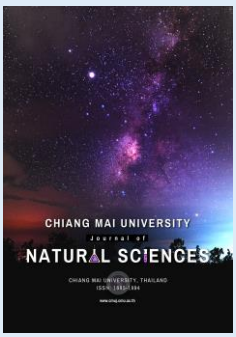

Editor:
Wasu Prathum-Aree,
Chiang Mai University, Thailand

Article history:
Received: May 3, 2022;
Revised: July 22, 2022;
Accepted: August 11, 2022;
https://doi.org/10.12982/CMUJNS.2022.054

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Review article

Gene Mutations in the FGF-MAPK Signaling Pathway and Targeted Therapy in Ameloblastoma

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Abstract Ameloblastoma is one of the most common odontogenic tumors in Asia. In the past decade, many studies have shown gene mutations in the mitogen-activated protein kinase (MAPK) signaling pathway, especially on an extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway. Mutations of *fibroblast growth factor receptor 2 (FGFR2), rat sarcoma virus (RAS),* and *B-rapidly accelerated fibrosarcoma (BRAF)* are able to cause a continuous activation of the ERK1/2 signaling pathway, hence uncontrolled tumor cell proliferation. Due to the ERK1/2 signaling pathway role in cell growth and cell survival, upregulation of this pathway can cause approximately one-third of human tumors including ameloblastoma. After the discovery of gene mutations in several cancers, many inhibitors have been designed to target these mutations. We, here, reviewed the alteration of the FGF-MAPK signaling pathway in ameloblastoma and targeted treatment used as an adjuvant or neoadjuvant therapy for ameloblastoma especially in cases where wide surgical resection is needed.

Keywords: Genetic, Growth factor, Mutation, Targeted therapy

Funding: Research Funding for graduate students from Faculty of Dentistry and Chiang Mai University Presidential Scholarship, Chiang Mai University, Thailand.

Citation: Boonsong, N., Laosuwan, K., Kitkumthorn, N., Lapthanasupkul, P., Thosaporn, W., Iamaroon, A., 2022. Gene mutations in the FGF-MAPK signaling pathway and targeted therapy in ameloblastoma. CMUJ. Nat. Sci. 21(4): e2022054.

INTRODUCTION

Ameloblastoma is a benign, slow-growing, and locally invasive odontogenic tumor. It is one of the most common odontogenic tumors in Asia (Dhanuthai et al., 2012; Saghravanian et al., 2016). Although the etiology of ameloblastoma is unclear, previous studies have implicated that dysregulation of cell cycle, apoptosis, tumor suppressor proteins, osteoclastic mechanism, matrix metalloproteinase activity, and certain signaling pathways involve in the pathogenesis of ameloblastoma (You et al., 2019). Recent studies have shown gene mutations particularly of *B-rapidly accelerated fibrosarcoma* (*BRAF*) in the extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway, a part of the mitogen-activated protein kinase (MAPK) signaling pathway, may play a role in the etiology of ameloblastoma. Once *BRAF* is mutated, a continuous activation of the ERK1/2 signaling pathway follows, leading to autonomous cell proliferation (Guo et al., 2020). Approximately one-third of human tumors including ameloblastoma are caused by mutations in the ERK1/2 signaling pathway (Uehling and Harris, 2015). Moreover, the ERK1/2 signaling pathway may play an important role in tumor invasion, angiogenesis, and metastasis (Guo et al., 2020). After the discovery of gene mutations in several cancers, many inhibitors have been designed to target these mutations (Uehling and Harris, 2015). A few case reports of using RAF and mitogen-activated protein kinase kinase (MEK) inhibitors in ameloblastoma have shown a reduction in tumor sizes. Collectively, these inhibitors are suggested as an adjuvant or neoadjuvant targeted therapy in ameloblastoma to help in improving functions and esthetics in patients with ameloblastoma (Fernandes et al., 2018; Kaye et al., 2015).

Ameloblastoma

Ameloblastoma is a benign, slow-growing, and locally invasive odontogenic tumor. Ameloblastoma is one of the most common odontogenic tumors, believed to arise from rests of the dental lamina, a developing enamel organ, the epithelial lining of an odontogenic cyst, or the basal cells of the oral mucosa (Neville BW et al., 2016; Saghravanian et al., 2016; Konchanthes and Chamusi, 2018). According to The World Health Organization (WHO) Classification of Odontogenic Tumors in 2017, apart from the conventional ameloblastoma, there are other variants, including unicystic ameloblastoma, extraosseous/peripheral ameloblastoma, and metastasizing ameloblastoma (El-Naggar et al., 2017).

Ameloblastoma, also known as multicystic/solid ameloblastoma, occurs in a wide range of ages but is more common in the third to the fifth decades of life with no significant gender predilection. Approximately 10–15% of ameloblastoma occurs in the younger population (Effiom et al., 2018). The mandible, especially in posterior part, is the most common location involved. The radiographic feature of ameloblastoma can be either unilocular or multilocular radiolucency (Neville BW et al., 2016). Due to the high recurrence rate of ameloblastoma, the recommended treatment for ameloblastoma is surgery with wide resection. For a wide resection, a margin of 1.5-2 cm beyond the radiological limit of the lesion is recommended. Even after the resection with adequacy, the recurrence rate remains 13-15% (El-Naggar et al., 2017; Neville BW et al., 2016). The quality of life of patients with ameloblastoma after surgical treatment may be poor due to facial deformity and limitation of masticatory functions. These may also affect the psychological status of the patients (Effiom et al., 2018).

Recent studies have shown that gene mutations in the FGF-MAPK signaling pathway may play a significant role in the pathogenesis of ameloblastoma (El-Naggar et al., 2017). Some inhibitors of the FGF-MAPK signaling pathway are currently used as targeted therapies for ameloblastoma. Moreover, novel inhibitors are being explored, aiming to help in the reduction of surgical treatment for patients with ameloblastoma (Uehling and Harris, 2015; Chae et al., 2017; Kommalapati et al., 2021).

The FGF-MAPK signaling pathway with tumorigenesis

The MAPK signaling pathway comprises a signaling pathway that operates through sequential phosphorylation events. This pathway has a crucial role in responding to various extracellular factors such as mitogens, hormones, and stresses and regulating many cellular processes such as cell proliferation and differentiation. In the MAPK signaling pathway, the transmission of signals is initiated by the activation of a small G protein, RAS. Subsequently, the signals are transmitted downstream by three to five tiers of specific cytosolic protein kinases, including RAF, MEK, and ERK. The kinases in each tier are phosphorylated and then activate the kinases located in their downstream signaling proteins (Keshet and Seger, 2010).

The MAPK pathway has four minor pathways, namely ERK1/2, c-Jun N-terminal kinase 1–3 (JNK1–3), p38 MAPK α, β, γ, δ (p38 α–δ), and ERK5. Each of the pathway regulates several cellular biological processes through various stimuli, including epidermal growth factor (EGF) and fibroblast growth factor (FGF) (Keshet and Seger, 2010; Johnson et al., 2014; Guo et al., 2020). In this review, we will focus mainly on the ERK1/2 pathway on the basis that gene mutations of this particular pathway have frequently been found in ameloblastoma (Figure 1).

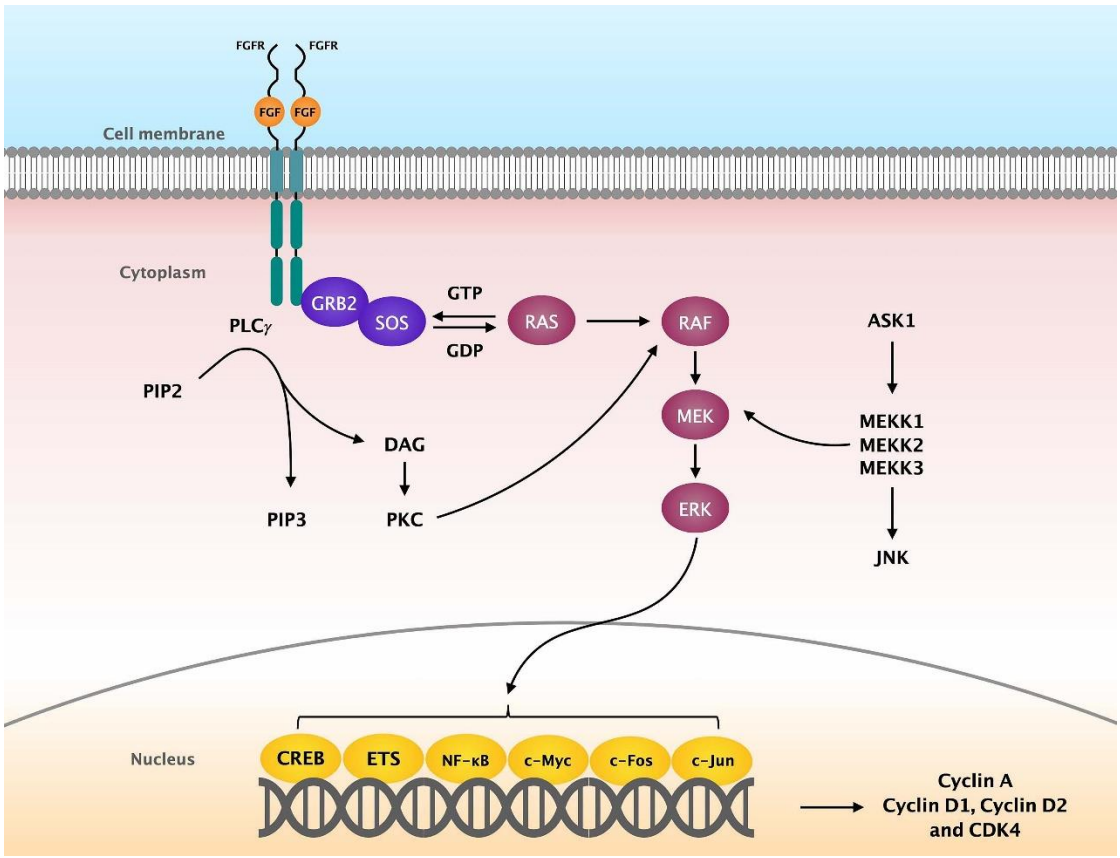

Figure 1. The FGF-MAPK signaling pathway (modified from Xie et al., 2020).

Fibroblast growth factors, a stimulus that activates the ERK1/2 signaling pathway, are present in almost all tissues functioning in regulating embryogenesis, tissue maintenance, repair, and regeneration (Ornitz and Itoh, 2015). The binding of FGF to fibroblast growth factor receptors (FGFR) results in dimerization of FGFR and autophosphorylation of the kinase domains (Katoh and Nakagama, 2014; Ornitz and Itoh, 2015). Subsequently, growth factor receptor-binding protein 2 (GRB2), an adapting protein of FGFR, is signalized and interacts with another adaptor, son of sevenless (SOS), and forms FGFR-GRB2-SOS complex (Johnson et al., 2014; Guo et al., 2020). These are the early events of the ERK1/2 signaling pathway.

Upon activation by the FGFR-GRB2-SOS complex, the inactive form of GDP-binding RAS protein, located close to the cell membrane, is turned into the GTP-binding form or active RAS. RAS has three subtypes: KRAS, HRAS, and NRAS (Simanshu et al., 2017). Mutations of RAS subtypes implicate in tumorigenesis of many human cancers. The next downstream signaling protein is RAF. RAF is a protein kinase encoded by the RAF gene. RAF has three subtypes: RAF-1 or CRAF, ARAF, and BRAF. ARAF appears to be the weakest kinase, while BRAF shows the strongest kinase activity and has the highest mutation rate (Matallanas et al., 2011; Guo et al., 2020). After binding to RAS, RAF protein is activated. Moreover, protein kinase C (PKC), a part of phospholipase C gamma (PLCγ) signaling, can also phosphorylate RAF to promote the activation of the MAPK pathway (Turner and Grose, 2010). Phosphorylated RAF then activates downstream protein kinases, including MEK and ERK (Guo et al., 2020; Liu et al., 2018). MEK is a main component in the MAPK signaling pathway. Besides RAF, MEK can be activated by several protein kinases, including mitogen-activated protein kinase kinase kinase 1-3 (MEKK1-3), protein kinases of the JNK signaling pathway (Junttila et al., 2008). MEK is the completely specific activator of ERK: therefore, MEK plays a key part as "a gatekeeper" of the MAPK signaling pathway (Liu et al., 2018). ERK is localized in the cytoplasm as an inactive form. Upon activated, ERK translocates into the nucleus and regulates the activity of various transcription factors, including cyclic-adenosine monophosphate (AMP) response element-binding protein (CREB), E26 transformation-specific (ETS), nuclear factor kappa-light-chain-enhance of activated B cell (NF-κB), cellular Myelocytomatosis (c-Myc), c-Fos and c-Jun (Guo et al., 2020; Johnson et al., 2014; Liu et al., 2018). CREB plays a critical role in cell survival by activating the expression of cyclins A and D1 (Chang et al., 2003; Sandoval et al., 2009). ETS and NF-κB regulate the expression of cyclin D1. c-Myc, cFos, and c-Jun directly activate the expression of cyclin D1, cyclin D2, and cyclin dependent kinase 4 (CDK4), which are associated with the cell cycle process (Chang et al., 2003; Schreiber et al., 1999).

Since the ERK1/2 signaling pathway plays a pivotal role in cell proliferation, aberration of this signaling pathway mainly caused by gene mutations of *FGFR, RAS, RAF, MEK,* and *ERK* results in uncontrolled cell growth, hence inducing tumorigenesis of many human neoplasms, including malignant melanoma, thyroid, ovarian, colorectal, lung cancer, and ameloblastoma (Brown and Betz, 2015; Burotto et al., 2014; Guo et al., 2020).

Gene mutations in the FGF-MAPK signaling pathway in ameloblastoma.

Table 1. Previous studies on gene mutations in the FGF-MAPK signaling pathway in Ameloblastoma.

Gene mutations in MAPK signaling pathway in ameloblastoma					
Gene	**Study**	**Sample size (n)**	**Mutation site**	**Frequency (%)**	**Locations**
FGFR2	Brown et al., 2014	50	C382R and V395D	6.0	Mandible (33.3%) Maxilla (66.7%)
	Sweeney et al., 2014	28	C382R and N549K	18.0	Mandible (40.0%) Maxilla (40.0%) Other (20.0%
RAS	Sweeney et al., 2014	28	G12S	14.0 (*KRAS*)	Maxilla (100.0%)
	Brown et al., 2014	50	G12S, Q61R, and Q61K	20.0 (8.0% of *KRAS*, 6.0% of *NRAS* and 6.0% of *HRAS*)	Mandible (30.0%) Maxilla (70.0%)
BRAF	Sweeney et al., 2014	28	V600E	46.0	Mandible (69.3%) Maxilla (23.0%) Other (7.7%)
	Brown et al., 2014	50		62.0	Mandible (94.4%) Maxilla (5.6%)

Gene mutations in MAPK signaling pathway in ameloblastoma					
Gene	**Study**	**Sample size (n)**	**Mutation site**	**Frequency (%)**	**Locations**
	Bartels et al., 2018	20		25.0	Not available
	Kelppe et al., 2019	36		72.2	Mandible (100.0%)
	do Canto et al., 2019	84		78.6	Mandible (100.0%)
	Oh et al., 2019	30		90.0	Mandible (92.6%) Maxilla (7.4%)
	Lapthanasupkul et al., 2020	51		72.5	Mandible (97.3%) Maxilla (2.7%)
	Seki-Soda et al., 2020	21		76.0	Mandible (100.0%)
	Derakhshan et al., 2020	50		92.0	Mandible (78.3%) Maxilla (21.7%)

Gene mutations in FGF-MAPK signaling proteins, including FGFR, RAS, RAF, MEK, and ERK lead to tumorigenesis of many human cancers aforementioned (Burotto et al., 2014; Brown and Betz, 2015; Guo et al., 2020). BRAFV600E, in particular, is the most frequent gene mutation in ameloblastoma (Gültekin et al., 2018).

Recent studies have shown that mutation of *BRAF* at *BRAF*V600E position, resulting in replacement of valine to glutamic acid at codon 600, is mainly involved in ameloblastoma. Mutation of *BRAF*V600E can also be found in other human neoplasms, including melanoma, thyroid, ovarian, colorectal, and lung cancers (Davies et al., 2002; Dhillon et al., 2007; Ranjbari et al., 2013). A recent study in Thai patients showed that BRAFV600E mutation occurred in 72.5% with no specific association with either demographic or clinicopathologic parameters (Lapthanasupkul et al., 2020). Similarly, *BRAF*V600E mutation were shown to be present in 76% of patients with ameloblastoma in Japan (Seki-Soda et al., 2020). The studies in Europe and South America have also shown similar findings, 46%-62% in the U.S.A. (Brown et al., 2014; Sweeney et al., 2014), 72.2% in Finland and 78.6% in Brazil (do Canto et al., 2019; Kelppe et al., 2019). Interestingly, BRAFV600E mutation in ameloblastoma in other Asian countries had higher rates, with 90% in South Korea and 92% in Iran (Derakhshan et al., 2020; Oh et al., 2019).In contrast, a study in Germany revealed only 25% of *BRAF*V600E mutations in ameloblastoma (Bartels et al., 2018). Collectively, these studies indicate that the frequency of *BRAF*V600E mutation in ameloblastoma may vary among geography or ethnic groups (Seki-Soda et al., 2020). The etiology of this variation remains unknown. It is of interest to note that high percentages of *BRAF*V600E mutation are found in the mandible, while the maxillary ameloblastoma demonstrates the wild-type. (do Canto et al., 2019; Lapthanasupkul et al., 2020; Sweeney et al., 2014).

Besides *BRAF*V600E mutations, *FGFR* mutations are also identified, particularly *FGFR1* and *FGFR3*, in almost all human cancers. Specifically, *FGFR2* mutations are common in endometrial adenocarcinoma, cholangiocarcinoma, and gastric adenocarcinoma (Weaver et al., 2020). *FGFR2* mutations have also been found in ameloblastoma, ranging from 6% to 18% (Brown et al., 2014; Sweeney et al., 2014). It was suggested that overexpression of *FGFR2* plays an important role in the tumor invasion and recurrences of ameloblastoma (Tang and Ji, 2017). Currently, an immunohistochemical investigation demonstrates the overexpression of FGFR2 in ameloblastoma, showing an intense cytoplasmic staining in the peripheral ameloblast-like cells and mild cytoplasmic staining in some central stellate reticulum-like cells (unpublished data) (Figure 2).

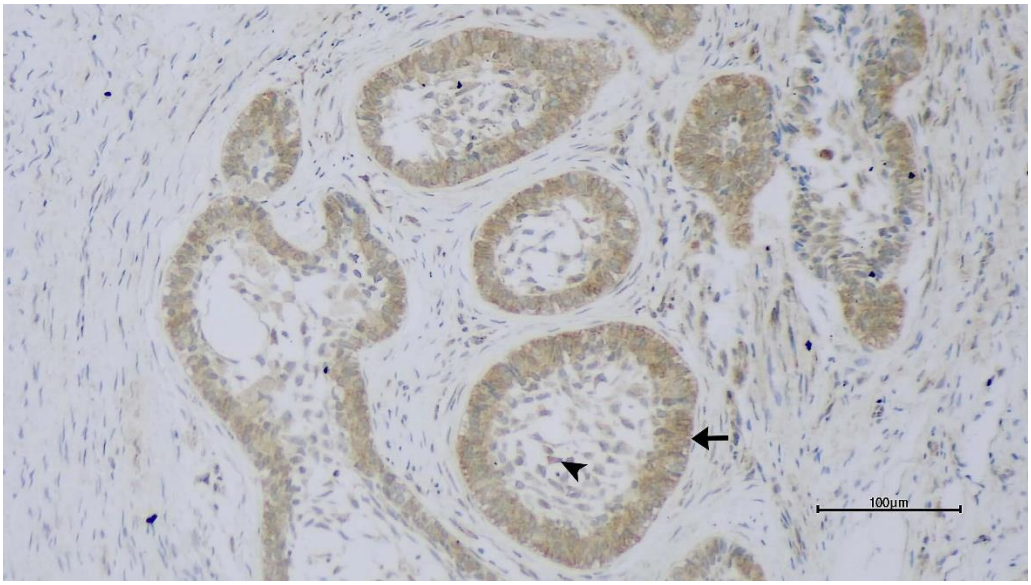

Figure 2. The immunostaining of FGFR2 in the follicles of ameloblastoma showing intense cytoplasmic staining in the peripheral ameloblast-like cells (an arrow) and weaker staining in the central stellate reticulum-like cells (an arrowhead) (Original magnification 100x).

Mutation of downstream genes in the FGF-MAPK signaling pathway, *RAS* was identified in approximately 20% of patients with ameloblastoma comprising 8%-15% of *KRAS* mutations, 6% of both *NRAS* and *HRAS* mutations (Brown et al., 2014; Sweeney et al., 2014). RAS mutations are also found in craniofacial syndrome and 20%-25% of all human cancers, including melanoma, non-small cell lung cancer, colorectal cancer, and ovarian cancer (Bromberg-White et al., 2012; Panyavaranant et al., 2019).

Aberrant genes in the FGF-MAPK signaling pathway may play a significant role in the pathogenesis of ameloblastoma. Based on these knowledges, targeted therapies are designed to target these mutated genes intending to help in the treatment for patients with ameloblastoma.

Targeted therapies on ameloblastoma

After the discovery of *BRAF*V600E mutation in several cancers, many MAPK inhibitors have been designed to target these mutations (Uehling and Harris, 2015). The first BRAF inhibitor targeting *BRAF*V600E mutation is vemurafenib. Vemurafenib (Zelboraf®) has been approved by the US Food and Drug Administration (FDA) to be used in unresectable or metastatic melanoma with BRAFV600E mutation since 2011 (Kim et al., 2014). The second BRAF inhibitor is dabrafenib (Tafinlar®). It has also been approved by the FDA since 2013. Moreover, dabrafenib has been approved as a combination therapy with trametinib (Mekinist®), a MEK inhibitor (Uehling and Harris, 2015). Apart from vemurafenib and dabrafenib, encorafenib (Braftovi®) has also been approved by the FDA since 2018, and there are several other *BRAF* inhibitors undergoing development such as MLN-2480, LY-3009120, and PLX8394 (Uehling and Harris, 2015; Degirmenci et al., 2020; Davis and Wayman, 2022). Trametinib, cobimetinib (Cotellic®), and binimetinib (Mektovi®) are MEK inhibitors approved by the FDA to be used as monotherapy or in combination with a BRAF inhibitor in unresectable or metastatic melanoma (Uehling and Harris, 2015; Shirley, 2018). Other MEK inhibitors include selumetinib (Koselugo®), pimasertib, and refametinib (Uehling and Harris, 2015; Markham and Keam, 2020; Tran and Cohen, 2020; Mukhopadhyay et al., 2021). Similarly, ERK inhibitors remain to go through human clinical trial phases (Degirmenci e t al., 2020). Adverse effects of these inhibitors, particularly dermatologic reactions including rash, photosensitivity, and alopecia, have been reported (Welsh and Corrie, 2015). Minor adverse effects

include arthralgia, hepatotoxicity, and secondary malignancy (Hagen and Trinh, 2014; Welsh and Corrie, 2015).

Besides MAPK inhibitors, targeted therapies specific for FGFR, including tyrosine kinase inhibitors (TKIs), neutralizing monoclonal antibodies (mAbs) against FGFR, and FGF traps have also been used in various human cancers, for example, breast cancer, gastric cancer, lung cancer, thyroid cancer, and ovarian cancer (Babina and Turner, 2017; Xie et al., 2020). TKIs are divided into 2 groups: non-selective TKIs/multi-targeting TKIs and selective TKIs (Xie et al., 2020). TKIs are ATP-competitive molecules activated by binding to tyrosine kinase domains, resulting in inhibition of autophosphorylation of the receptor (Chae et al., 2017). Non-selective TKIs are the first-generation of targeted therapy strategized to block FGFs signaling. Subsequently, several non-selective TKIs such as lenvatinib (Lenvima®), lucitanib, nintedanib (Ofev®), dovitinib (Novartis®), and ponatinib (Iclusig®) have been developed. Moreover, many non-selective TKIs are currently undertaken for preclinical and clinical phases (Goodman et al., 2007; Nguyen and Shayahi, 2013; Fala, 2015; Babina and Turner, 2017; Chae et al., 2017; Aljubran et al., 2019; Nair et al., 2021; Xie et al., 2020). However, these non-selective TKIs have caused many adverse effects due to the fact that their activity may be against other tyrosine kinase receptors such as vascular endothelial growth factor (VEGF) receptor. These could lead to unfavorable adverse effects, including cardiotoxicity, proteinuria, skin reactions, and digestive disorders (Babina and Turner, 2017; Kommalapati et al., 2021). To reduce adverse effects caused by non-selective TKIs, selective TKIs have therefore been developed to specifically target FGFR (Babina and Turner, 2017; Chae et al., 2017). Erdafitinib (Balversa®), pemigatinib (Pemazyre®), AZD4547, BGJ398, and PD173074 are examples of selective TKIs (Babina and Turner, 2017; Chae et al., 2017; Weaver et al., 2020). Thus far, there are only two FGFRs inhibitors approved by FDA: erdafitinib and pemigatinib (Weaver et al., 2020) (Table 2).

Table 2. MAPK inhibitors and tyrosine kinase inhibitors.

Type	Drug	Status	References
BRAF inhibitors	Vemurafenib (Zelboraf®)	Approved by FDA to use in unresectable or metastatic melanoma with BRAFV600E mutation	Kim et al., 2014
	Dabrafenib (Tafinlar®)	Approved by FDA to use in unresectable or metastatic melanoma with BRAFV600E mutation (as a single agent or combination with Trametinib)	Uehling and Harris, 2015
	Encorafenib (Braftovi®)	Approved by FDA to use in combination for patients with unresectable or metastatic melanoma with BRAFV600E mutation	Davis and Wayman, 2022
	MLN-2480	Ongoing clinical trials	Uehling and Harris, 2015
	LY-3009120	Ongoing clinical trials	
	PLX8394	Ongoing clinical trials	
	BGB-283	Ongoing clinical trials	
	CEP-32496	Ongoing clinical trials	
	TAK 632	Ongoing clinical trials	
	RAF265	Ongoing clinical trials	
	XL-281	Ongoing clinical trials	
	ARQ-736	Ongoing clinical trials	
MEK inhibitors	Trametinib (Mekinist®)	Approved by FDA to use with patients with metastatic melanoma with V600E/K mutation (monotherapy or combination with dabrafenib)	Uehling and Harris, 2015
	Cobimetinib (Cotellic®)	Approved by FDA to use with patients with metastatic melanoma with V600E/K mutation (monotherapy or combination with vemurafenib)	Uehling and Harris, 2015

Type	Drug	Status	References
	Binimetinib (Mektovi®)	Approved by FDA to use with patients with metastatic melanoma with V600E/K mutation (monotherapy or combination with encorafenib)	Shirley, 2018
	Selumetinib (Koselugo®)	Approved by FDA to use for patients with neurofibromatosis-1	Markham and Keam, 2022
	PD-0325901	Ongoing clinical trials	Uehling and Harris, 2015
	Pimasertib	Ongoing clinical trials	
	Refametinib	Ongoing clinical trials	
	RO5126766	Ongoing clinical trials	
	E06201	Ongoing clinical trials	
ERK inhibitors	Ulixertinib	Ongoing clinical trials	Uehling and Harris, 2015
	GDC-0994	Ongoing clinical trials	
	(S)-14k	Ongoing clinical trials	
	VTX11e	Ongoing clinical trials	
	SCH772984	Ongoing clinical trials	
	SCH900353	Ongoing clinical trials	
Non-selective TKIs	Lucitanib	Ongoing clinical trials	Xie et al., 2020
	Nintedanib (Ofev®)	Approved by FDA	Fala, 2015
	Dovitinib (Novartis®)	Ongoing clinical trials	Xie et al., 2020
	Regorafenib (Stivarga®)	Approved by FDA	Aljubran et al., 2019
	Brivanib	Ongoing clinical trials	Xie et al., 2020
	Ponatinib (Iclusig®)	Approved for market	Xie et al., 2020
	Lenvatinib (Lenvima®)	Approved by FDA	Nair et al., 2021
	Pazopanib (Votrient®)	Approved by FDA	Nguyen and Shayahi, 2013
	Orantinib	Ongoing clinical trials	Xie et al., 2020
	Sunitinib (Sutent®)	Approved by FDA	Goodman et al., 2007
	Cediranib	Ongoing clinical trials	Xie et al., 2020
Selective TKIs	Erdafitinib (Balversa®)	Approved by FDA	Weaver et al., 2020
	Pemigatinib (Pemazyre®)	Approved by FDA	Weaver et al., 2020
	AZD4547	Ongoing clinical trials	Xie et al., 2020
	BGJ398	Ongoing clinical trials	
	Debio-1347	Ongoing clinical trials	
	TAS-120	Ongoing clinical trials	
	BAY-1163877	Ongoing clinical trials	

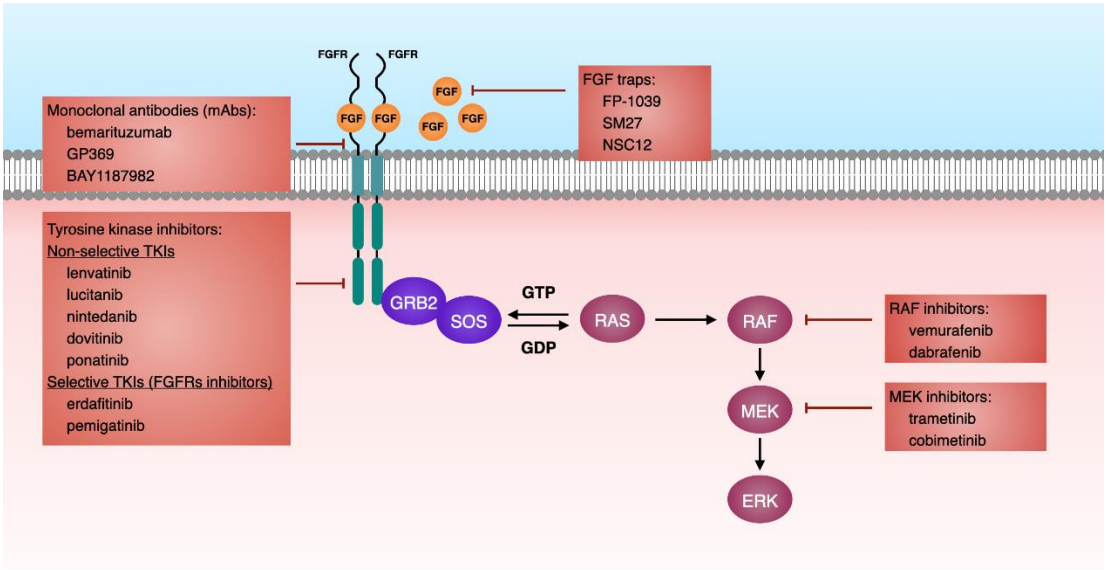

Figure 3. TARGETED THERAPIES ON AMELOBLASTOMA.

Immunotherapy using neutralizing monoclonal antibodies appears to be more effective and less toxic than TKIs. These may be due to the specificity of antibody-antigen interactions. Bemarituzumab, GP369, and BAY1187982 are examples of mAb specifically targeting *FGFR2* (Babina and Turner, 2017; Chae et al., 2017). FGF traps are alternative molecules strategized to block the activity of the FGF-MAPK signaling pathway by binding the molecules to the FGF ligands. FP-1039, SM27, and NSC12 are examples of FGF traps tested in ongoing human clinical trials (Babina and Turner, 2017; Chae et al., 2017; Xie et al., 2020).

Although there have been several investigations of MAPK and FGFR inhibitors used for treating ameloblastoma, randomized controlled trials of these inhibitors in patients with ameloblastoma have not been studied. Only a few case reports have been undertaken with promising results. For example, BRAF and MEK inhibitors including, vemurafenib, dabrafenib, and trametinib in ameloblastoma cases with BRAFV600E mutation have shown a significant reduction in tumor sizes (Kaye et al., 2015; Faden and Algazi, 2016; Tan et al., 2016; Fernandes et al., 2018; Brunet et al., 2019). Moreover, lenvatinib and erdafitinib revealed a remarkable reduction in tumor sizes in ameloblastoma cases with *FGFR2* mutation (Lawson-Michod et al., 2022; Weaver et al., 2020). Therefore, the using of BRAF, MEK, and FGFR inhibitors in the treatment of ameloblastoma are recommended. However, there is only one case report that showed no response to using trametinib in a 13-year-old female with mutated *BRAF* ameloblastoma. Further studies on the efficacy and appropriate dosage for trametinib for *BRAF* mutated ameloblastoma were then suggested (Daws et al., 2021) (Table 3).

Table 3. Case reports using targeted therapies in patients with ameloblastoma.

Study	Gender	Age	Tumor	Location	Mutation	Treatment	Outcome
Kaye et al., 2014	Male	40	Recurrent ameloblastoma with pulmonary metastases	Left mandible and bilateral lung	*BRAF*V600E	dabrafenib + trametinib	Decreased tumor size and metastases
Tan et al., 2016	Male	85	Primary ameloblastoma	Left mandible	*BRAF*V600E	dabrafenib	Decreased tumor size with skin lesion (actinic keratosis)
Faden et al., 2017	Female	83	Recurrent ameloblastoma	Right mandible	*BRAF*V600E	dabrafenib	Decreased tumor size
Fernandes et al., 2018	Female	29	Recurrent ameloblastoma	Left mandible	*BRAF*V600E	vemurafenib	Decreased tumor size
Brunet et al., 2019	Female	26	Metastatic ameloblastoma	Bilateral lung	*BRAF*V600E	Dabrafenib + trametinib	Complete remission
Weaver et al., 2020	Male	62	Primary ameloblastoma	Right maxilla	*FGFR2*	lenvatinib	Decreased tumor size
Daws et al., 2021	Female	13	Primary ameloblastoma	Right mandible	*BRAF*V600E	trametinib	Failed response
Lawson-Michod et al., 2022	Male	40	Recurrent ameloblastoma	Right pterygopalatine fossa, skull base, and maxilla	*FGFR2* and *SMO*	erdafitinib	Decreased tumor size

Although treatment of ameloblastoma with BRAF and MEK inhibitors and TKI have been investigated, using ERK inhibitors for treatment of ameloblastoma have never been explored. Further studies on the use of ERK inhibitors may warrant benefits to patients with mandibular ameloblastoma.

CONCLUSION

Recent data have revealed that gene mutations in the FGF-MAPK signaling pathway including *BRAFV600E, FGFR2,* and *RAS* play a crucial role in the pathogenesis of ameloblastoma particularly in the mandible. Current treatment of ameloblastoma remains aggressive surgical resection in order to prevent recurrences. The results of this treatment modality enormously impact the quality of life of the patients. Targeted therapy aiming to inhibit specific altered proteins in the FGF-MAPK signaling pathway may be used as an adjuvant treatment along with the surgical approaches which may help minimize complications after treatment and provide the better quality of patients' lives. Targeted therapies in ameloblastoma are therefore envisaged as a promising novel treatment modality for ameloblastoma.

ACKNOWLEDGMENTS

The authors are grateful to Research Funding for graduate students, Faculty of Dentistry and Chiang Mai University Presidential Scholarship, Chiang Mai University, Thailand for providing financial support.

AUTHOR CONTRIBUTIONS

All authors assisted in the data researching, analyzing, and summarizing. Nattanit Boonsong and Anak Iamaroon conducted all of the reviewing processes and wrote the manuscript. All authors have read and approved of the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Chiang Mai University Journal of Natural Sciences [ISSN 16851994]
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