health and fertility as well. Specifically, androgens are necessary for granulosa cell proliferation and follicle survival and growth. Excess androgen levels in females are a hallmark in polycystic ovary syndrome (PCOS), whereas insufficient androgen signaling due to androgen receptor (AR) knockout leads to diminished ovarian reserve (DOR) – with both extremes resulting in anovulatory infertility. However, little is known about the factors regulating AR in granulosa cells. Our previous findings demonstrate that paxillin, a cytoplasmic adaptor protein, mediates AR signaling in prostate cancer cells. However, our current interest is whether this interaction is also found in granulosa cells. As such, our results show that paxillin indeed enhances AR protein expression in granulosa cells. We have also demonstrated through immunofluorescence and proximity ligation assays that paxillin colocalizes with AR, notably in membrane-bound complexes. Moreover, paxillin-null KGN and mouse granulosa cells express lower levels of AR, as demonstrated through Western blotting and immunofluorescence imaging. We then conducted mRNA and protein degradation experiments in paxillin-null KGN cells in order to determine the mechanism by which paxillin increases AR expression. These results suggest that paxillin acts by preventing AR mRNA and protein degradation, possibly by trafficking AR to focal adhesions, where it may be sequestered from degradation. Finally, to investigate the role of paxillin in female fertility, we developed a novel granulosa cell-specific paxillin knockout mouse model using an Amhr2-driven Cre/lox system. These knockout mice experience altered estrous cycles compared to controls, spending fewer days in estrus and more days in metestrus/diestrus. When bred continuously through 6 months of age, the paxillin KO mice produced significantly more litters compared to their littermate controls. Taken together, these results suggest that paxillin acts as a regulator of androgen-mediated female fertility in granulosa cells, and may serve as a potential target for therapeutics in fertility-related diseases such as PCOS and DOR.

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Paxillin and Androgen Receptor Interact to Modulate Female Fertility

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While androgens are traditionally associated with male physiology, recently it has become more apparent that balanced levels of androgens are crucial to maintaining female