MicroRNA, Stem Cells and Brain Tumors

MiR-7, miR-124 and miR-128

Cancer cells and normal stem cells share common features. Stem cell behavior is strongly influenced by microRNAs (miRs), and in cancer cells miRs play a key role in promoting tumorigenicity. Studies in brain tumors strongly suggest that miRs involved in neural development and stem cell maintenance are dysregulated in cancer cells. A theme is now emerging in which miRs drive tumor growth through promoting the stem cell-like properties of tumor cells.

Cancer and Stem Cells

Tissue development and maintenance is controlled by rare tissue-specific stem cells that provide a source of new cells for regeneration and repair throughout life. Like cancer cells, stem cells have the capacity for unlimited proliferation, and pathways involved in stem cell regulation such as Wnt, Notch and Hedgehog are important in cancer biology. It was initially shown that leukemia and breast cancer may be driven by a sub-population of cells known as cancer stem cells [1]. Similar cells have been identified in glioblastoma multiforme (GBM), the most common and aggressive primary brain tumor, with a median survival of just 14 months. GBM cells share many similarities with neural stem cells; they can be grown under conditions used for the propagation of neural stem cells, and can differentiate along neural, astrocytic and oligodendroglial lineages. Stem cell genes such as Nestin, Bmi1, Olig2 and Sox2 are expressed in GBM. Tumor cells may exploit mechanisms of stem cell self-renewal in order to proliferate, and the mechanisms that allow normal neural stem cells to fully differentiate maybe blocked in GBM, promoting aggressive tumor growth.

There is a great need for new therapeutic approaches for GBM. Recent developments include the discovery of miRs, which have a central role in the regulation of gene expression, and are clearly linked with cancer [2].

MiRs and Neural Development
MiRs are approximately 23 nucleotide RNA molecules that suppress translation of mRNAs through binding to complementary sequences in their 3'-untranslated regions. There are potentially thousands of miRs in the human genome, each with hundreds of target mRNAs.

The newly transcribed precursor miR forms a hairpin structure that is processed by the RNAse Dicer, to form the mature single-stranded miR that binds to its target sequences and suppresses translation (fig. 1) [3]. MiRs play an important role in the regulation of development. Indeed, the first miR discovered, lin-4, was identified based on its involvement in the control of development in C. elegans [4]. In mammals, miRs regulate embryonic stem cell differentiation as well as other tissue-specific stem cells including those in the CNS [5].

The exquisite regulation of neural stem cells gives rise to progenitor cells that ultimately form the fully differentiated repertoire of glia and neurons that constitute the bulk of the CNS. 70% of known miRs are expressed in the brain, where many are exclusively expressed [5]. The most highly expressed miRs in brain are miR-124 and miR-128, both of which are preferentially expressed in neurons, with other miRs showing specific expression in astrocytes. Ablation of the miR processing machinery blocks miR action and prevents proper brain development. Thus miRs strongly influence the behavior of neural stem and progenitor cells - the normal cell types thought to be most similar biologically to glial tumor cells.

MiR-124 is the most abundant miR in the brain. It is expressed in differentiating and mature neurons, where it promotes differentiation by repressing non-neural genes. In neural stem cells, miR-124 expression is blocked by the REST (RE1 transcription factor) repressor of transcription. REST represses many neural genes and is lost during neural differentiation, allowing miR-124 expression. Furthermore,
miR-124 targets include SCP1, which acts as part of the REST complex [6]. This results in the establishment of a double-negative feedback loop between miR-124 and the REST complex, where miR-124 repression of REST activity may lock neural differentiation in place. This kind of feedback loop is an increasingly common theme in miR action. The basic principle is shown in figure 2 [7].

MiRs in GBM - the Stem Cell Connection

Like other cancers, a characteristic miR expression profile is seen in GBM. Altered miRs play roles in cell proliferation, invasion, angiogenesis, and in glioma stem-like cell behavior. There is a striking correlation between miR alterations in GBM and those so far identified in neural development (table 1). MiR-124 and miR-7 have been shown to play roles in promoting neural development and are highly expressed in neurons and not in neural stem cells. They are also very weakly expressed in GBM, and have profound tumor suppressive effects on glioma cells when ectopically expressed [8,9]. Similarly, miR-128 is weakly expressed in GBM and highly expressed in neurons, and may play a role in stem cell self-renewal [10]. These observations suggest that certain miRs allow continued tumor growth through the suppression of differentiation and the maintenance of the stem cell-like properties of tumor cells.

MiR-124 is the most differentially expressed miR between GBM and normal brain [9,10]. miR-124 expression increases during neural stem cell differentiation, and GBM-derived stem cells over-expressing miR-124 display a dramatic increase in neural differentiation markers accompanied by reduced self-renewal and tumorigenicity. Moreover, miR-124 induced G1 cell cycle arrest in GBM cells, associated with decreased expression of CDK6 - a direct target of miR-124 [9]. These results suggest that low levels of miR-124 in GBM increase tumorigenicity by preventing differentiation and allowing cell cycle progression.

Like miR-124, miR-128 is downregulated in GBM, and miR-128 expression reduces glioma proliferation in vitro and in vivo [10]. The known oncogene and stem cell renewal factor Bmi1 was demonstrated to be an important target of miR-128. Bmi1 is a polycomb family transcriptional repressor required for maintenance of neural stem cells, and functions in the repression of many genes including known tumor suppressors. Thus Bmi1 maintains neural stem cells in an undifferentiated self-renewing state. In glioma-derived stem cells stably over-expressing miR-128, Bmi1 levels were reduced and self-renewal was severely impaired [10]. MiR-128 has been shown to be enriched in brain, specifically in neurons, especially in the cortex and hippocampus in the mouse, but its function in neural differentiation is not known.
These glioma studies suggest that the regulation of Bmi1 by miR-128 may be relevant to normal stem cell regulation. The potential roles of miR-124 and miR-128 as they related to stem cell self-renewal are shown in figure 3.

Concluding Remarks

Several miRs have been identified with functional importance in neural development. In parallel, miR alterations have been identified in GBM. There is a remarkable co-incidence in the miRs studied in these fields thus far. In particular, miR-7 and miR-124 promote neural differentiation and are not readily detected in glioma. MiR-128 plays a role in glioma, and its low levels in glioma promote stem cell self-renewal driven by Bmi1. The combined effects of miR alterations to increase self-renewal, and block differentiation may be a key part of the pathology of GBM and other cancer types. It may be possible in the near-future to harness these activities for improved cancer treatment.

References


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