Changes in microRNA (miRNA) expression during pancreatic cancer development and progression in a genetically engineered Kras^{G12D};Pdx1-Cre mouse (KC) model

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ABSTRACT

Differential expression of microRNAs (miRNAs) has been demonstrated in various cancers, including pancreatic cancer (PC). Due to the lack of tissue samples from early-stages of PC, the stage-specific alteration of miRNAs during PC initiation and progression is largely unknown. In this study, we investigated the global miRNA expression profile and their processing machinery during PC progression using the Kras^{G12D};Pdx1-Cre (KC) mouse model. At 25 weeks, the miRNA microarray analysis revealed significant downregulation of miR-150, miR-494, miR-138, miR-148a, miR-216a, and miR-217 and upregulation of miR-146b, miR-205, miR-31, miR-192, and miR-21 in KC mice compared to controls. Further, expression of miRNA biosynthetic machinery including Dicer, Exportin-5, TRKRA, and TARBP2 were downregulated, while DGCR8 and Ago2 were upregulated in KC mice. In addition, from 10 to 50 weeks of age, stage-specific expression profiling of miRNA in KC mice revealed downregulation of miR-216, miR-217, miR-100, miR-345, miR-141, miR-483-3p, miR-26b, miR-150, miR-195, Let-7b and Let-96 and upregulation of miR-21, miR-205, miR-146b, miR-34c, miR-1273, miR-223 and miR-195 compared to control mice. Interestingly, the differential expression of miRNA in mice also corroborated with the miRNA expression in human PC cell lines and tissue samples; ectopic expression of Let-7b in CD18/HPAF and Capan1 cells resulted in the downregulation of *KRAS* and *MSST1* expression. Overall, the present study aids an understanding of miRNA expression patterns during PC pathogenesis and helps to facilitate the identification of promising and novel early diagnostic/prognostic markers and therapeutic targets.

INTRODUCTION

Cancer is a compendium of perturbed genome functions and is characterized by the deregulation of several genes and their regulatory molecules, including microRNAs (miRNAs) [1, 2]. In general, miRNAs are 19–24 nucleotides long, noncoding RNA molecules that regulate the expression of 30% of protein-coding genes at the posttranscriptional level [3, 4]. These miRNAs are transcribed by RNA polymerase II as pre-miRNAs, which