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Mini Review

RAS Oncogene in Brain Tumors, Let-7 MicroRNA Involvement

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Abstract

RAS oncogenes are master regulators of cancers. Somatic mutation in *KRAS*, *HRAS* and *NRAS* genes account for approximately 30% of human cancers. KRAS is the most frequently mutated isoform in *RAS*-driven cancers. Brain cancers are *RAS*-driven cancers despite have no *RAS* mutation or amplification and its pivotal role in brain tumorigenesis has been well documented. Indeed, it's generally accepted that glioblastoma shows aberrant activation of RAS/MAPK cascade due to mutations in upstream and downstream regulators. Since pioneering study reporting that let-7 miRNA acted as tumor suppressor by repressing RAS oncogene, growing evidence has suggested the importance of miRNA targeting the RAS-MAPK in brain oncogenesis. Let-7 family members are direct and strong regulator of the RAS family. KRAS, NRAS and HRAS mRNAs contain let-7 binding sites in 3'UTR sequences with clinical outcomes in some cancer. Although the expression levels of let-7 miRNA family are not reduced in brain tumors (with few exceptions), growing evidences show that let-7 miRNA inhibits the malignant behavior - proliferation, migration and invasion - of glioma cells and glioma stem-like cells as well as the tumor size in nude mice xenograft transplanted glioblastoma (GBM) via *KRAS* inhibition. More recently, genetic loss of let-7 is involved in neuroblastoma oncogenesis placing *let-7* disruption at the center of neuroblastoma pathogenesis. In addition, loss of let-7 increases resistance to certain chemotherapeutic drugs and to radiation therapy in GBM. We aim this review at summarizing and updating current knowledge on the contribution of let-7 miRNA interplay with KRAS to oncogenesis of brain tumors.

ABBREVIATIONS

miRNA: microRNA; let-7: lethal-7; GBM: Glioblastoma; 3'UTR: 3' Untranslated Region; NSCL: Non-small Lung Cancer; ERK: Extracellular Signal-regulated Kinase; MAPK: Mitogen-activated Protein Kinase; HMGA2: High-mobility Group AT-hook 2; CSCs: Cancer Stem-like Cells; EGFR: Epidermal Growth Factor Receptor; NF1: Neurofibromin 1; PDGFR: Platelet-Derived Growth Factor; TMZ: Temozolomide; BBB: Blood Brain Barrier; ICV: Intracerebro-ventricular

INTRODUCTION

The observation that RAS is directly regulated by microRNAs (miRNAs) added a new facet to the regulation of RAS [1]. MicroRNAs (miRNAs) are a class of non-coding RNAs that function as endogenous triggers of the RNA interference pathway. Aberrant miRNA expression can contribute to tumorigenesis, but which of the many miRNA-target relationships are relevant to this process has been unclear. *Lethal-7* (*let-7*) is a *bona fide* tumor suppressor gene, at least in lung and colon cancers.

Let-7 Targets Multiple Oncogenes (*RAS*, *c-MYC, HMGA2,* and so on) and the prominent (but not exclusive) mechanisms by which let-7 exerts a tumor suppressive role is by repressing the translation of the three RAS proteins (HRAS, NRAS, and KRAS) and c-MYC, a downstream effector of RAS-ERK[1-6]. There are also reports that suggest an oncogenic function for let-7 [7,8]. Thus, it is conceivable that let-7 may have pleiotropic cell-type specific biological effects depending on the milieu of expressed genes inside the cells.

The past decade has provided considerable insight into the critical regulatory roles that miRNAs exert over key cancer relevant signaling networks such as the RAS-ERK pathway. Our knowledge of how miRNAs can modulate RAS-ERK pathway activation continues to grow as potential miRNA-mRNA regulatory networks are identified using a variety of strategies. Three major paradigms of miRNA-mediated RAS-ERK regulation have emerged from these studies. miRNAs can impact the translation of (i) core RAS-ERK pathway components (e.g., let-7 targets *HRAS*, *NRAS*, and *KRAS*) [1], (ii) critical pathway regulatory proteins that are required for the proper spatio-temporal control of RAS-ERK signaling [8-10] and (iii) upstream drivers and downstream effector/regulatory molecules [11,12]. Exist many examples of miRNAs that regulate RAS-ERK pathway activity in a variety of cancer [6]. Indeed, these miRNAs represent potential therapeutic

substrates and targets that can be modulated in the treatment of cancer. In general, there is a very clear link between loss of let-7 expression and the development of poorly differentiated, aggressive cancers [13,14]. Studies analyzing *in vitro* and *in vivo* models of non-small cell lung cancer (NSCLC) show that let-7 expression is inversely correlated with the expression of KRAS, a critical promoter of NSCLC tumorigenesis. Let-7 abrogates tumor development and RAS-ERK signaling in an autochthonous model of NSCLC driven by activated KRAS (*KRASG12D*) [15,16]. Consistent with this previous result, a tumor suppressive role for let-7 was observed in a study analyzing a xenograft model of NSCLC [2] and increased expression of *let-7a* substantially reduces tumor burden in a *KRAS* murine lung cancer model [17]. Additionally, in a breast cancer context, let-7 antagonizes the maintenance, survival, and self-renewal of cancer stem-like cells (CSCs), and this suppressive activity was correlated with the reduced expression of *RAS* and *HMGA2* [18]. Thus, by suppressing *RAS* expression, let-7 can attenuate RAF-MEK-ERK signaling and dependent oncogenic phenotypes regardless of the RAS-mutation status of cancers. These studies suggest that let-7 can act as both a cancer-preventative and cancer-therapeutic agent, and point to let-7 supplementation as a promising strategy to target RAS-ERK signaling in the treatment of cancers. In this review, we evaluate miRNA let-7 that hold great promise as potential therapeutic targets in the treatment of brain cancers by impacting RAS-ERK signaling.

Let-7 in brain tumors

Brain tumors encompass a wide spectrum of over 120 histologically, demographically, clinically and molecularly distinct diseases [19] (Table 1).

Glioblastoma is the most common malignant primary brain tumor in adults. Despite advances in understanding the molecular mechanisms underlying these tumors, current treatments are ineffective [28-32]. Therapeutic trials against driving genetic abnormalities amenable to therapeutic targeting such as the epidermal growth factor receptor EGFR, have been largely negative in most brain cancers [33]. The standard of care for most brain tumors remains focused on maximal surgical resection, radiotherapy and chemotherapy. Indirect targeting of the tumor through anti-angiogenics (for example, bevacizumab) and immunotherapies (vaccines, adoptive therapies, immune checkpoint inhibitors and oncolytic viruses) have demonstrated preclinical activity but mixed efficacy in clinical trials [34,35].

Let-7 family members are direct and strong regulator of the RAS family. K-RAS, N-RAS and H-RAS. mRNAs contain let-7 binding sites in 3'UTR sequences [36,37].There is a small but growing body of literature regarding the predictive utility of a Let-7 microRNA-binding-site polymorphism in the 3′-untranslated region 3'UTR of *KRAS* (*KRAS-LCS6*) formany cancer outcome, although the results are conflicting [38-40]. MicroRNA detection has rapidly emerged as potential biomarkers, in patients with glioblastoma [41]. Based on the complete sequencing of the human genome as well as several high-throughput genomic technologies, the Cancer Genome Atlas (TCGA) has defined RAS/MAPK as one of the main pathways involved in GBM [42] and the expression levels of let-7 miRNA family are not reduced in GBM [43]. Regardless its expression levels, let-7 miRNA is able to impair glioblastoma growth and cellular migration via RAS inhibition [25,44]. Specifically, the authors showed that forced expression of let-7 miRNA reduced expression of pan-RAS, N-RAS, and K-RAS reducing proliferation and migration as well as the tumor size in nude mice xenograft transplanted GBM [45]. Particularly, over expressed let-7a inhibited glioma cell malignancy by directly targeting KRAS [23] and, more recently, let-7b inhibits the malignant behavior (proliferation, migration and invasion) of glioma cells and glioma stem-like cells [24]. In other brain tumors, indeed, tumor suppressor microRNA let-7 is able to inhibit cell proliferation in human neuroblastoma by targeting MYC [45] and its repression by lin28 in an *in vivo* mouse model induces neuroblastoma development [46]. Indeed, focal deletion of let-7 family members was found in medulloblastoma (let-7a-2 and let-7e) [18] and the let-7 family was validated in spontaneous and radiation-induced medulloblastoma (MB) [22]. More recently, genetic loss of let-7 is involved in neuroblastoma oncogenesis placing *let*-7 disruption at the center of neuroblastoma pathogenesis [23]. Conversely, miR-let7g found up-regulated in anaplastic medulloblastoma (MB) and differentially expressed in desmoplastic medulloblastoma (MB) [21] although the functional consequences of their dysregulation were not still investigated. Moreover, human glioblastomas often develop resistance to radiation therapy and recently has been suggested that let-7 could exert a role in mediating such resistance in down- or up-regulation the relative expression level of let-7 family in irradiated human glioblastoma cells [47]. It is perplexing how let-7 affects oncogenesis, as the large influx of new miRNAs and other kinds of non-coding RNAs are continuously defined. Numerous oncogenes and signaling pathways were demonstrated to be targets of let-7 miRNAs besides *RAS* (as such *MYC*) and *KRAS* is target of many other miRNA in gliomagenesis [48,49].

Table 1: WHO classification of tumors of the central nervous system [adapted by ref.19] and summary of main studies reporting let-7 miRNA expression in brain tumors.

Grade	Examples	Criteria	Reference
WHO I	Pilocytic astrocytoma	Low proliferating, discrete non-invasive tumor	
WHO II	Diffuse astrocytoma	Modest proliferating, partly invasive tumor	
WHO III	Anaplastic astrocytoma Anaplastic ependymoma	Fast proliferating invasive tumor	
WHO IV	Embryonal tumors Medulloblastoma Neuroblastoma Glioblastoma multiforme	Rapidly proliferating highly invasive tumor	Wang *et al* 2012; Turner *et al* 2010; Tanno*et al* 2016; Powers *et al* 2016; Song *et al* 2016; Wang *et al* 2013; Lee *et al* 2011; Wang *et al* 2016[20-27]

RAS oncogenes in brain tumors

The biological functions of the RAS family (Harvey rat sarcoma viral oncogene homolog (HRAS), Kirsten rat sarcoma viral oncogene homolog (KRAS) and neuroblastoma RAS viral oncogene homolog (NRAS) have been extensively studied for decades. Though only 1% of the GBM tumors have a *RAS* mutation or amplification, 10% of GBM tumors contain *neurofibromin 1* (*NF1)* inactivating genetic alterations that lead to hyperactive RAS activity by enhancing the intrinsic GTPase activity [42,50]. Three recent reports focused on miRNAs targeting RAS in GBM and showed that miR-143-3p directly targets NRAS [51], let-7a-5p directly targets KRAS [25], and both NRAS and RRAS (related RAS viral oncogene homolog, HRAS homolog) are direct targets of miR-124-3p [52].

Deregulated RAS signaling is an important step in cancer initiation, with activating RAS mutations implicated in 30% of all cancers [53]. Unlike many human tumors, *RAS* mutation is not common in human glioma with some exceptions such as cerebellar GBM [54]. Hyperactive *RAS* signaling alone is sufficient to produce gliomas that closely resemble human tumors in glioma mouse models. Thus the RAS pathway is central in human gliomagenesis. Primary GBMs, and more recently relapsed neuroblastoma, are associated with disturbed RAS signaling and expression of oncogenic HRAS results in a malignant phenotype in glioma cell lines [55-58]. Particularly K-RAS oncogene is strongly involved in glioblastoma tumorigenesis [56,59-61] although KRAS mutations are nearly absent in malignant gliomas [62]. Therefore, the observed deregulation of the Ras-RAF-ERK signaling pathway in gliomas is generally attributed to its upstream positive regulators, including, EGFR and Platelet-Derived Growth Factor (PDGFR) known to be highly active in the majority of malignant gliomas [50]. It is likely that mechanisms other than mutations contribute to RAS-MAPK pathway activation in wild-type cancers. Recently, epigenetic alterations were described to potentiate this activation in human tumors [6] and dysregulation of physiologic microRNA (miR) activity has been shown to play an important role in tumor gliomagenesis but the functional relevance of this regulatory layer is currently unknown [63-68].

mi-RNA in treatment of brain tumors

Current postoperative standard treatment for GBM patients is mainly based on unselective induction of DNA damage via radiotherapy and alkylating agents such as Temozolimide (TMZ) [28-32]. The majority of drugs specifically targeting key signalling pathways and mechanisms of gliomagenesis, such as RTK signaling (erlotinib, gefitinib, cetuximab and imatinib) or angiogenesis (bevacizumab and cediranib) do not provide a significant survival benefit when tested alone or in combination with other therapies [31,69]. Though development and optimization of improved miR delivery methods (the principal problem) is necessary [70], targeting RAS-ERK signaling by miR-based therapeutics holds great promise in the treatment of cancers that are reliant on this signaling pathway. Therapeutic anti-miRs are currently being developed for cancer therapy [71,72], however, this is still at an early stage and has not yet been introduced in a clinical setting. Thus far, no clinical trial on miRNA intervention has been conducted in GBM [73]. Interestingly, some authors reported the functional efficiency of anti-miR Let-7a delivery *in vivo* evaluating its practicality for preclinical study in glioblastoma [74]. In this report authors demonstrate that anti-miRs are able to penetrate the Blood Brain Barrier (BBB) (which makes systemic treatment more difficult) without the use of any viral or lipid carriers, and intracerebro-ventricular administration of anti-miRs could lead to whole-brain distribution, including the tumor region.

CONCLUSION

Control of KRAS expression by the let-7 family of miRNAs has been well documented. The significance of this control mechanism has been highlighted in a number of studies that report a correlation between let-7 expression and cancer. Low levels of let-7 expression in human tumors correlate with high levels of KRAS (at least in lung and colorectal cancers). The control over KRAS expression and activity in glioblastoma (wild-type *KRAS* tumors) indicates that let-7, even without oncogenic mutation, can regulate *RAS* activity and that this might be a general phenomenon related to the interactions between tumor suppressor genes (let-7) and proto-oncogenes (*KRAS*) or oncogenes (KRASG12V or G12D). The possibility of upregulation of tumor suppressor along epigenetic downregulation of proto-oncogenes is an interesting phenomenon and should be studied in future research.

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