Developmental Programming: How Early Life Exposure Influences the Occurrence of Leiomyoma in Adults

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Developmental exposure to environmental estrogens can impart a hormonal imprint on the reproductive tract that has been associated with dysregulation of reproductive function and promotion of tumors in both humans and experimental animal models. This effect has been termed "Developmental Programming", wherein an adverse stimulus or environmental insult during critical periods of development can reprogram normal physiological responses and give rise to metabolic and hormonal disorders later in life (1). For cancer, previous studies have focused primarily on the effects of developmental programming on relatively rare neoplasias of the reproductive tract epithelium such as cervico-vaginal clear cell carcinoma. Little information exists on the possible contribution of developmental programming on more common tumors such as uterine leiomyoma.

In our investigations of the molecular mechanisms contributing to uterine leiomyoma, we have focused on the role of the tuberous sclerosis complex 2 (TSC-2) tumor suppressor gene. The product of the TSC-2 gene, tuberin, is an important regulator of PI3K/AKT signaling, serving to negatively regulate cell growth by suppressing AKT signaling to TOR (2). The Eker rat, which carries a germline defect in the Tsc-2 gene, develops spontaneous uterine leiomyoma and is one of the most well studied animal models for this disease (3-5). Female Eker rats develop uterine leiomyoma with a frequency of ~65% and these tumors resemble their cognate human disease at both the phenotypic and biochemical level. Like the human disease, tumors that develop in Eker rats are hormone-dependent and express receptors for estrogen and progesterone. Interestingly, we have observed that ~25% of human leiomyomas also exhibit loss of tuberin expression, pointing to the importance of this tumor suppressor gene in the development of these tumors.

Using the Eker rat model, we are investigating the potential contribution of environmental exposures to the development of uterine leiomyoma. We found that exposure to an environmental estrogen during the neonatal period, when the rodent myometrium is undergoing differentiation, reprogrammed the normal hormone-responsiveness of target cells, leading to an increase in tumor incidence, size and multiplicity. A 3-day exposure to the xenoestrogen DES during neonatal development promoted the development of tumors in 16-month old carrier females ($Tsc\text{-}2^{Ek/+}$), but did not induce tumors in wild-type ($Tsc\text{-}2^{+/+}$) rats. In carrier females, neonatal DES exposure resulted in an increase in tumor incidence from 65% to >90%, an increase in tumor size from 2.3 to 10.5 cm^3 and an increase in tumor multiplicity from 0.82 to 1.33 tumors/rat (all statistically significant at the level of $p < 0.02$).

To determine the mechanism responsible for tumor promotion, we examined the hormonal responsiveness of the myometrium of exposed animals and observed that neonatal DES exposure had reprogrammed the response of the myometrium to estrogen. 5-month old females that had been exposed neonatally to DES exhibited elevated expression of estrogen-responsive genes including the progesterone receptor (PR), the androgen receptor (AR) and calbindin, with elevated expression observed at both the RNA and protein level. Tumors that developed in the

DES-exposed animals also displayed an enhanced proliferative response to steroid hormones relative to tumors from unexposed animals, consistent with the enhanced hormone-responsiveness seen in exposed myometrium.

These data demonstrate that developmental programming following exposure of the uterus to an environmental factor such as a xenoestrogen can permanently reprogram normal physiological tissue responses, leading to an enhanced responsiveness to steroid hormones that can promote tumor development.

References

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