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Female fertility is dependent on functional expression of the E3 ubiquitin ligase Itch

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The post-translational addition of ubiquitin to proteins by enzymes of the E3 ubiquitin ligase family is largely recognized as a means to target misfolded or unwanted proteins for degradation by the proteasome. However, it is now understood that ubiquitination serves as a signal to modify a number of cellular functions such as protein trafficking, cell signaling, DNA repair, chromatin modifications, cell-cycle progression, and cell death. Though these functions are integral for all cells throughout the body, the physiologic role of specific E3 ligases must yet be defined in the context of various tissues. For example, very few studies exist that interrogate the function of specific E3 ubiquitin ligases in the reproductive system.

The physiologic roles of E3 ubiquitin ligases have been examined in knockout or mutant mouse models. In previous work with a mouse model that contained a loss of function mutation in the ITCH E3 ubiquitin ligase gene (mice termed itchy due to the chronic dermatitis phenotype) it was discovered that male mice displayed a number of alterations in testicular germ cells. Although there were phenotypic changes in the germ cells of the itchy male mice, fertility assays suggested that male reproduction remained functional. Itchy females, however, produced fewer offspring when bred to either itchy or wild type male mice. This led Richburg and colleagues from the University of Texas at Austin to evaluate the physiologic role of ITCH in the female reproductive system.

Their findings reported in the February 2016 issue of *Experimental*

Biology and Medicine reveal several alterations in reproductive function in itchy female mice when compared to wild type female mice. Itchy females had both fewer implantations and tended to have fewer corpora lutea. Additionally, the itchy females remained in estrus longer, resulting in extended estrous cycles. The loss of ITCH within the ovary was confirmed, yet alterations in the expression of prototypical ITCH targets in the ovaries were not indicated. These results suggest the existence of an ovary-specific ITCH substrate or non-degradation dependent signaling pathway responsible for these phenotypic alterations. Alternatively, because ITCH works in the immune system to polarize T-cells towards an autoimmune type 2 activation state, these results may be indicative of immune interactions within the female reproductive system. The results of this work illustrate the functional participation of E3 ubiquitin ligases, specifically ITCH, in physiologic female reproduction. The lead author further reflects, "The female reproductive tract has long been recognized as a specialized immune environment, from macrophages that aid in luteal progression to T-cell tolerance in the uterus during fetal implantation. The results reported in this manuscript suggest that the Itchy mice could provide a useful model to evaluate the repercussions of preferential T-cell differentiation towards the type 2 phenotype on ovulation, estrus, and implantation."

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine* said "the results of this study indicate that female itchy mice have altered reproduction. Future studies are required to determine the mechanism by which altered ubiquitination leads to this physiological effect."

More information: A. R. Stermer et al. Featured Article: Female mice with loss-of-function ITCH display an altered reproductive phenotype, *Experimental Biology and Medicine* (2015). DOI: 10.1177/1535370215610656