Re-dicing the pancreatic β-cell: do microRNAs define cellular identity?

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Understanding the mechanisms which contribute to successful growth and function of the pancreatic β-cell is essential to our ability to combat the global epidemic of diabetes. To date, there is limited in vivo data addressing the role of microRNAs or components of the RNAi machinery in the pancreatic β-cell. In this issue of The EMBO Journal, Melkman-Zehavi et al provide further evidence of how small RNAs contribute to the normal growth and function of this cell type, characterizing the metabolic consequences of Dicer depletion. Their study highlights the role of miR-24, miR-26, and miR-148 in promoting insulin mRNA levels and begins to suggest potential for many other microRNAs to contribute to an already complex story.

The ribonuclease III (RNaseIII) enzyme Dicer is widely recognized for its role in the processing of double-stranded RNA (Bartel, 2009). As the initial publications by Greg Hannon and colleagues reporting its identification and role in development, subsequent conditional knockout studies have continuously re-emphasized that Dicer is essential for the processing of mature microRNAs and for cellular survival. Furthermore, as total loss of Dicer in mice results in embryonic lethality, and also impairs the assembly of centromeric heterochromatin, it is clear that this gene impacts a broad range of cellular processes (Siomi and Siomi, 2009). What remains to be determined is how its functions are interwoven, and how the microRNAs processed by Dicer coordinately facilitate the needs of the cell.

To date, the compound loss of both miR-106b-25 and miR-17-92 is the only microRNA mutant to result in lethality (Ventura et al, 2008). Also, murine loss of function models for microRNAs, such as miR-21 (Patrick et al, 2010), have been reported with phenotypes apparent only under stress. Taken together, these observations make it difficult to weigh the relative contribution of each Dicer function to the lethal phenotype. Does the global decrease in microRNAs that are processed by Dicer outweigh the effects on chromatin assembly or other functions yet to be ascribed to this gene?

Figure 1 Loss of Dicer decreases the expression of insulin in pancreatic β-cells. Sox6 and Bhlhe22 are targeted by miR-24, miR-26, and miR-148 to facilitate insulin production. Dicer deficiency decreases these microRNAs and allows for these transcriptional repressors to inhibit the expression of insulin mRNA.
Nonetheless, given previous studies using Dicer conditional mutants, the observations reported here by Melkman-Zehavi et al. (2011) show a somewhat surprising outcome. Strikingly, Dicer-deficient pancreatic β-cells lose their expression of insulin with only a slight but insignificant effect on pancreatic β-cell mass. A subtle decrease in cell number due to apoptosis would not be surprising as genetic ablation of Dicer is frequently associated with cell death. Evidence is provided that miR-24, miR-26, and miR-148 contribute to the direct regulation of two target genes known to repress expression of insulin, Sox6 and Blhle22 (Peyton et al., 1996; Iguchi et al., 2005) (Figure 1). Both genes are well-established regulators of developmental processes, but the relevance of their regulation by these microRNAs with respect to the growth of β-cells remains to be explored. Still, the question remains: is the decrease in insulin expression due solely to alterations in the expression of specific microRNAs or also to changes on the heterochromatin? In addition, if pancreatic β-cells in this model have lost expression of Dicer, and in turn insulin, can they still be considered β-cells? The expression of insulin is generally seen as the sole attribute to distinguish pancreatic β-cells from all other cell types. If this population of mutant cells has lost expression of this hormone, have they in fact transformed into another cell type? Immunofluorescence has been employed to confirm expression of established pancreatic markers such as Pdx1, MafA, Nkx6.1, and Pax6 to suggest that these Dicer-deficient cells maintain a part of their β-cell identity. Of note, electron microscopy could have proved useful to determine dramatic changes in their morphological composition such as the complete absence of insulin-containing secretory granules or changes to β-cell size. With the establishment of a link between insulin levels and the expression of Dicer, this raises the point that the small RNA profile can be used to identify specific cell types or their origins. Can the microRNAs addressed in this study, miR-24, miR-26, and miR-148, and their expression levels along with miR-375 and miR-7, be used to establish a β-cell-specific expression ‘signature’? As the expression of microRNAs is known to differ between tissues, it is possible the small RNA profile may one day be used for classification.

Of note, the data presented here are in contrast to a report implementing a constitutively active RIP2-Cre line to deplete Dicer, where the authors reported no abnormalities with respect to pancreatic β-cell maintenance, islet development, or on circulating glucose levels (Lynn et al., 2007). Curiously, data on this mouse line were only discussed at a point that the small RNA profile can be used to identify specific cell types or their origins. Can the microRNAs addressed in this study, miR-24, miR-26, and miR-148, and their expression levels along with miR-375 and miR-7, be used to establish a β-cell-specific expression ‘signature’? As the expression of microRNAs is known to differ between tissues, it is possible the small RNA profile may one day be used for classification.

Conflict of interest

The authors declare that they have no conflict of interest.

References


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