fibronectin levels. Used in FAVA and CLOVE treatment.

5. Discussion

PIK3CA encodes the p110α catalytic sub-unit of phosphatidylinositol-4,5-bisphosphate 3-kinase. This protein is a part of the PI3K enzyme, which plays a role in many important functions within cells, including cell proliferation, differentiation, migration, and survival (Graupera et al., 2008). The PIK3CA gene mutations primarily affect cell growth and differentiation by activating the PI3K signaling pathway. These mutations tend to enhance PI3K signaling, stimulate downstream AKT signaling pathways, promote growth factor of independent cell, and increase cell invasion and metastasis. However, when PIK3CA mutations occur, they can cause an aberrant activation of the encoded p110α protein, leading to a loss of the normal regulatory mechanisms of the PI3K signaling pathway. This allows the pathway to be activated without growth factors, supporting excessive cell growth and abnormal differentiation (Hafner et al., 2007). However, although the mutation of PIK3CA was found in these rare vascular diseases, it may not be the major factor contributing to the progression of the diseases. According to Hori et al., correlation between PIK3CA gene mutation status, clinical pathological features, and immunohistochemical expression of the mTOR pathway in FAVA was studied. The investigation revealed that even in the absence of PIK3CA mutations, the clinical manifestations and histological analysis results of FAVA remain similar. which provides important insights into understanding the pathophysiology of FAVA and potential treatment methods (Hori et al., 2022). Therefore, although the PIK3CA is the important index for PROP, the result of the genetic test on the FAVA patients cannot be considered as the single standard for FAVA diagnosed and further research is needed. Moreover, the finding of novel drugs for these rare vascular diseases is difficult. Taselisib is the small molecule phosphoinositide 3-kinase (PI3K) inhibitor that selects α, δ, and γ isoforms of PI3K as the targets, which was initially developed for breast cancer (Dent et al., 2021). Luu et al. stated that to test the six-month tolerability and efficacy of low-dose taselisib, 19 patients were gathered to test dose-limiting toxicity (DLT). The result declared that the patients consumed with the 1mg cohort had no adverse reaction; thirteen patients had pain reduction, chronic bleeding resolution, and functional improvement. Only two patients experienced DLT due to the complication. However, based on the registered and approved TOTEM trial, the low-dose taselisib has an unfavorable safety profile on KTS and CLOVE treatment (Luu et al., 2021). In addition, the combination between two individual PIK3CA induced rare vascular diseases is rare but existed. According to Ivars et al., four unrelated patients were found with characteristic findings of CLAPO and MCAP syndrome (Ivars et al., 2020). Therefore, in spite of the fact that the pathogenic factor is the same, the differences in the mechanism between PIK3CA gene-mutation induced rare vascular diseases and other PIK3CA mutation related diseases needed more research.

6. Conclusion

In conclusion, this review includes the research in recent years about the PIK3CA gene mutation-induced rare vascular diseases. Although the treatment strategies for the rare vascular diseases are becoming mature and the drug development on PIK3CA inhibitors has already given patients better choices, the rare situation and some of the branches of the disease still cannot be handled. But, along with the patient registries and networks that are being established to aid research and the development of new treatment options, new cases with diseases will be reported and shared easier, which will attract more researchers to focus on them to figure out better options for the patients.

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Author contributions

Meng Gu and Xuanzhe Zhu contributed to the design and wrote the manuscript. Yizhun Zhu supervised the study and revised the manuscript, and other people contributed to literature searching and chart drawing. All authors have read and agreed to the published version of the manuscript.

Conflict of interests

The authors declare no conflicts of interest.

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