Fusion genes as diagnostic and predictive biomarkers for tumor

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Abstract

Structural variants, including chromosomal rearrangements and translocations, may result in the formation of fusion genes. Glioma is the most frequent brain tumor among adults. Due to complex tumor classifications, characterization of recurrence, inadequate sample size and controversial mechanisms of tumor malignancy, clinical strategies have not been developed for almost 30 years. Fusion gene is one of the strong driver events in glioma tumorigenesis and has provided fundamental insights into the disease mechanisms. This review elucidates the literature on the discovery of fusion genes, the development of detection techniques, and their clinical implementations. In conclusion, fusion genes are important diagnostic and predictive biomarkers for brain tumors.

Keywords: Glioma; Fusion gene; Target therapy; PTPRZ1-MET fusion

1. Introduction

Brain tumors are one of the top ten common lethal tumors in the world, with an incidence rate of 15 – 20/100,000 and a prevalence rate of 130.8/100,000. According to the latest statistics in 2019, the incidence of brain tumors has gradually increased, and it has become the main cause of death in intracranial lesions[1]. According to foreign data estimates, it is projected that there will be approximately 200,000 new cases of brain tumors each year and there are about 2 million patients with brain tumors in China[2]. In the United States, about 13,000 people die from primary brain tumors and spinal cord tumors each year. The increase of the mortality rate of brain tumors even elevates their ranking from the 10th to the 9th most lethal human malignant tumors[3]. Despite the improvement of the treatment strategies for various types of tumors and the prolongation of patients’ survival period, the incidence of brain tumor progression was still on the rise in the last decade. Up to 20 – 40% of malignant tumors eventually undergo tumor progression, which has a great impact on human health[4]. Gliomas are the most common and lethal form of intracranial tumor in adults.

According to the World Health Organization classification of tumors of the central nervous system (CNS), adult gliomas are classified into Grade II to IV based on their morphological features[5-7]. In turn, Grade IV gliomas, or glioblastoma multiforme (GBM), can generally be classified into two subgroups[4]. Primary GBMs with isocitrate dehydrogenase (IDH) wild type, which are thought to be the predominant form of GBMs,
develop de novo in the elderly. By contrast, secondary GBMs, which are IDH mutant and typically progress from low-grade diffuse gliomas within 5 – 10 years of diagnosis[5], usually affect younger patients.

The median survival period of Grade IV patients with either primary GBM or secondary GBM is only 14 – 16 months[6], although standard treatment including maximal surgical resection and chemoradiotherapy is applied. The chemotherapy standard in current clinical practice is based on the alkylating agent temozolomide, but this agent may engender severe side effects and chemoresistance because of nonselective DNA damage[7]. Molecular therapies targeting the genetic alterations that drive glioma pathogenesis is expected to be more effective than temozolomide and cause fewer side effects. Thus, to improve therapies for glioma, it is crucial to identify new genomic alterations driving glioma progression and discover corresponding targeted drugs. Either National Comprehensive Cancer Network[8] or Chinese Glioma Cooperative Group[9] guideline has suggested standard therapeutic strategies for GBM patients. However, a more standard treatment guideline for recurrent glioma is currently not available; at the present stage, only a few evidence-based therapy suggestions have been made.

Since the discovery of Philadelphia chromosome in chronic myeloid leukemia (CML) back in 1960, many fusion genes and proteins have been identified using different approaches in other kinds of cancers over the past 60 years[10]. Deep sequencing provides a new means for identifying fusion genes. The FGFR3–TACC3[11] and MYB-QKI[12] fusion transcripts were at first recognized as the recurrent fusion transcripts in GBMs and pediatric gliomas, respectively. In addition, recurrent fusion rearrangement involving PTPRZ1 and MET genes (ZM) was found in 15% of secondary GBMs[13]. The nature and incidence of ZM fusion in secondary GBMs and other grades of gliomas have been investigated to elucidate the mechanisms by which ZM fusion contributes to glioma progression.

2. Gene fusion

Chromosomal rearrangements, followed by translocation and gene fusion, lead to the formation of hybrid genes from two originally separate genes. Gene fusion can occur as a result of translocation, interstitial deletion, or chromosomal inversion. In cancers of epithelial origin, the overall rate of balanced rearrangements or gene fusions has been evaluated as only 3%, while it is 29% in acute myelogenous leukemia and 19% in mesenchymal tumors[14]. The formation of a pathogenic fusion protein involves several mechanisms, including cell-extrinsic and intrinsic process: (1) Double-strand breaks (DSBs) are initiated by the cell-extrinsic mechanisms; (2) the ends of the breakpoint of DNA are led to close proximity; and (3) DNA junctions frequently demonstrate small stretches of homology that is associated with VDJ abnormality and class switch recombination (CSR), and genomic or transcriptomic stress[15].

It was thought that the DNA breakpoints are randomly selected and that many selections lead to various chromosomal rearrangements. However, it is now clear that various cell types, including tumor tissues, have abnormal nuclear and morphological changes that may promote specific DNA breakpoint. The low frequency of RET-CCDC6 breakpoints in breast cancer cells may lead to the chromosomal rearrangement in breast cancers samples[16,17].

3. Major research findings on gene fusions in cancer

The discovery of Philadelphia chromosome in CML in 1960[18] has brought about a series of studies that successfully identified fusion genes in a multitude of other neoplasia. The detailed analysis of neoplastic cell genome only became possible in the early 1970s when the chromosome banding technique was introduced[19]. These new techniques enabled detection of previously undetectable small genomic or transcriptomic rearrangements. The first analysis of genomic or transcriptomic rearrangements revealed that the Philadelphia chromosome in CML was one of the two normal chromosomes between chromosomes 9 and 22 (t(9;22)(q34;q11)), and t(8;21)(q22;q22)[20]. In the late 1970s, the conception of how chromosome abnormality contributes to tumor transformation by breakpoints of genes or regulatory elements laid a foundation to the emergence of fluorescence in situ hybridization (FISH) technique, which can simultaneously locate and identify different structure variants in different colors; this technique has dramatic impact on the elucidation of molecular mechanisms governing the tumor-associated chromosome rearrangements[21,22]. High throughput technology for global genetic analyses, including gene expression microarray and copy number profiling, provided better means for the detection fusion genes, and obviated the need for cell culturing. The first fusion gene detected by the high-throughput methods was the fusion of PAX3 and nuclear receptor coactivator 1 (NCOA1) in alveolar rhabdomyosarcoma[23]. In addition, deep sequencing provided a means, which was of better quality and resolution, to identify fusions some 10 years ago (Figure 1)[24,25].

4. Gene fusions in different types of cancer

Either chromosomal translocation or RNA fusion may lead to aberrant activation of oncogenic kinase with a traditional paradigm in epithelial cancers. Nowell
found a minute chromosome replacing one of the four smallest autosomes of chronic granulocytic leukemia cultured from peripheral blood in 1962 [20]. The aberrant chromosomal rearrangement was then named as “Philadelphia chromosome” to commemorate University of Pennsylvania where they both work in. The fusion protein encoded by BCR-ABL fusion is an abnormal tyrosine kinase that drives the development of myeloid leukemia; a drug was successfully developed against this fusion protein for healing CML [28]. Structure variants that lead to tumorigenesis by kinase activation are found in less frequency in solid tumor than that in hematologic malignancies, due to the difficult sample collection and technological limitation. RET fused to neurotrophic tyrosine kinase receptor type 1 (NTRK1) protein in thyroid cancer was the first fusion kinases found in solid tumors in 1985 [29]. With the advancement of Sanger sequencing, cytogenetic analysis and FISH, ETS variant 6 (ETV6) and NTRK3 fusion was identified in a rare subgroup of breast cancer, the secretory breast carcinoma [30]. The FET fusion gene was first reported in the early 1990s in patients with malignant soft-tissue cancers, for example, Ewing's sarcoma [31]. The respective RNA-binding proteins are fused to DNA-binding domains, forming ectopic condensates on DNA [32]. Overexpression of FET gene recruits the transcriptional machinery, including RNA polymerase II, thereby activating BRD4 and SWI/SNF pathway [33]. Nucleoporins belong to a multi-subunit complex that acts as a gateway between the cytoplasm and the nucleus [34]. Nucleoporin fusion consist of the N-terminal FG-repeat intrinsically disordered regions of nucleoporin fused to DNA-binding factors [35]. Also, the activation of RNA polymerase II activates BRD4 and SWI/SNF pathway. Receptor tyrosine kinase (RTK) signaling is an essential process for conveying signals from the marginal part to the inner part of cell [36]. Fusion genes between RTKs play an important role in tumor differentiation and progression [37]. The transcription of NPM-ALK fusion in anaplastic large-cell lymphoma produces mRNAs that are distinct from stress granules and are dependent on the activation of anaplastic lymphoma kinase (ALK) fusion protein [38]. In a similar way, the phosphorylation of the intracellular domain of the RTK activates the downstream signaling pathway to induce tumor malignancy. Multiple recent studies have reported that EML4-ALK (an RTK oncofusion) is fused to the cytoplasmic domain of the ALK, undergoing phase separation of the cell cycle with downstream effectors to form signaling-competent condensates in both lung cell lines and patient-derived xenografts [39, 40]. Enrichment of protein binding counterparts of ALK, such as SOS1 and growth factor receptor-bound protein 2, is necessary for forming punctuated fusion protein to enhance signaling activity [41]. Another RTK fusion gene, CCCD6-RET, demonstrates a kinase-independent fusion pattern that the N-terminal coiled-coil domain of CCCD6 is sufficient to drive dimeric interactions. Inhibiting CCCD6-RET leads to decreased downstream signaling, indicating...
that the formation of ectopic fusion is necessary for oncogenesis, although the formation of the fusion is distinct from that of RTK onco-fusion genes\textsuperscript{49}. Another interesting study also reported differences in component properties of condensates formed by different variants of EML4-ALK fusion protein. EML4-ALK variant 3 is more liquid-like compared to EML4-ALK variant 1\textsuperscript{41}. Compared to variant 3, the EML4-ALK variant 1 harbors an additional tandem atypical propeller in EMLs’ domain, leading to increased valence and more binding sites that reduce the mobility of the EML4-ALK protein. G protein-coupled receptors (GPCRs) proteins activate ligand-dependent signaling pathways such as the protein kinase A (PKA) pathway. Pathway activation by GPCRs is coupled with the conversion of ATP to cAMP, a second messenger protein that relates PKA subunit to active downstream signaling proteins. The regulatory subunit of PKA in the presence of cAMP induces phase separation of the cell cycle\textsuperscript{41}. However, the DnaJb1-PKAcat fusion protein formed by fused N terminus of DnaJb1 and the C terminus of PKAcat disrupts the formation of DNA condensate through a specific mechanism\textsuperscript{44}, leading to increased release of cAMP and its dispersion to other cellular effectors. The decreased activation of downstream signaling contributes to the activation of reprogramming and oncogenesis of undesirable pathways. Promyelocytic leukemia protein (PML) protein, which is often found in the nucleus, is involved in multiple functions, including DNA damage response, transcriptional regulation, and immune suppression. In addition, the PML protein serves as a scaffold that is paramount for condensate formation\textsuperscript{45}. The PML - retinoic acid receptor (RAR\alpha) fusion protein embodies the domain of RAR\alpha and PML, which could lead to acute promyelocytic leukemia (APL). Depicted as the dominant-negative regulator that inhibits the transcript variant of PML,\textsuperscript{46} PML-RAR\alpha fusion protein could dysregulate the DNA strand repair function\textsuperscript{47}. ABL is another famous tyrosine kinase that has DNA-binding activity and is involved in apoptosis and DNA damage repair; CML could be resulted due to the juxtaposition of ABL to BCR protein\textsuperscript{48}. The fusion proteins are characterized as having liquid-like properties, while the ABL kinase activity is necessary for promoting oncogenesis\textsuperscript{49}. The fusion proteins activate pathways involved in cell proliferation, adhesion, differentiation, and cell survival\textsuperscript{48}, and promote the enrichment of stress granules\textsuperscript{49}. It is believed that the fusion protein alters the properties and composition of stress granules. Nonetheless, low resolution of sequencing for the detection of fusion gene continually limited the search for chromosomal rearrangements until the emergence of next-generation sequencing and the declining price after 2005. Focusing on genes with abnormal expression values, Tomlins et al. identified prevalent genomic translocation of the transmembrane protease serine 2 gene (TMPRSS2), which fused to two genes encoding avian erythroblastosis virus E26 homologue (ERG; resulting in the TMPRSS2-ERG fusion gene) or ets variant 1 (ETV1; leading to the TMPRSS2-ETV1 fusion gene); these were the first fusion genes that have been found to define a major subgroup of an epithelial tumor\textsuperscript{50}. Intriguingly, the chromosomal rearrangement underlying a gene fusion, which retains two loci at the same chromosome band, could not have been investigated with the use of chromosome banding technology. Peptidomimetic inhibitors against the product of ERG fusion have been proven to inhibit prostate cell growth in prostate cancer\textsuperscript{41}, in a rate that is half of the cell inhibition rate caused by the inhibitors against TMPRSS2-ERG fusion protein. In the recent 5 – 10 years, the most frequently reported fusion event has been ALK fusion in lung cancer\textsuperscript{52,53}. Furthermore, Shinji et al. identified a novel CD74-NRG2a fusion from Japanese patients with lung adenocarcinoma who were either nonsmokers or light smokers\textsuperscript{54}. Jerby-Arnon et al. reported SS18-SSX fusion-induced suppressive immune microenvironment that shapes oncogenic programs in synovial sarcoma\textsuperscript{55}, revealing the association between the fusion event and tumor microenvironment.

5. Gene fusions in brain tumor

Although an increasing amount of gene fusions have been identified in some major neoplasia subtypes, there are few recurrent fusion events in CNS\textsuperscript{12}, especially in the pediatric CNS tumors. RAF kinases, such as BRAF and RAF1, exist as fusion proteins with various and different counterparts. BRAF is associated with an array of hematological as well as solid malignancies. Most of the BRAF aberrations are mutations, occurring within the kinase domain at amino acid V600. However, BRAF inhibitors, such as dabrafenib and vemurafenib, which are effective in other tumors, do not seem to be able to inhibit tumor proliferation in pediatric astrocytomas bearing BRAF fusions\textsuperscript{56}. In pediatric CNS neoplasia, 14 different BRAF fusions have been reported. The C-terminal part of BRAF is fused to the N-terminal part of other partners, including KIAA1549, CLCN6, GNA11, GTF21, GIT2, and FAM131B\textsuperscript{57,62}. The breakpoints often take place at the 9th exon of BRAF, which is the inhibitory regulatory domain. So far, there has not been found that the N-terminal counterparts is of great importance other than the removal of the inhibitory domain\textsuperscript{63}.

Selumetinib, one of the MEK inhibitors, has been demonstrated to be effective in a phase I/II trial where
pediatric low-grade glioma patients harboring KIAA1549-BRAF fusion gene were administered with the inhibitor\textsuperscript{64}. RAF1 is another member of the RAF kinases that is associated with the activation of the RAS/MAPK pathway. Owing to the limited number of fusion events of RAF1, its prevalence and characterizations as well as effectiveness of inhibitory compounds are still unclear. The second-generation RAF inhibitors are effective for pediatric astrocytoma harboring BRAF fusions by inhibiting the activation of the RAS/MAPK pathway, but are not effective for RAF1 fusions\textsuperscript{65}. It has also been reported that the N-terminal partners in RAF1 fusions are key factors for the tumorigenesis involving the fusion proteins. Furthermore, several counterparts such as SGRAP and QKI have already been implicated in other malignancies as well\textsuperscript{66}. This implies that the dimerization of these fusion counterparts is necessary for the tumorigenesis of the fusion protein.

ALK is a member of the insulin receptor superfamily of RTKs, which is a membrane-bound receptor in nerve cells, and can activates the PI3K/AKT/mTOR and JAK/STAT pathways\textsuperscript{67}. ALK fusion proteins are common in all kinds of pediatric and adult cancers. HIP1-ALK, EML4-ALK, and PPP1CB-ALK fusions have been described in various tumor types\textsuperscript{68}. The extent of oligomerization of ALK protein differs per counterpart, leading to a diversity in the tumorigenesis of different ALK fusion counterpart\textsuperscript{69}. Different ALK fusion proteins exhibit varying degree of sensitivity to ALK inhibitors, which should be considered when treating patients with ALK inhibitors. Fusion proteins that induce the phosphorylation of ALK can activate the MAPK pathway\textsuperscript{69}. In vitro and in vivo tests with ALK inhibitors demonstrated pre-clinical characterizations for tumor shrinkage in a PPP1CB-ALK-positive tumor as a response to lorlatinib, an ALK inhibitor\textsuperscript{70}. ROS1 is another member of RTKs that have an extracellular domain, a transmembrane domain and an intracellular kinase domain, and is associated with the activation of RAS/MAPK as well as the JAK/STAT and PI3K/AKT/mTOR pathways\textsuperscript{71}. In pediatric CNS tumors, the most common ROS1 fusion is G0PC-ROS1, which induces oncogenic signaling by translocating to the Golgi apparatus rather than by dimerization\textsuperscript{72}. All the fusion counterparts consist of a coiled-coil domain and occasionally a zipper domain, leading to the dimerization and activation of the ROS1 kinase. More in-depth research is required to understand whether other pathways and interactions also play a role in ROS1 kinase activation\textsuperscript{73}.

In high-grade pediatric gliomas, neurotrophic RTK (NTRK) fusion gene has been identified as an oncogene that activates MAPK-AKT pathway\textsuperscript{74,75}. The NTRK family consists of three members, namely, NTRK1, NTRK2, and NTRK3, which can activate the PI3K/AKT/mTOR and the PLCγ/PLK pathways\textsuperscript{76} and have been identified in several pediatric gliomas such as pilocytic astrocytoma, high-grade glioma and glioblastoma\textsuperscript{76,77,78}. In vitro and in vivo tests showed that ETV6-NTRK3 fusion protein mainly activates RAS/MAPK and PI3K/AKT/mTOR pathway. The activation of both pathways might induce the tumorigenesis of pediatric CNS tumor\textsuperscript{79}. While the percentage of NTRK fusion in other solid tumors is relatively low with a prevalence of around 5% in pediatric high-grade glioma and diffuse infiltrating pontine glioma, this fusion event still occurs in 40% of infants with non-brainstem high-grade glioma\textsuperscript{74}. NTRK could be a potential target for further targeted therapy in these tumors.

On the other hand, Quaking homolog genes (QKI), which are tumor suppressor genes, have been reported to fuse to MYB gene that suppresses expression of QKI, leading to malignancy in low-grade middle-line pediatric gliomas\textsuperscript{14}. A similar fusion event, which is associated with FGFR3 gene, has been identified in adult glioma samples by RNA sequencing. All FGFR fusion proteins retain all C-terminal partners that consist of a coiled-coil domain of FGFR and a kinase domain. In the fused mRNA, exon 16 of FGFR3 fused to exon 8 of TACC3\textsuperscript{13}. At the same time, the constitutive activation of FGFR3 also induces the activation of RAS/MAPK pathway\textsuperscript{80}. Parker et al. showed that FGFR3-TACC3 gene fusion escapes miR-99a inhibition in GBM patients, inducing over-expression of FGFR, leading to glioma malignancy\textsuperscript{81}. Then, Frattini et al. found the correlation between FGFR3-TACC3 fusion and metabolism of mitochondrion, indicating a novel mechanism of fusion-induced pathway activation\textsuperscript{82}. Bao et al. recently identified a novel recurrent fusion gene in glioma, PTPRZ1-MET fusion (ZM) in approximately 15% of secondary GBM patients. The four fusion transcripts contain four different breakpoints within the PTPRZ1 coding sequence, whereas the breakpoints in the MET gene are exactly the same. Survival analysis demonstrated that secondary GBM patients with ZM fusion had poorer overall survival than those without this fusion. The researchers performed a screening on 19 GBM cell lines using fusion-specific PCR primers to verify the recurrent nature of ZM fusion, and they were able to detect the fusion sequence in three cell lines and found significant MET, PT3K, and AKT overexpression in the ZM fusion-bearing GBM patients\textsuperscript{15}. Hu et al. subsequently identified a novel glioma-associated MET alteration, that is, MET exon 14 skipping (METex14), which promotes MET overexpression and hyperactivation of MET signaling. The co-expression of METex14 and ZM fusion activates...
MET and STAT3 signaling, followed by tumor-associated macrophage recruitment, which contribute to tumor malignancy. Some rare but recurrent fusion events, including ROS1 and PTPRZ1-ETV1 fusion, were also identified in adult glioma patients. MET fusion is the least common RTK fusion in pediatric CNS neoplasms. CLIP2-MET, TFG-MET, and PTPRZ1-MET fusions have been reported in pediatric CNS tumors with the kinase domain of MET retained. The CLIP2-MET and TFG-MET fusion proteins retain only the C-terminal part of the fusion and lack the domain that facilitates the activation of MET pathway. In addition, TFG has also been reported as a counterpart for fusing with MET in chimeric proteins. In addition to the MET fusion proteins, all patients possessed CDKN2A and CDKN2B deletions and/or TP53 mutations, indicating that the oncogenic potentials due to MET fusions are probably dependent on additional genomic or transcriptomic alterations in the cell cycle regulation.

6. Fusion gene targeted therapy in cancer

The development of fusion gene-targeted therapy strategies generally focuses on either the chimeric protein or one of the fusion proteins. Most fusion genes consist of one tyrosine kinase at least at the end of fusion protein. Hence, tyrosine kinase inhibitors (TKI) are frequently chosen to inhibit fusion-induced tumor malignancy. TRK fusions are oncogenic drivers of various adult and pediatric tumors. An intracranial activity has been recently reported in TRK inhibitor-treated patients with TRK fusion-positive solid tumors, specifically with brain metastases and primary brain tumors. ROS1, NTRK, and FGFR inhibitor have been selected to treat patients with different types of cancer, respectively. In addition, the combination of selpercatinib and crizotinib has been administered to RET fusion-positive lung cancer patients who were resistant to RET inhibitor as a result of MET fusion. Similar fusion event, BRAF fusion, has been recognized as a novel mechanism of acquired resistance to vemurafenib in BRAFV600E mutant melanoma. Fusion events are probably the mechanisms of TKI resistance, which could be treated using alternative or combined therapeutic strategies.

Of note, it has been reported that structural alterations of MET responded to MET inhibition in lung cancer patients. Hu et al. described a highly selective ATP-competitive small-molecule MET inhibitor known as PLB-1001, which has been shown to improve selectivity compared with Crizotinib (a well-known targeted inhibitor for glioma treatment) and inhibit the phosphorylation of MET and STAT3. Based on their in vitro analysis results, compared to other MET inhibitors such as Crizotinib, Cabozantinib, and Foretinib, PLB-1001 has higher permeability and lower efflux rate. On the other hand, the in vivo analysis demonstrated that PLB-1001 treatment significantly reduce the growth of ZM-harboring xenografts as compared to Crizotinib and vehicle treatments. Interestingly, a deep learning model that combines with the application of computed tomography image for predicting ALK fusion status and response to TKI therapy in non-small cell lung cancer patients provides a novel strategy for investigating the response of TKI targeting the fusion transcripts.

7. Clinical trials targeting fusion events

The chromosomal instability in gliomas and other solid tumors leads to tumor heterogeneity and structural variations, including exon skipping, fusion transcripts and chromothripsis, which are maintained by the selective pressure from a broad-spectrum approach involving chemotherapy and other targeted treatments that might provide the direction of further treatment and solve the problem of tumor heterogeneity and drug resistance. Despite some clinical trials that target fusion-induced tumor malignancy, most of these clinical trials focused on DNA-based rearrangement rather than fusion transcripts generated by alternative splicing. Various clinical trials focused on ALK, RET, FGFR, and ROS1 fusion-positive patients with lung cancer showed that progression-free survival and overall survival were prolonged after the patients were administered with fusion-targeted TKIs. Larotrectinib and Selitrectinib had marked and durable antitumor activity in patients with TRK fusion-positive solid tumors, regardless of the tumor type. However, there has been no breakthrough in the development of drug intervention for MET-induced genetic variation, including MET fusion and exon skipping in glioma and other types of cancer. In a Phase I, open-label study (NCT02978261), PLB-1001 was orally administered to recurrent high-grade glioma patients with ZM fusion and/or METex14. Out of the six enrolled secondary GBM patients, two achieved partial response, two in stable disease, and two in progressed disease with no severe adverse events; this finding indicates the potential inhibitory effect of PLB and help determine the dose required for further investigation in Phase II clinical trial. The median overall survival of the patients increased from 183 days to 466 days, and the 1-year survival rate increased from 8% to 67%. More in-depth mechanism studies, identification of more targets, and more Phases 2 and 3 clinical trials are urgently needed. We have identified MET fusion in brain metastases, which may mark the start of investigating the use of MET inhibitors on MET fusion-positive patients with different types of cancer from bench to clinic.
8. Conclusions and future perspectives

The exploration of fusion genes in variety types of cancer is conducive to the development of big data research of neoplasm-omics, which will lay a solid foundation for basic research and promote the integration of molecular pathology and bioinformatics disciplines. The data and findings from gene fusion studies, cancer mechanism research, bioinformatics data mining, molecular function verification studies, and targeted drug development and screening can be employed to elucidate development of brain tumor and other types of solid tumor. More in-depth research results are needed to advance the field of neuroscience so as to devise and improve treatment strategies for protecting brain health.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization: Zhaoshi Bao
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All authors have read and approved the manuscript.

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Table 1. Clinical trial targeting fusion events in various types of cancer

<table>
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<td>[100]</td>
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<td><strong>FGFR</strong> amplifications and fusions</td>
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<td>[103]</td>
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<tr>
<td>Solid tumors</td>
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<td><strong>TRK</strong> fusion</td>
<td>FoundationOne® (a hybrid-capture DNA assay)</td>
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<td>[104]</td>
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<td>RNA-seq and real-time PCR</td>
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</table>

FISH: Fluorescence in situ hybridization, NGS: Next-generation sequencing, PCR: Polymerase chain reaction, RNA-seq: RNA sequencing

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Fusion events identified in tumor


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