Recruitment of miR-8080 by luteolin inhibits AR-V7 in castration-resistant prostate cancer

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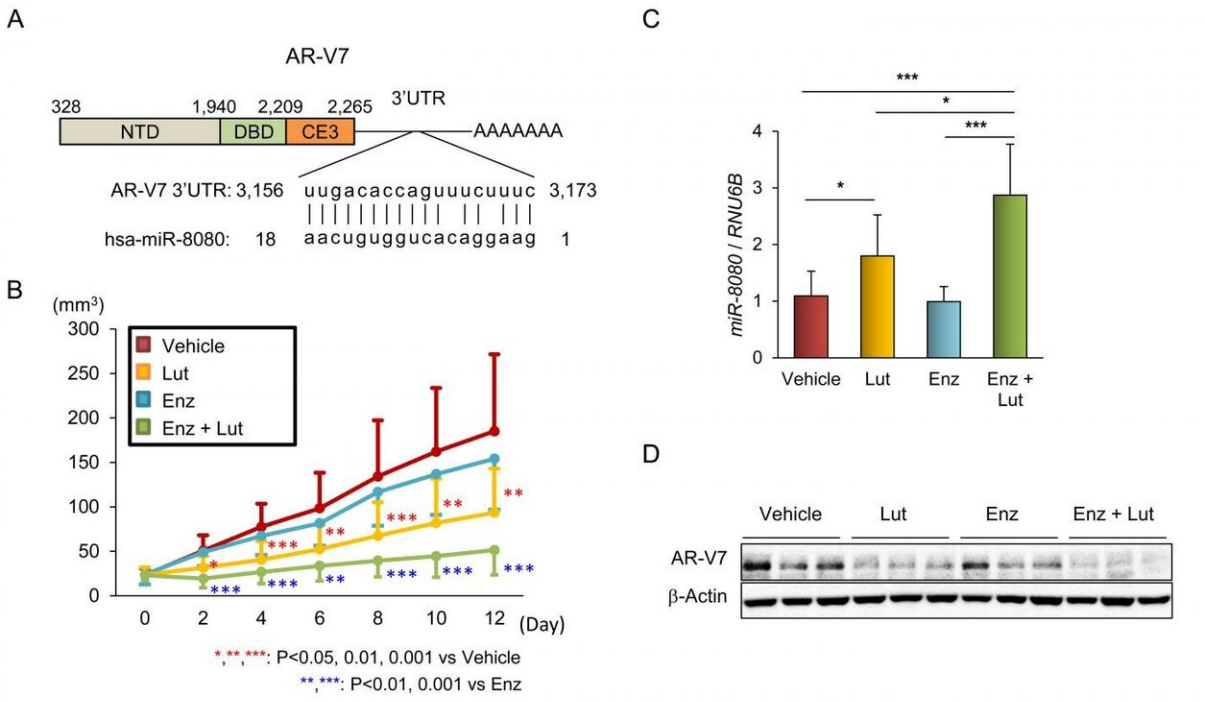

MiR-8080 recruited by luteolin enhances the chemotherapeutic effect of enzalutamide in 22Rv1 CRPC tumor (A) MiR-8080 can bind the 3'-untranslated region of AR-V7. (B-D) Effect of luteolin (Lut) on the chemotherapeutic efficacy of enzalutamide (Enz) in 22Rv1 xenografts in castrated nude mice. (B) Tumor volumes of 22Rv1 xenografts. (C) Quantitative miR-8080 expression by qRT-PCR in 22Rv1 xenografts. (D) Western blotting analysis for AR-V7 in 22Rv1 xenografts. Credit: © Aya Naiki-Ito

Prostate cancer is the most common noncutaneous malignancy in the United States and is responsible for many male deaths. The development of prostate carcinogenesis is initially androgen-dependent.

However, the progression of castration-resistant prostate cancer (CRPC) following androgen deprivation therapy is a major clinical problem. Although enzalutamide and abiraterone have been approved for CRPC hormone therapy, the efficacy of these drugs is limited. Androgen receptor splice variant 7 (AR-V7) which lacks a functional ligand-binding domain, stands out as one of a major contributor of cell proliferation and therapeutic resistance in CRPC.

In the present study, Dr. Aya Naiki-Ito (Associate professor, Nagoya City University), Dr. Satoru Takahashi (Professor, Nagoya City University) and their collaborators investigated the chemopreventive and chemotherapeutic potential of luteolin, a flavonoid with anti-oxidative properties, on prostate cancer, including CRPC. Luteolin inhibited the progression of rat prostate carcinogenesis by induction of apoptosis in a transgenic rat for adenocarcinoma of prostate (TRAP) model. Luteolin decreased cell proliferation in a dose-dependent manner and induced apoptosis with the activation of caspases-3 and 7 in both rat (PCai1) and human (22Rv1) CRPC cells.

Dietary luteolin also suppressed tumor growth via an increase in apoptosis and inhibition of angiogenesis in PCai1 and 22Rv1 xenografts implanted in castrated nude mice. Luteolin dramatically suppressed AR-V7 protein expression in 22Rv1 cells in vitro and ex vivo. Microarray analysis identified MiR-8080, which contains a possible target sequence for AR-V7 3'UTR, as a gene up-regulated by luteolin. MiR-8080 transfection decreased the AR-V7 expression level and the induction of apoptosis in 22Rv1 cells. Furthermore, miR-8080 knock-down canceled luteolin decreasing AR-V7 and the cell growth of 22Rv1.

Finally, we confirmed the effect of luteolin on the chemotherapeutic efficacy of enzalutamide against CRPC in 22Rv1 t xenografts in castrated nude mice. Enzalutamide-only treatment did not affect the tumor growth of 22Rv1. However, miR-8080 induced by luteolin intake down-regulated AR-V7 and greatly enhanced the therapeutic effect of enzalutamide on 22Rv1 tumors.

In conclusion, luteolin suppresses both the early stage of prostate carcinogenesis and CRPC via the induction of apoptosis. MiR-8080 recruited by luteolin supplementation has an important role in the reduction of AR-V7 protein, resulting in inhibiting tumorigenesis and the enzalutamide resistance of CRPC. Therefore, miR-8080 may be a novel therapeutic target for CRPC.

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