Interactions between Estrogens and Cyclin D1 are Crucial for Epithelial Cell Recovery in the Initial Segment of the Mouse Epididymis

Yu-Da Jeong, Kyu-Sang Lim, Hee-Bok Park, Ji-Hyuk Kim, and Bongki Kim

Department of Animal Resources Science, Kongju National University, Chungnam, Korea

The estrogen receptor (ER) plays a crucial role in regulating growth and differentiation in various types of epithelium. Recent evidence suggests that a deficiency of ER is related to the failure of recovery in the mouse epididymal epithelium. However, little is known about the detailed molecular mechanisms that link ER and cyclin D1 in the recovery of epithelial cells in the mouse epididymis. In this study, we utilized two mouse models: the efferent duct ligation mouse model and the estrogen receptor-alpha knockout (ERαKO) model. These models were used to induce cell death programs in the epididymal epithelium and to gain insight into the roles of estrogens in the mechanism of epithelial repair, respectively. Deprivation of testicular luminal factors through efferent duct ligation (EDL) induces degeneration of epithelial cells in the initial segment (IS) of the epididymis, followed by regeneration. EDL was performed when the mice were 10-12 weeks old, and apoptotic and proliferating epithelial cells were quantified at 24 hours, and at days 2 and 3 post-EDL, respectively. All collected epididymides were fixed and evaluated using immunofluorescence (IF) with specific markers, including caspase3 (cell death), Ki67 (cell proliferation), B1-VATPase (clear cells), and cytokeratin 5 (basal cells). A significant increase in apoptotic basal cells (BCs) and principal cells (PCs) was observed in both the control and ERαKO groups at 24 hours after EDL. There were no differences in the rate of apoptosis between the groups. However, ERαKO mice exhibited a significant decrease in the number of proliferating BCs and PCs compared to the control group at 2 and 3 days after EDL, respectively. Additionally, ERαKO mice showed a low level of cyclin D1 protein. Treatment with anti-cdk4/6 after EDL resulted in a complete cessation of cell proliferation in both the control and ERαKO groups. In summary, 1) the epididymal epithelium can be repaired and regenerated through the proliferation of BCs and PCs at 2 days and 3 days after EDL, respectively. 2) The interaction between estrogens and cyclin D1 is crucial for the repair of BCs and PCs after injury in the mouse epididymis. These results indicate that ERα plays a crucial role in the repair and regeneration phase by activating the cell cycle, rather than apoptosis, through its interactions with cyclin D1 in the initial segment of the mouse epididymis.