Manipulating MicroRNAs to Regulate Macrophage Polarization in Gliomas

Sudarshan Anand, Lisa M. Coussens

Correspondence to: Lisa M. Coussens, PhD, 3181 SW Sam Jackson Park Road, Richard Jones Hall Room 5508, Portland OR 97239 (e-mail: coussenl@ohsu.edu).

Tumor associated macrophages (TAMs) play a critical role in solid tumor development where they regulate neoplastic cell proliferation, survival and invasion, promote angiogenesis, and impact effector functions of T cells (1). Typically, TAMs activated by toll-like receptor (TLR) signaling or interferon (IFN)-γ are considered classically activated or Th1-type cells, whereas those activated by interleukin (IL)-4/13 or IL-10 are characterized as alternatively activated Th2-type macrophages (2). Although these are simplistic descriptions of a complex heterogeneous and dynamic population of myeloid cells in tumors, these variably polarized states enable a broad understanding into how these important cells provide either a restrictive (antitumor) or permissive (protumor) environment regulating tumor progression (1). Notably, functional significance of TAMs in several tumor types (breast, melanoma, and pancreas) has recently been revealed (3–5), as well as in glioma, wherein functional reprogramming of TAMs via blockade of colony-stimulating factor-1 receptor (CSF1R) markedly limits tumor development (6).

MicroRNAs (miRs) are small, 20–24 nucleotide-long RNAs that regulate gene expression by binding to mRNAs (7). miRs represent approximately 1% to 2% of genes in several species, including mammals. Current estimates indicate that the human genome contains 1872 miR precursors that are processed into 2578 mature miRs (1186 precursors processed into 1908 mature miRs in mouse). Accordingly, miRs have been found to play a role in regulating essentially all physiological and pathological processes in mammals, including functions of TAMs (8–10).

In this issue of the Journal, Xu et al. (11) reveal the role of a specific miR, miR-142-3p, in regulating TAM polarization and thus function in glioblastoma. The authors identified dysregulated miRs in the glioma tumor microenvironment (TME) by comparing miR profiles of TAMs and monocytes derived from glioblastoma patients vs healthy donors. Their results identified miR-142-3p as being statistically significantly downregulated in glioma-associated TAMs as compared with monocytes. Experimentally, the authors addressed the functional significance of this observation by revealing that ectopic expression of miR-142-3p led to downregulation of transforming growth factor beta receptor I (TGFBRI) in vitro in Th2- but not Th1-type TAMs, thus leading to cell death. Based on higher levels of miR-142-3p expression in Th1-polarized TAMs, the authors postulated that repression of miR-142-3p actively fosters Th2 polarization and TAM survival, and thus hypothesized miR-142-3p targeting as a therapeutic strategy to reduce presence of protumoral TAMs in glioma. Indeed, the authors demonstrated that treatment of mice with miR-142-3p decreased tumor burden and survival in subcutaneous and orthotopic models of murine glioma.

In addition, the authors demonstrated that in a transgene-induced glioma model there was decreased TAM presence upon miR-142-3p treatment. Notably, whereas the authors’ data indicates that administration of miR-142-3p leads to decreased F4/80-positive cells in tumors, it is unclear if this is also associated with alterations in expression of critical Th1/Th2 cytokines or chemokines, and, as noted by the authors, a mechanistic basis for proapoptotic functions of miR-142-3p via inhibition of TGFB signaling remains to be elucidated. Through a loss-of-function study with a miR inhibitor in Th1-type macrophages, the authors did reveal repolarization of cells to favor a Th2-phenotype, thus supporting the notion that miR-142-3p directly regulates macrophage polarization and function. This study provides proof of concept that manipulating miR levels in TAMs can effect tumor development in murine glioma.

miR-142-3p is one of the more abundant and well-described miRs in the hematopoietic system (12–14). For example, Nimmo and colleagues reported that miR-142-3p was responsible for definitive hemangioblast specification during development by its regulation of TGFB signaling (15). More recent studies using reporter mice harboring a loss-of-function allele indicate that miR-142-3p plays a critical role in the differentiation of platelets by regulating the actin cytoskeleton during megakaryopoiesis (16). There are also contradictory studies reporting that miR-142-3p promotes monocyte-to-macrophage differentiation via CSF-1 in in vitro systems (17), as well as inhibiting TAM differentiation during cancer-induced myelopoiesis (18). These findings are not surprising given that TAMs possess numerous regulatory activities in tumors, owing to the local concentrations of cytokines, chemokines, and oxygen levels to which they are exposed (1). It will be interesting to determine whether mice harboring defects in platelet differentiation also harbor altered TMEs as a function of miR-142-3p regulation.

Although Xu et al. (11) focus their efforts on the TGFB pathway, given its role in macrophage polarization and tumor progression, there are many other targets that could mediate phenotypes, owing to activity of miR-142-3p. Considering that each miR can target several hundred transcripts, there are literally several thousand permutations of miR-target interactions possible, especially in the complex milieu of a dynamic TME. However, recent research indicates that RNA secondary structures determine the nature of these interactions, leading to a more defined set of miR targets than are likely to be physiologically relevant in different cell types (19,20). While investigating all targets of miR-142-3p in TAMs is beyond the scope of a single manuscript, such data either
by analysis of gene expression or proteomic approaches will add a wealth of information to our current understanding of TAMs. Specifically, if miR-142-3p regulates IL-6Rβ, IL-7/7R, IL-17C, or IL-1 receptor-associated kinase (IRAKs) 1–4 (all predicted by multiple algorithms), it would then also exert a profound influence on TME structure and function well beyond macrophage polarization.

In conclusion, this study highlights a miR-based approach to manipulate the TME by altering macrophage polarization and thus phenotype. Since their discovery in 1993, understanding of miRs has substantially progressed both as fundamental regulators in biological systems and as agents of therapeutic promise for multiple human diseases (21). The first in-human clinical trial of a miR therapy with an anti-miR-122 in hepatitis C virus demonstrated an excellent safety profile and efficacy (22). Although cancer is a more daunting challenge for miR therapies, there is hope that miRs can alter pathological processes just enough for other conventional therapies, particularly immunotherapies, in order to be more effective.

References


Funding

SA acknowledges funding support from the National Heart, Lung, and Blood Institute/National Institutes of Health (R00HL112962) and the Knight Cancer Institute/OHSU. LMC acknowledges support from the National Cancer Institute/National Institutes of Health (R01CA130980, R01CA140943, R01CA15531, U54CA163123), the Department of Defense Breast Cancer Research Program (W81XWH-11-1-0702), the Susan G Komen Foundation (KG110560, KG111084), and the Breast Cancer Research Program (W81XWH-11-1-0702), the Susan G Komen Foundation (KG110560, KG111084), and the Breast Cancer Research Foundation.

Affiliation of authors: Department of Cell, Developmental and Cancer Biology, and Knight Cancer Institute, Oregon Health and Science University, Portland, OR.