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MicroRNAs and the cellular response to rapamycin

Potential role in diagnosis and therapy

Hana Totary-Jain* and Andrew R. Marks

Department of Physiology and Cellular Biophysics and The Clyde and Helen Wu Center for Molecular Cardiology; College of Physicians and Surgeons of Columbia University; New York, NY USA

The mammalian target of rapamycin (mTOR) is a major regulator of cell growth, motility and angiogenesis that is often deregulated in malignancies. mTOR inhibitors have been approved for the treatment of renal cell carcinoma and mantle cell lymphoma. Currently, second-generation mTOR inhibitors are under clinical evaluation.[1] Major challenges remain in the identification of patients who will respond to mTOR inhibitors and the development of therapeutics that can overcome intrinsic resistance or acquired resistance. There are currently no biomarkers that predict tumor response to mTOR inhibitors.

MicroRNAs (miRNAs) are endogenous small non-coding RNAs that regulate gene expression. MiRNAs participate in many biological processes, including proliferation and apoptosis. MiRNAs are often deregulated in cancer and act as tumor suppressors or oncogenes.[2] Recently miRNAs emerged as diagnostic and prognostic markers to assess therapeutic responses, giving rise to the field of miRNA pharmacogenomics.[3] Numerous studies indicate that mTOR and its signaling pathway is regulated by miRNAs. However, little is known as to whether miRNAs play a role in the intrinsic tumor resistance or the development of acquired resistance to mTOR inhibitors.

In our recent studies we used rapamycin-resistant (RR1) variants of the murine brain tumor cell line BC3H1, developed by chronic rapamycin treatment. We previously showed that these RR1 cells exhibit persistent hyperphosphorylation of retinoblastoma protein, releasing the transcription factor E2F to increase the expression of Skp2 (substrate recognition subunit of the SCF^{SKP2} ubiquitin ligase complex), which, in turn, increases the turnover of the cyclin-dependent kinase inhibitor p27.[4,5] We also showed that in both RR1 cells and the parental rapamycin-sensitive BC3H1 cells, rapamycin inhibited mTORC1 and mTORC2 in the same manner, suggesting that RR1 cells have developed an mTOR-independent mechanism to survive (**Fig. 1**).[6] Intriguingly, RR1 cells exhibited extensive reprogramming of miRNA expression, characterized by upregulation of oncogenic miR-17-92 clusters and downregulation of tumor suppressors miRNAs. In contrast, rapamycin-sensitive cells exhibited an increase in tumor suppressor miRNAs.[6] The dysregulated miRNAs found in RR1 cells affected global gene expression and were associated with an increase in the expression of the oncogene Myc (**Fig. 1**). Downregulation of Myc or inhibition of miR-19 or miR-17, which share seed sequences with other members of the miR-17-92 cluster, restored the sensitivity of RR1 cells to rapamycin, suggesting that the miR-17-92 cluster may mediate Myc-induced resistance to rapamycin. We also showed that RR1 cells have adopted a miRNA-based homeostatic mechanism to resist tumor-suppression networks such as TGFβ (**Fig. 1**).

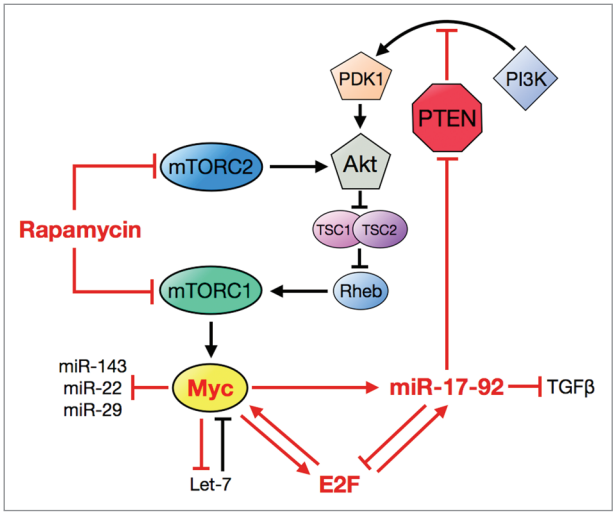

Figure 1. MicroRNAs affect the cellular response to rapamycin. In rapamycin-resistant cells, both mTORC1 and mTORC2 were inhibited by rapamycin and also exhibited upregulation of Myc and the oncogenic miR-17-92 and related clusters (in red) and downregulation of tumor suppressors miRNAs (in black). Upregulation of let-7 or downregulation of miR-19 or miR-17, members of miR-17-92 cluster, restored sensitivity to rapamycin.

*Correspondence to: Hana Totary-Jain; Email: ht2167@columbia.edu
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Myc upregulates the oncogenic miR-17-92 clusters and miR-19, a key component of these clusters promoted cell survival by targeting PTEN.[7] On the other hand, Myc also downregulates numerous tumor-suppressor miRNAs, including the let-7 family of miRNA, which suppresses its own expression. In fact, we showed that the let-7 family of miRNAs antagonizes the expression of Myc and mediates the inhibitory effect of rapamycin.

This work has numerous implications for cancer therapies. It shows that miRNAs may affect the cellular responses to rapamycin and therefore can be used as biomarkers to assess the efficacy of mTOR-targeted therapy. Moreover, these recent studies may lead to the development of novel miRNA-based targeted therapy to treat rapamycin-resistant tumors.

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