Review

Oncogenic signalling pathways in benign odontogenic cysts and tumours

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A B S T R A C T

The first step towards the prevention of cancer is to develop an in-depth understanding of tumourigenesis and the molecular basis of malignant transformation. What drives tumour initiation? Why do most benign tumours fail to metastasize? Oncogenic mutations, previously considered to be the hallmark drivers of cancers, are reported in benign cysts and tumours, including those that have an odontogenic origin. Despite the presence of such alterations, the vast majority of odontogenic lesions are benign and never progress to the stage of malignant transformation. As these lesions are likely to develop due to developmental defects, it is possible that they harbour quiet genomes. Now the question arises – do they result from DNA replication errors? Specific candidate genes have been sequenced in odontogenic lesions, revealing recurrent BRAF mutation in the case of ameloblastoma, KRAS mutation in adenomatoid odontogenic tumours, PTCH1 mutation in odontogenic keratocysts, and CTNNB1 (Beta-catenin) mutation in calcifying odontogenic cysts. Studies on these benign and rare entities might reveal important information about the tumorigenic process and the mechanisms that hinder/halt neoplastic progression. This is because the role of relatively common oncogenic mutations seems to be context dependent. In this review, each mutation signature of the odontogenic lesion and the affected signalling pathways are discussed in the context of tooth development and tumorigenesis. Furthermore, behavioural differences between different types of odontogenic lesions are explored and discussed based on the molecular alteration described. This review also includes the employment of molecular results for guiding therapeutic approaches towards odontogenic lesions.

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Introduction

The compilation of a Precancer Atlas has been proposed to integrate large-scale research and thus improve the understanding of the events that drive oncogenesis [1]. The study of benign tumours is considered as important as the study of malignant ones, as they may reveal relevant aspects of neoplastic progression [2]. The genomic stability inherent in benign tumours contributes to the identification of remarkably clear genetic fingerprints, pointing to specific molecular alterations that are likely to be responsible for tumorigenesis.

In a similar fashion to malignant neoplasms, benign tumours harbour one or several oncogenic mutations that lead to clonal cell proliferations. Notably, benign tumours share five of the six putative “hallmarks of cancer”, with metastasis being the exception [3,4]. It is intriguing that some benign tumours lack fibrous capsules and can show markedly aggressive behaviour, while others grow no more than a few cubic centimetres inside a thick fibrous capsule. Odontogenic lesions mainly comprise benign cysts and neoplasms of the tooth apparatus, including lesions that can perforate the cortical plate and infiltrate the soft tissues, such as ameloblastomas, and encapsulated lesions with indolent behaviour, such as adenomatoid odontogenic tumour (AOT). These benign tumours can harbour oncogenic genetic alterations that were previously considered as the drivers of specific, invasive cancers originated in other organs, such as melanomas, lung and colorectal adenocarcinomas [5]. It is not clear why the majority of the benign conditions never progress to cancer, even in the presence of pathogenic mutations. In this
review, we used the odontogenic cysts and tumours as the models to discuss the context-specific role of oncogenic signalling pathways, which are important for understanding tumour biology in a broader perspective.

The morphology of odontogenic lesions resembles the stages of tooth embryonic development (i.e. odontogenesis) (Fig. 1), while the molecular mechanisms associated with odontogenesis have been associated with the pathobiology of such entities. While in ameloblastomas, the gene expression profile reflects differentiation from the dental lamina towards the cap/bell stage of tooth development, odontogenic keratocysts (OKCs) show differentiation towards keratinocytes [6]. Every step of normal odontogenesis is regulated by BMP, FGF, Shh and Wnt cell signalling pathways [7]. During the past years, pathogenic gene mutations affecting downstream signalling cascades of these signalling pathways were described in odontogenic lesions, including BRAF mutation in ameloblastoma, KRAS mutation in AOT, PTCH1 mutation in OKC, and CTNNB1 (Beta-catenin) mutation in calcifying odontogenic cyst (COC).

In this review, we discuss the mutation signatures of some odontogenic cysts and tumours, together with their significance in cell signalling pathways in the context of odontogenesis and tumorigenesis. Furthermore, insights into the histopathogenesis and behavioural differences between the lesions are brought into light on the basis of the described molecular alterations.

**The MAPK pathway, ameloblastoma and adenomatoid odontogenic tumour**

The prototypical MAPK cascade, the Ras-Raf-MEK-ERK, is commonly dysregulated in several human cancers. In this pathway, the activation of a family of cell-surface tyrosine kinase receptors triggers the proteins of the Ras superfamily of small GTPases, which includes molecules encoded by KRAS, Hras, and NRAS [8]. Activated Ras binds and activates Raf kinases, encoded by BRAF, RAF1, and ARAF. Raf phosphorylates and activates MEK1/2, which in turn phosphorylates and activates ERK-1/2. ERKs phosphorylate a vast array of substrates both in the cytosol and in the nucleus [9] (Fig. 2), including receptors, protein kinases, signalling effectors, and transcription factors. Recently, alterations of prototypical MAPK cascade components were reported in a high proportion of benign odontogenic lesions, mainly in ameloblastoma and AOT [10,11].

The activating mutation BRAFV600E occurs in 60–80% of ameloblastoma cases, regardless of clinical and histopathological variants, including its malignant counterpart, ameloblastic carcinoma (AC) [10,12–15]. Interestingly, MAPK activation had previously been detected by immunohistochemistry in ameloblast-like cells neighbouring the basement membrane of ameloblastomas, as well as in tooth germs [16]. Other odontogenic lesions were also shown to be BRAFV600E positive, including clear cell odontogenic carcinoma, ameloblastic fibroma, ameloblastic fibrodentinoma, and ameloblastic fibro-odontoma [12,13,17].

Genetic mutations mutually exclusive of BRAFV600E, such as those in KRAS, NRAS, Hras, and FGFR2, were described in BRAF wild-type ameloblastomas [12,14]. Additionally, a high-density whole-genome microarray analysis showed only a few rare DNA copy-number alterations, mostly affecting genes associated with MAPK activation [18]. These results support the crucial role of the MAPK pathway activation in the pathogenesis of ameloblastomas. Secondary events, such as changes in tumour suppressor...
genes, may also play a role in cytodifferentiation and tissue struct-
turing of these neoplasms [19,20].

The MAPK pathway is also altered in AOT, which is similar to
ameloblastoma – an epithelial odontogenic neoplasm (Fig. 2). In
2016, we reported the activating pathogenic mutation KRASG12V
in 7/9 AOT samples by carrying out a targeted next-generation
sequencing approach in a panel containing ~2800 COSMIC mu-
tations in 50 genes [11]. Even though ameloblastoma and AOT ne-
oplasm harbour gene mutations affecting MAPK cascade, their
clinical behaviours are markedly distinct. While ameloblastoma
is locally aggressive and can perforate the cortical bone plate and
infiltrate soft tissues, AOT is encapsulated with limited growth
potential and very low tendency of recurrence. Notably, both
the odontogenic tumours show expression of the MAPK transcriptional
targets, c-Myc, which regulate cell proliferation [21–
25]. In colorectal cancer, it has been shown that BRAFV600E and
KRASG12V oncogenes have a different impact on morphology
and invasive phenotype [26]. Furthermore, in contrast to
KRASG12V, BRAFV600E caused an increased expression of unique
target genes, such as SOX2 [27]. In lungs, different tumorigenic
capacity of oncogenic BRAF and KRAS were reported [28,29]. On
this basis, although MAPK pathway is activated in ameloblastoma
and AOT, distinct roles of BRAF and KRAS oncogenes within each
tumour context, including the cell-of-origin and the prevalent loca-
tion at the jaws, may account for the distinct biological behaviour
of these neoplasms.

The high prevalence of mutations affecting MAPK signalling
pathway in ameloblastoma and AOT indicates that this is likely
an early pathogenic event. The evidence that MAPK cascade plays
a central role in odontogenesis, including ameloblast development,
had shed light on the intimate connection between oncogenic
MAPK signalling, ameloblastoma, and AOT tumorigenesis, as we
discuss below.

Growth factors, such as FGF and EGF, are the major regulators of
the MAPK cascade in many physiological and cellular contexts,
including odontogenesis. At the bell stage of tooth development,
the downregulation of FGF-R2, a FGF receptor, was reported in
the pre-ameloblast cells [30] in association with the cessation
of cell proliferation [31]. Curiously, FGF-R2 was found to be over activ-
ated by mutation in some ameloblastoma samples [14], suggest-
ing that a sustained hyper-proliferation is mediated by oncogenic
FGF signalling. Corroborating these findings, treatment with FGF
ligands lead to ameloblastoma cultured cells’ increased prolifera-
tion through ERK-1/2 signalling, an effect blocked by MEK inhibi-
tion [32].

The EGF receptor, erbB-1, is encoded by EGFR, and its abnormal
function is implicated in tumorigenesis [33,34]. The expression of
EGFR in ameloblasts varies throughout the developmental stages.
It is expressed in the inner enamel epithelium (IEE), which con-
tains proliferative and differentiating cells, while it is expressed
in low levels in polarizing ameloblasts, and its expression remains
low during the enamel secretion stage [35]. Interestingly, EGFR is
overexpressed in ameloblastomas [10,36], in a similar fashion to
other epithelial neoplasms such as head and neck, cervical, and
oesophageal cancer [37]. In ameloblastoma cultured cells, EGF
knockdown blocked the activity of matrix metalloproteinases
(MMPs), and abolished EGF-stimulated cell migration and invasion
[38].

In addition to studies with human tumours and in vitro experimen-
tation, in vivo experiments support that MAPK pathway dys-
regulation impacts the ameloblasts’ function. Activation of MAPK
cascade caused by HrasG12V mutation led to compromised prolif-
eration and differentiation of enamel-producing ameloblasts and
their precursors in mice incisors [39]. Notably, HrasG12V amelo-
blastos were shown to be disorganised and with abnormal cell
 polarity [39], a characteristic shared with ameloblast-like cells in
ameloblastoma and AOT. Further analyses supported the conclu-
sion that low levels of phosphorylated ERK-1/2 (i.e. the MAPK
downstream effector) might be necessary for the normal amelo-
blast progenitors to exit the cell cycle and to differentiate [39].
Studies with Hras transgenic mice reported the development of
jaw tumours compatible with the diagnosis of odontogenic
tumours [40–42].

MAPK-targeted therapy has been tested in ameloblastoma cells in vitro. Treatment with erbB-1 monoclonal antibodies (cetuximab and panitumumab) and erbB-1 tyrosine kinase inhibitors (erloti-
nib, gefitinib, and AG1478) resulted in ameloblastoma cell growth
suppression [10]. Conversely, resistance to erbB-1 inhibition was
observed in BRAFV600E ameloblastoma cells [10]. Such resistance
to Erb-1 inhibition was attributed to nuclear translocation of erbB-
1 in certain cancer types [43]. This erbB-1 nuclear localization was
observed in ameloblastomas by Pereira and colleagues [21], raising
a concern about an additional resistance mechanism of anti-erbB-1
therapy in ameloblastomas [21]. In addition to in vitro testing,
BRAF-mutant targeted therapy has already been clinically tested in human ameloblastomas [44,45]. In one case, a patient with metastatic ameloblastoma was treated with a dual therapy with BRAF/MEK inhibition (dabrafenib and trametinib) [44], whereas in the other case, a patient with recurrent ameloblastoma received only dabrafenib [45]. Both the case reports described a reduction in the tumour mass and suggested the possibility of using neoadjuvant and/or adjuvant targeted therapy in a subset of aggressive ameloblastoma undergoing surgery [44,45]. However, there are important adverse effects of this treatment, and its long-term complications include an increase in the chances of developing squamous cell carcinomas.

**Shh pathway and odontogenic keratocyst**

In mammals, there are three Hedgehog-family members, SHH, IHH and DHH. SHH triggers short and long-range signalling activities [46,47]. The Shh signalling activity takes place after the secreted ligand undergoes a series of post-translational modifications, including a covalent modification by a cholesterol moiety added to its carboxyl-terminal domain and attachment of a palmitic acid group to its amino-terminal end [48]. Cooperation between two transmembrane proteins, Dispatched and SCUBE2, culminates with the SHH release from the surface of the signalling cells [49,50]. The secreted SHH ligand binds to its receptor PTC1, a twelve-pass transmembrane protein, encoded by *PTCH1* [51]. In the absence of its ligand, PTC1 works as a ligand-independent inhibitor of the downstream SMO, a seven-pass transmembrane protein member of the G-protein coupled receptor superfamily [50,52]. The current concept is that this is not a direct inhibition, as biochemical assays demonstrated that PTC1 and SMO do not physically interact [53].

The fine-tuning of SHH activity has recently been shown to take place in the primary cilium, a nonmotile microtubule-based organelle present in most mammalian cells, by an as-yet-undefined place in the primary cilium, a nonmotile microtubule-based organelle [59]. The fine-tuning of SHH activity has recently been shown to take place after the secreted ligand undergoes a series of post-translational modifications, including a covalent modification by a cholesterol moiety added to its carboxyl-terminal domain and attachment of a palmitic acid group to its amino-terminal end [48]. Cooperation between two transmembrane proteins, Dispatched and SCUBE2, culminates with the SHH release from the surface of the signalling cells [49,50]. The secreted SHH ligand binds to its receptor PTC1, a twelve-pass transmembrane protein, encoded by *PTCH1* [51]. In the absence of its ligand, PTC1 works as a ligand-independent inhibitor of the downstream SMO, a seven-pass transmembrane protein member of the G-protein coupled receptor superfamily [50,52]. The current concept is that this is not a direct inhibition, as biochemical assays demonstrated that PTC1 and SMO do not physically interact [53].

**PTCH1** mutation leads to constitutive activation of the Shh pathway, and it is considered as the major mechanism underlying OKC tumorigenesis [60]. OKC occurs in isolation or as part of the nevoid basal cell carcinoma syndrome (NBCCS) (OMIM #109400) [61]. In 1996, *PTCH1* genetic mutation was reported as the underlying cause for NBCCS [62,63]. Subsequently, loss of heterozygosity (LOH) and mutations at *PTCH1* were reported in syndromic and sporadic OKCs [64–66]. Recently, the DNA analysis of the microdissected OKC epithelium revealed that a *PTCH1* genetic alteration is present in ~80% of the sporadic OKC [67]. Activating *SMO* mutations [68], as well as transcriptional and immunohistochemical studies reinforce Shh pathway overactivation in human OKC [60,65,70]. In vivo, *Ptc1* knockout and constitutive activation of *Gli2* were reported to drive mandibular OKC-like lesions in mice [71,72]. This evidence strengthens the link between Shh signalling pathway misregulation and OKC tumorigenesis. Despite the exciting possibility of *PTCH1* mutations being an OKC signature, LOH at the *PTCH1* loci occurs in other odontogenic lesions such as the orthokeratinized odontogenic cyst and ameloblastomas [73–76]. Also, *PTCH1* mutation was previously described in the calcifying epithelial odontogenic tumour (CEOT) [77]. However, the effects of these genetic alterations in *PTCH1* function were not determined.

Although OKC was recently reclassified by World Health Organization (WHO) as an odontogenic cystic lesion [78], numerous studies have considered it as a true cystic neoplasm. OKC epithelium has an intrinsic growth potential that is not seen in other cysts, and this lesion presents an elevated recurrence rate of 30% [79]. Moreover, OKC can attain a large size resulting in massive bone destruction [79].

In the past, the concept of “primordial cyst” was used to refer to OKC. The cyst was believed to have a primordial origin, arising from the dental lamina (tooth bud) before enamel formation had taken place, and even by substituting a tooth [80]. A recent study showed that OKC cells harbour expression profiles similar to keratin-producing cells (i.e. keratinocytes) [6]. In this study, Affymetrix whole-genome arrays were used to hybridise total RNA from 12 sporadic OKC. In addition to Shh pathway genes, squamous and terminal epithelial differentiation markers were found to be overexpressed [6]. This study provided molecular evidence to support the concept that OKC originates from fetal oral epithelium or dental lamina at early stages of odontogenesis rather than the enamel organ (Fig. 1).

It is well known that Shh signalling has pivotal roles in early odontogenesis, stimulating epithelial cell proliferation to drive the formation and growth of the tooth bud and increasing epithelial cell survival during the development of the cap-staged tooth germs [81]. One of the most important targets of Shh signalling is *Bcl2*, which encodes a pro-survival protein. In human tooth germs, a strong immunoreactivity of Bcl-2 occurs in the dental lamina and tooth bud, the most primitive form of odontogenic epithelium [82]. Moreover, Bcl-2 protein was also observed in dental lamina cells even when it is fragmented into cell nests, but it disappears after squamous maturation [82]. Interestingly, Bcl-2 overexpression is a hallmark of OKC epithelium [83] and basal cell carcinoma (BCC) [84]. We propose the hypothesis that during OKC tumorigenesis, Shh misregulation might lead to persistent Bcl-2 production in the primitive odontogenic epithelium, reactivating its proliferative and survival potential. Supporting this hypothesis, mice overexpressing the Shh pathway effector Gli2, under the control of keratin 5 promoter, were shown to develop OKC-like and Bcl-2-expressing BCC-like lesions [72,85]. Although a direct link between Bcl-2 overexpression and Shh pathway misregulation were only analysed in the BCC [85], it is very likely that Bcl-2 overexpression at OKC epithelium line is driven by Shh signalling activation.

Another important gene regulated by Shh signalling in several contexts is the transcription factor SOX-2 [86], which is a marker of stem cells and progenitor cells in epithelial tissues [87]. During tooth development in mammals, SOX-2 is associated with the epithelial competence of dental lamina, both for the successional tooth formation and the serial addition of molars [88]. SOX-2 expression was also described in dental lamina and in its fragments associated with the developing third and fourth molars [88,89]. Interestingly, this transcription factor is implicated in cell proliferation and self-renewal in the Shh-associated tumours [86,90] and was also reported to be highly expressed in basal and suprabasal epithelial cell layer of OKC [6,91]. These findings support the idea that Shh-associated OKC arises from SOX-2-positive dental cells [6], especially those cells located at the posterior extension of the dental lamina in the mandible, the site most frequently affected by some odontogenic lesions (Fig. 3). Likewise, SOX-2-positive cells are linked with odontoma, ameloblastoma, and AC tumorigenesis (Fig. 3) [92–94].

As the alteration in Shh signalling is the main feature in OKC, the pathway inhibitors have been tested therapeutically. In OKC primary cultured cells, the use of the SMO antagonist cyclopamine showed a dose-dependent growth arrest of the cells, together with Shh pathway downregulation [95]. A nearly complete resolution of
The Wnt pathway and calcifying odontogenic cyst

The canonical Wnt pathway activation involves binding of Wnt ligands to the frizzled receptors and the co-receptor LRPs-5/6. Once Wnt binds to the receptor complex, a signal is transduced to the cytoplasmic phosphoprotein DVL-1 and it induces events that disrupt the multiprotein "destruction complex" of Beta-catenin (encoded by CTNNB1), formed by Axin-1, APC, GSK3β, and CKI-alpha. Once stabilised and accumulated in the cytoplasm, Beta-catenin is translocated into the nucleus and exerts its effect by binding with the transcription-factors TCF/LEF-1, promoting downstream gene expression [98] (Fig. 2). Beta-catenin accumulation in the cytoplasm and nucleus is a hallmark of canonical Wnt pathway activation. Abnormal activation of the Wnt pathway is associated with the pathogenesis of several types of cancer [99] and odontogenic lesions, especially COC.

In a study in 2003, an abnormally-strong nuclear and cytoplasmic Beta-catenin immunostaining was reported in six out of six NBCCS cases [100]. Subsequently, CTNNB1 DNA sequencing with primers spanning the phosphorylation site for GSK3β revealed genetic mutations in 10 COC samples [101]. Nuclear co-expression of LEF-1 and Beta-catenin were also reported in COC [102]. In 2016, de Sousa and her colleagues simultaneously interrogated the somatic mutations in 50 oncogenes and tumour suppressor genes in three COC cases [103]. The only pathogenic genetic alteration found was in CTNNB1, supporting the concept that constitutive activation of the Wnt signalling pathway through Beta-catenin mutation is the pivotal event underlining the COC tumorigenesis.

Besides COC, the dentinogenic ghost cell tumour (DGCT) and the ghost cell odontogenic carcinoma (GCOC) were found to harbour CTNNB1 genetic alterations at different codons [104,105]. Furthermore, the nuclear and cytoplasmic Beta-catenin accumulation were observed in all these lesions by immunohistochemistry [105], indicating that aberrant signalling in odontogenic epithelium coordinated by Beta-catenin plays a role in their pathogenesis. Notably, COC, DGCT and GCOC can form dentinoid material or odontoma-like structures (Fig. 1). The formation of dental hard tissues is intimately associated with the crucial role of Wnt signalling pathway in inducing tooth formation. For example, the Wnt activation by Ctnnb1 mutation or Apc deletion in mouse's oral epithelium generated ectopic teeth formation [106–108]. Furthermore, the constitutive activation of Beta-catenin in dental epithelium was shown to lead to the formation of odontoma-like lesions with osteodentine and dysplastic dentine in mice jaw, as we detail later [93].

Wnt/Beta-catenin signalling is considered a potent regulator of calcified tissue development and homeostasis in many contexts, such as bones and teeth. Over-activity of Wnt signalling caused by persistent Beta-catenin stabilisation in the dental mesenchyme induced excessive dentin and cementum formation [109]. Conversely, Wnt pathway inhibition by overexpression of Dkk-1 in mice odontoblasts impaired dentin formation in mandibular molars [110]. An attractive hypothesis is that the over-activity of mutated Beta-catenin in epithelial cells of COC might cause aberrant signalling networks of communication with stromal cell compartments, resulting in the production of abnormally calcified dentin-like material, which explains odontoma formation in this lesion. In fact, the paracrine induction of surrounding tissues induced odontoma-like lesions in mice conditionally mutated for Beta-catenin [93]. In this enlightening study, a non-degradable
form of Beta-catenin was conditionally expressed in mice in a Sox2-expressing subset of dental epithelial stem cells after the cessation of normal tooth induction. Remarkably, these mice showed calcified structures that histologically resembled the odontomas. The odontoma-like structures had only a partial contribution of cells derived from the epithelium sustaining a Beta-catenin mutation, suggesting that the tumour is also derived from adjacent wild-type mesenchymal tissue [93]. The Wnt ligand WNT5A is also related to the development of dental hard tissue and odontogenic lesions. Wnt5A-deficient mice exhibited reduced levels of cell proliferation in the dental epithelium and delayed odontoblast differentiation [111]. In human dental papilla cells, WNT5A overexpression increased the formation of calcified nodules [112]. Interestingly, WNT5A overexpression was reported in COC [113] and ameloblastomas [114]. In enamel epithelium cultured cells, WNT5A overexpression resulted in tumorigenic properties, such as growth factor independence [114], suggesting a role of WNT5A in the biology of ameloblast-like cells in odontogenic tumours.

Ghost cells are a common histological finding in COC. These cells may accumulate enamel-related proteins and undergo calcification [115]. Interestingly, COC ghost cells express WNT1 and WNT5A ligands, as well as Beta-catenin [116,117]. In immature odontomas, ghost cells showed weak Beta-catenin immunostaining, while adjacent epithelial cells exhibited a strong pattern in the nucleus and cytoplasm. Moreover, a positive staining for LEF-1 was found in the cytoplasm of the ghost cells and in the nucleus of adjacent odontogenic epithelial cells [118]. These results provide further support to the idea that the Wnt signalling is involved in the formation of the ghost cells.

Odontogenic lesions, mainly COC, are of particular interest, as they are well known to have striking histological similarities with the brain tumour craniopharyngioma. This can be attributed to their common embryologic origin from oral ectoderm [119]. The calcified material, ghost cells, and the CTNNB1 mutation are common findings in the adamantinomatous tumour subtype, which frequently mimics COC histology [119,120]. Conversely, the papillary craniopharyngioma subtype is highly correlated with recurrences already studied in the context of odontogenesis. Odontogenic cysts and tumours probably arise due to developmental defects, and no environmental mutation sources have been identified as a causative for them, they probably harbour quiet genomes similar to some paediatric tumours.

Different odontogenic cysts and tumours arise from different stages of dental lamina cells, as evidenced by their histopathologic features that resemble the embryologic patterns seen in the developing tooth. Pathogenic mutations affecting the same pathway are seen in different tumours, reinforcing the idea that the cell of origin, including its location in the jaws, is dominant to oncogenic signalling in these kinds of tumours.

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The authors declare that there is no conflict of interest.

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