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Levels matter: miR-206 and cyclin D1

Comment on: Alteri A, et al. Cell Cycle 2013; 12:3781–90; PMID:24107628; http://dx.doi.org/10.4161/cc.26674

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The complexities of cellular regulations seem to never end. RNA, in particular, appears to exert ever-new regulatory functions in an astonishing variety of ways. miRNAs are especially wondrous, in that they can modulate hundreds of targets at once. Dissecting the cellular effects of myriad such multiplex regulations will probably keep biologists busy for many years to come.

In this issue of *Cell Cycle*, a study by Alteri et al.[1] shows that cyclin D1 (CycD1) is an important target for miR-206. This miRNA is highly expressed late in skeletal muscle differentiation and—the authors find—in heart and lung.

CycD1 lies at a crucial crossroad, being one of the main transcriptional targets of several signal transduction pathways and, in fact, behaving as a sensor for growth factors and cell adhesion.[2] In many cell types, this cyclin is essential to activate cdk4 and/or cdk6 and initiate pRb phosphorylation, which, once completed, allows entry into S phase. Thus, CycD1 is a major mediator of the proliferative response elicited by growth factors and cell adhesion. Because of this role, it is also a proto-oncogene, being frequently overexpressed in a variety of tumors[3] and contributing to pRb dysregulation and unrestricted proliferation.

In their paper, Alteri and coworkers show that miR-206 reduces CycD1 protein levels in a functionally significant fashion. They find that knocking down miR-206 in terminally differentiated skeletal muscle cells (myotubes) induces accumulation of CycD1 protein in a histotype normally devoid of this molecule but capable of expressing its mRNA. Thus, the authors speculate that miR-206, by suppressing CycD1 expression, might contribute to the maintenance of the postmitotic state. Though unproven, this contention is made plausible by the observation that forced CycD1 expression can drive the cell cycle in both terminally differentiated myotubes[4] and cardiomyocytes.[5]

On the tumorigenesis side, miR-206 overexpression reduced CycD1 levels in and proliferation of ras-transformed NIH-3T3 cells and A549 lung carcinoma. More important, in a small number of primary human non-small cell lung tumors, expression of miR-206 was generally reduced and strongly anti-correlated with CycD1 protein levels. The latter results support the suggestion, repeatedly made in the literature, of an involvement of miR-206 in tumorigenesis. The new data imply suppression of CycD1 as one possible mechanism through which miR-206 might affect carcinogenesis. One might further speculate that, since miR-206 is capable of suppressing a known oncogene, it might be a true tumor suppressor gene and, as such, be deleted, modified, or directly repressed in human tumors.

References

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