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Current Understanding of Klippel-Trenaunay Syndrome: A Review Article

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Abstract

Klippel-Trenaunay Syndrome (KTS) is a rare congenital disease that causes improper lymph, capillary, and venous development that leads to malformations. The disease also causes hypertrophy of soft and bony tissues that, along with lymphedema and the previously stated malformations, causes localized enlargement. The most likely location for this localized enlargement is in the lower extremities. The genetic mutations associated KTS are within the Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA) and Angiogenic Factor With G-Patch And FHA Domains 1 (AGGF1) genes. These mutations result in enhanced cell proliferation (angiogenesis). Current treatments for KTS are focused on preventative measures (compression and laser treatment). If those are not adequate, surgery is the next option involving removal of vascular malformations and the associated excess tissue (including sclerotherapy, debulking procedures, and last resort amputation). This review article evaluates current developments in our understanding of the genetics, physiology, and anatomy of KTS in order to investigate the development of better treatments for KTS.

Keywords: Klippel-Trenaunay Syndrome, hypertrophy, venous malformations, PIK3CA gene, AGGF1 gene

Introduction

Research on Klippel-Trenaunay Syndrome continues on a disease that has no cure. This disease is characterized by the triad of capillary malformations, venous malformations, and bony or soft tissue hypertrophy (Jacob et. al. 1998). Abnormal varicosities, that are usually lateral, are common in KTS patients as well (Glovkzki & Driscoll 2007). The venous malformations are centralized in the lower extremities in the vast majority of patients (Cohen 2000). Hypertrophy of the affected areas is mainly determined by lymphedema and venous-lymphatic malformations (Brandigi et. al. 2018). Lymphatic stasis is the cause of edema in enlarged areas and can be treated primarily with compression (Samuel & Spitz 1995).

In regard to the development of KTS, current research shows that the PIK3CA mutations that cause malformations arise during embryogenesis (Luks et. al. 2015). Port wine stains and hypertrophy of the effected limb is present as early as 38 weeks of age (Pereira et. al. 2017). KTS occurs sporadically with equal sex distribution across the sexes. However, familial occurrences have been infrequently observed suggesting that the disease can be inherited (Oduber et. al. 2008). Recent identification of potential genetic causes has grouped KTS into the PIK3CA-related overgrowth spectrum or PROS (Keppler-Noreuil et. al., 2015).

Materials and methods

The research was done for this scientific article via searches through scientific article databases, such as Pubmed and Google scholar, to obtain sources dating from 1985 to 2018. The research was primarily done by searching the keywords 'Klippel-Trinaunay Syndrome', 'PIK3CA gene', 'AGGF1 gene', 'KTS treatment', 'mTOR', and 'Sirolimus'. All the articles used were peer reviewed articles in the English language published in academic journals.

Genetic Mutations associated with KTS

KTS is caused primarily by two genes, the PIK3CA and AGGF1 genes. The PIK3CA gene encodes for the catalytic subunit Phosphatidylinositol-4,5-Bisphosphate 3-Kinase (PI3K), made up of the p85α regulatory subunit and p110α catalytic subunit proteins This signaling pathway is coupled to a tyrosine kinase receptor which is activated when its ligand binds. In response to this activation, the PI3K converts phosphatidylinositol (4,5)–bisphosphate (PIP2) to phosphatidylinositol (3–5) -triphosphate (PIP3). This conversion

can be reversed by the tumor suppressor protein Phosphatase and tensin homolog (PTEN). PIP3 then activates Protein Kinase B (AKT) by phosphorylation. The phosphorylated AKT can then deactivate the tumor suppressor protein tuberous sclerosis (TSC1/TSC2). Without the suppression of TSC1/TSC2, the mammalian target of Rapamycin (mTOR) alters causing angiogenesis tissue overgrowth. However, mTOR can be inhibited by Rapamycin (Figure 1).

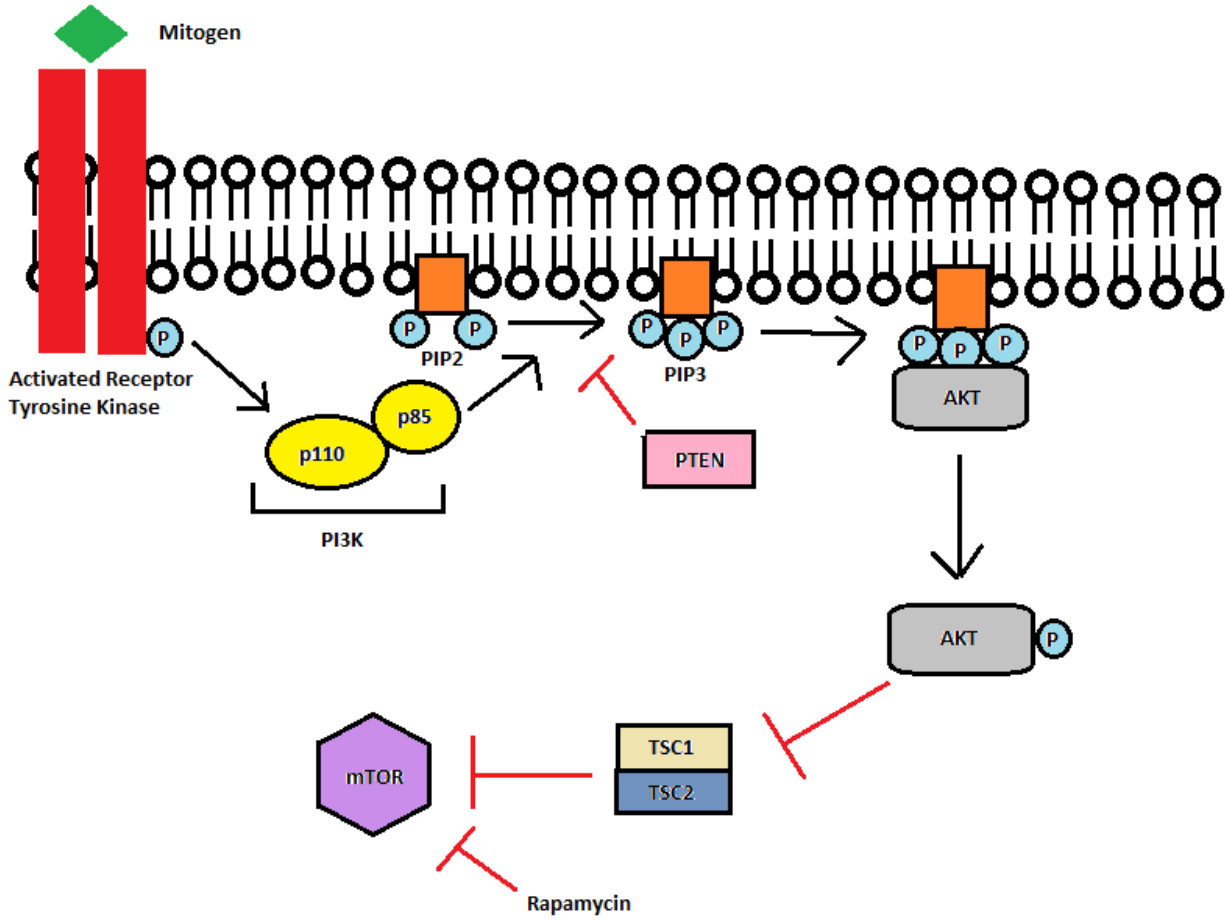

Figure 1
PI3K-AKT pathway associated with overgrowth in KTS

In KTS patients, changes in the PIK3CA gene are involved with the angiogenesis and tissue overgrowth. In particular, a missense mutation in PIK3CA at the p110α catalytic subunit was observed in patients with KTS (Samuels & Waldman 2010). This leads to an excessive activation of mTOR that affects vascular cell growth in KTS patients (Vahidnezhad et. al. 2016).

The AGGF1 gene also appears to be associated with the angiogenesis in KTS patients. In this case, the mutation is at the 5q13.3 breakpoint (Tian et al. 2004). Variants in the AGGF1 gene are association with a susceptibility for KTS, specifically the two variant single nucleotide polymorphisms rs13155212 and rs7704267 (Hu et al. 2008). The AGGF1 SNP E133K has also been suggested to be associated with KTS due to the resulting change in phosphorylation state of AGGF1 which results in venous malformations (Tian et al. 2004). However, the association between the E133k variant of AGGF1 and KTS is weak due to its presence in healthy controls. Thus, this polymorphism may be rather common rather than specific to KTS (Barker et al. 2006). Overexpression of the AGGF1 gene increases expression of venous gene markers flt4, dab2, and ephB4 and activated AKT (Chen et. al. 2012). Later studies confirm the finding that the AGGF1 gene can activate AKT, suggesting that AKT activation is responsible for angiogenesis and vascular development when mediated by AGGF1 (Zhang et al. 2016).

Alternatively, KTS may be caused by several gene mutations that have angiogenesis functions and other growth regulations which may explain the variability from patient to patient in phenotype and symptom expression (Oduber et. al. 2008). A translocation at t(8;14)(q22.3;q13) has also been suggested as a possible genetic cause for the vascular and tissue overgrowth (Wang et. al. 2001). KTS cases are sporadic yet there are some rare cases in which autosomal dominant inheritance seems to be present suggesting the sporadic mutations that cause KTS can be passed on (Ceballos-Quintal et. al. 1996).

Treatment of KTS

Management of KTS continues to be primarily non-invasive, such as compression and laser treatment, yet surgical treatment via excision of symptomatic varicose veins on KTS patients that have patent deep veins resulted in significant clinical improvement of those patients (Noel et. al. 2000). In 1991, invasive surgical treatment were rarely used and were controversial (Gloviczki et. al. 1991). The best means of controlling KTS has been compression (Baskerville et. al. 1985). This continues currently as the most common method for conservative management of the disease (Glovkzki & Driscoll 2007) due to its ability to reduce swelling via decreasing edema caused by lymphatic stasis (Samuel & Spitz 1995).

Several new treatments and changes in management have been implemented in recent years to treat the disease. The usage of a pulse-dye laser has been shown to treat KTS with no reoccurrence when it was used within 2 weeks after birth (Rahimi et. al. 2017). Though patients with KTS were often screened for Wilms tumor due to a perceived risk of developing the cancer, no link between Wilms tumor and KTS has been found and thus

this screening is unnecessary (Greene et. al. 2004). Sirolimus (Rapamycin) is being studied for patients with vascular malformations due to its ability to inhibit mTOR (Schlögel et. al. 2018), a pathway that functions to drive proper cell proliferation and growth via the regulation of ribosomal biogenesis and protein translation (Tee & Blenis 2005). Studies on several PROS patient cells via in vitro tests have shown that Sirolimus has a weak anti-proliferative effect (Ranieri et. al. 2018).

Conclusion

Though the disease remains incurable, the developments in understanding and treatment of KTS have made managing the disease much easier. Understanding of the genetics that underlie KTS has greatly increased in the last few years and with this increase in understanding has come available means of treating the disease, such as with the drug Sirolimus, not previously known. Sirolimus seems to be the best drug option available for treating KTS currently and further research into its full effects, both short and long term, upon KTS patients will allow for the drug to be truly determined as a safe and reliable drug option for the chronic disease. More research into other means of altering the PIK3-AKT pathway and inhibiting the effects of the mutated AGGF1 and PIK3CA genes will allow for other drug and treatment options of managing KTS to be available.

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Conflict of Interests

The author has no conflict of interests to declare.

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