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Loss of miR-21 delays Myc-driven prostate cancer progression in the Hi-Myc transgenic mouse model

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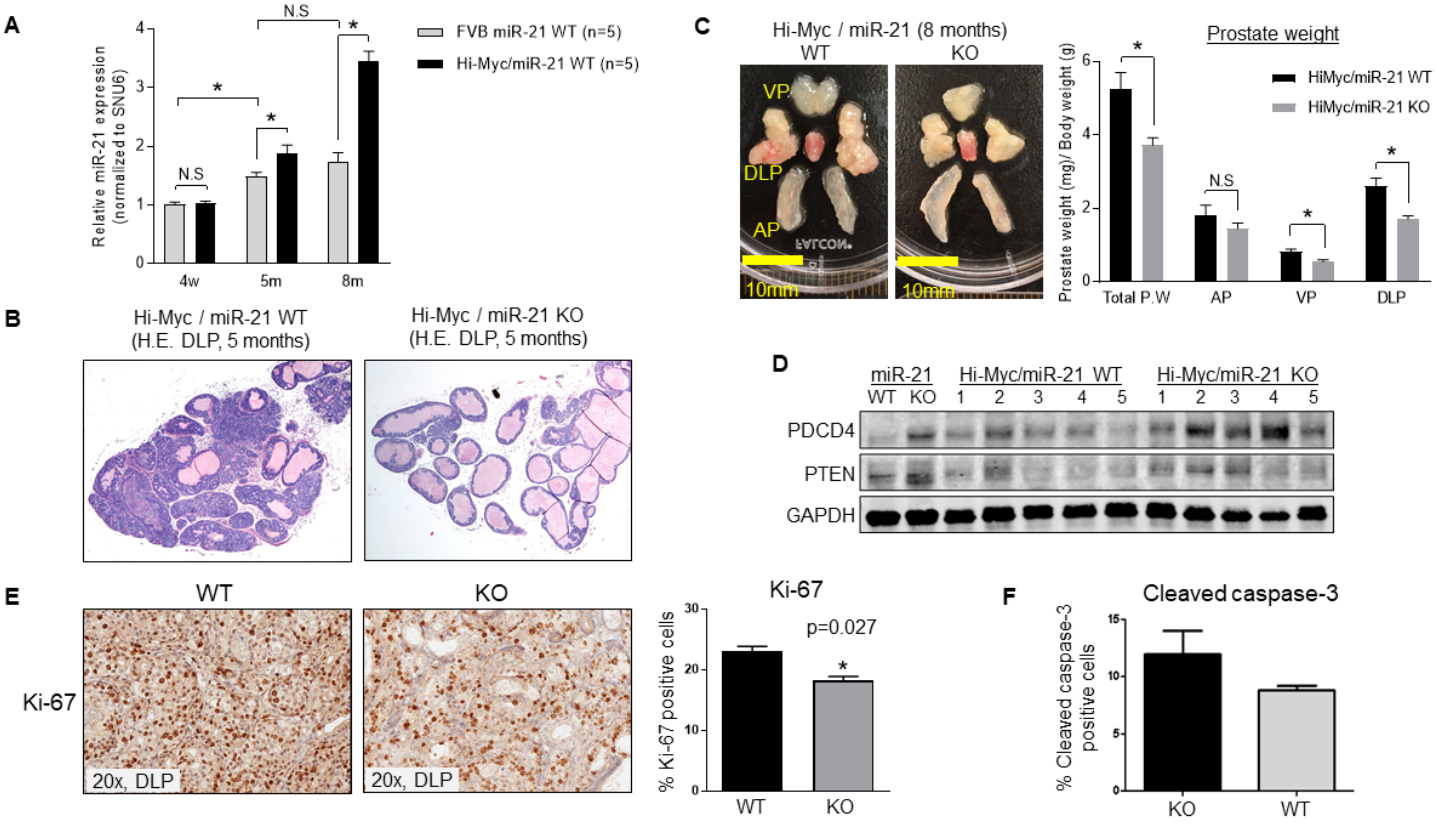
Introduction & Objectives: MicroRNA 21 (miR-21) is overexpressed in virtually all types of cancers including prostate cancer (PCa). We have previously reported that the androgen receptor (AR) induces miR-21 expression, and that elevated miR-21 is sufficient to drive PCa growth and castration resistance. However, the role of miR-21 in PCa initiation and progression has not been fully elucidated. To determine if the absence of miR-21 inhibits or delays prostate cancer incidence or progression, we crossed miR-21 KO mice with Hi-Myc mice. In this study, we identify that loss of miR-21 delays Myc-driven prostate cancer progression in the Hi-Myc transgenic mouse model.

Materials & Methods: miR-21 KO mice were backcrossed to FVB mice to generation F10. Resulting miR-21 WT or KO FVB progeny were crossed with Hi-Myc mice to generate Hi-Myc/miR-21 WT or KO mice. Prostates were harvested at 4 weeks (n=10), 3 months (n=10), 5 months (n=58), 6 months (n=25), 8 months (n=20) of age and prostate weight, histology, miR-21 expression levels and protein expression levels were quantified. Proliferation and apoptosis were examined by immunohistochemistry using Ki-67 and cleaved caspase-3.

Results: Cancerous prostates of Hi-Myc mice showed high miR-21 expression at 5m and 8m, when compared to FVB controls (Fig. 1A). Hi-Myc/miR-21 KO mice demonstrated a marked reduction in adenocarcinoma when compared to Hi-Myc/miR-21 WT mice at 5m (Fig. 1B). This is apparent in the reduced weight of effected prostate lobes of Hi-Myc/miR-21 KO versus WT mice at 8m (Fig. 1C). Protein levels of established miR-21 target genes, PDCD4 and PTEN, were up-regulated in the prostates of Hi-Myc/miR-21 KO mice (Fig. 1D). Also, IHC showed lower Ki-67 and higher cleaved caspase-3 positive cells in miR-21 KO than WT (Fig. 1E, F). However, miR-21 KO did not affect prostatic intraepithelial neoplasia (PIN) development.

Figure 1. miR-21 KO delays Myc-driven prostate cancer progression



Conclusions: Our results demonstrate that miR-21 delays Myc-driven prostate cancer progression through reduced proliferation and enhanced apoptosis, and that endogenous miR-21 suppresses prostatic PDCD4 and PTEN protein expression levels. Therefore, targeting of miR-21 or its downstream target genes may be useful for cancer prevention or cancer therapy.