Peptidylarginine Deiminase 2 and 4 Double Knockout Mice Reveal Citrullination is an Important Post Translational Modification that Regulates Female Reproduction

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Peptidylarginine deiminases (PADs) are a family of enzymes that post-translationally convert positively charged arginine residues into a neutrally charged citrulline, through a reaction termed citrullination. Citrullination, a novel post-translational modification, can alter target protein structure and function. Our previous work discovered that PAD expression is elevated during the estrus phase of the estrous cycle in anterior pituitary gonadotrope cells and citrullination can epigenetically regulate the production of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). To further explore the role of PADs *in vivo*, we utilized a PAD 2/4 double knock out (DKO) mouse model. Previous work found male PAD2/4 DKO mice have decreased testis size, altered gonadotropins, and are subfertile compared to wild type mice. Given the complexity of the female reproductive axis, it is unclear if PADs may play a sexually dimorphic role in regulating reproduction. To test this, we first measured pubertal onset in female PAD2/4 DKO mice and found that it takes approximately 5 days longer to initiate puberty. Additionally, female PAD2/4 DKO mice spend significantly longer in the diestrus phase of the estrous cycle and have smaller uteri and ovaries compared to wild type controls. In pituitaries from female PAD2/4 DKO mice, LHβ mRNA is decreased compared to controls during estrus, which is consistent with our previous work showing an epigenetic role for PADs in regulating histones around the *lhb* gene promoter. Taken together, our work suggests that PAD expression and activity may be a mechanism that facilitates puberty initiation and the high levels of gonadotropin gene expression necessary for ovulation. Ongoing work is examining PAD2/4 DKO serum gonadotropin levels and single cell transcriptomic profiles across the female reproductive axis.