Abstract 2025: Prevention of mammary tumor progression via intraductal injection of nanoparticle-formulated siRNA.

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Abstract

The contribution of specific genes to the development and progression of mammary tumors has been hampered by the inability to silence these genes locally in the mammary gland. Localized intraductal chemotherapy treatments have been explored and offer significant advantages in terms of reduced toxicity and side effects. Therefore, we wanted to explore the possibility of gene knockdown using siRNA delivery via intraductal injection. FVB C3(1)-SV40Tag transgenic female mice spontaneously develop hyperplastic mammary lesions that progress to invasive mammary tumors. Hyperplastic ducts form as early as 12 weeks of age and progress into DCIS-resembling tumors by 16 weeks of age. These further develop into invasive tumors that invade locally into adipose tissue and muscle and occasionally form metastases to lung by 18 to 20 weeks of age. We intraductally injected nanoparticle-formulated siRNA targeted to the SV40 T-antigen transgene beginning at 8 weeks of age through 23 weeks of age into the mammary gland twice a month. As controls, transgenic females were either left untreated or intraductally injected with a non-targeting siRNA. Tumor formation was monitored using ultrasound technology that allows for tumor detection as early as 0.4mm in diameter. At 23 weeks of age, when 100% of the control mice developed tumors, only 1 of 8 mice that received siRNA to the transgene had developed a small tumor. Histological analysis of the mammary glands confirmed development of early lesions but tumor progression was successfully prevented. Mammary lesions were analyzed for proliferation, apoptosis and expression of various markers of differentiation, including hormone receptor status. We showed that siRNA was not detectable in any other organs of the mouse, including the liver. Furthermore, we confirmed that frequent intraductal siRNA injection did not interfere with subsequent pregnancy or lactation, a period in which the mammary gland undergoes extensive remodeling to allow for milk production. Our long-term goal is to leverage the information we uncovered through this effort to target key genes we identified through gene network analysis aiming to prevent the progression of DCIS to invasive tumors. Moreover, this new technology can be utilized to explore the role of genes during specific times during development and tumor formation.