TGFβ1 DEFICIENT MICE EXHIBIT IMPAIRED FOLLICLE GROWTH AND LUTEAL MAINTENANCE

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Transforming Growth Factor β1 (TGFβ1) is essential for normal female reproduction. Mice with a targeted deletion in the TGFβ1 gene (TGFβ1–/–) have severely impaired fertility with pregnancy occurring in <25% of mated females. TGFβ1 is implicated in several aspects of ovarian function, including potentiation of granulosa cell proliferation and suppression of luteal cell apoptosis. Our initial observations indicate that estrous cycling is disrupted in TGFβ1–/– mice and that ovulation rate is reduced. To further investigate how impaired ovarian function contributes to the infertility of TGFβ1–/– mice, ovaries were isolated from TGFβ1+/+ and TGFβ1–/– littermates at proestrus and fixed and sectioned for examination of follicle morphology and growth. BrdU labelling was performed to detect granulosa cell proliferation and blood samples were obtained for analysis of gonadotrophins and ovarian steroid hormones. Histological examination showed that ovaries from TGFβ1–/– mice were smaller than those of TGFβ1+/+ mice, however large antral follicles were observed, indicating that TGFβ1 is not essential for granulosa cell proliferation. Compared to TGFβ1+/+ ovaries however, there were fewer antral follicles and only rare corpora lutea. Interestingly, in some cases there were large numbers of macrophages surrounding small follicles suggesting increased follicular atresia and/or altered macrophage activity in the TGFβ1–/– ovaries. Ovaries and serum were also isolated from females at d4 post-coital for assessment of corpora lutea morphology. TGFβ1–/– ovaries weighed less and had fewer corpora lutea than TGFβ1+/+ ovaries. TGFβ1–/– corpora lutea also contained increased numbers of apoptotic cells and infiltrating macrophages indicative of premature luteal regression. Circulating progesterone levels were reduced in TGFβ1–/– females, as was progesterone production per corpus luteum further indicating a functional defect in luteal maintenance. Cumulatively these observations show that TGFβ1 has essential roles in regulation of ovarian macrophage populations, in normal follicular development and in the generation, maintenance and steroidogenic function of corpora lutea.

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