Hormonal Havoc: Dysregulation of Hippo Signaling in Murine Gonadotropes Leads to Morphological Alterations and Dysfunction of the Anterior Pituitary Gland

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The Hippo transcriptional coactivators, YAP and TAZ, are expressed in cells throughout the anterior pituitary gland in mice. Although the potential physiological roles of YAP and TAZ in gonadotrope cells was unknown, we recently reported that conditional deletion of YAP and TAZ in gonadotrope cells results in increased circulating levels of LH (in males and females) and FSH (males only), and female hyperfertility in mice. Here, to further study the effects of Hippo signaling in gonadotropes, we conditionally expressed a constitutively active YAP (5SA) in these cells using the Cre-lox system with one of two Cre-driver strains, steroidogenic factor-1 (SF-1)-Cre or GnRH receptor-IRES-Cre (GRIC). Such crosses generated two distinct mouse models, which are referred to herein as YAP5SA;SF1-Cre and YAP5SA;GRIC, respectively. Expression of total YAP (YAP5SA and endogenous *Yap*) and the classic YAP-TEAD target genes, *Ankrd1, Ctgf* and *Cyr61*, and was significantly increased in pituitaries of 6-week-old mutant males and females in both the YAP5SA;SF1-Cre and YAP5SA;GRIC models. Animals from both models also showed significantly reduced serum LH and FSH levels as well as lower body mass and gonadosomatic indices when compared to respective controls. Six-week-old male and female mutants from both models showed significant morphological alterations in the pituitary. YAP5SA;SF1-Cre mutants exhibited proliferation of poorly differentiated cells, with high cellular and nuclear atypia with several mitoses. Similarly, YAP5SA;GRIC pituitaries were characterized by an increased number of poorly differentiated cells as well as follicle or papillary-like structure formation and increased cell proliferation and necrosis. Together, these preliminary findings strongly suggest pituitary blastoma or choriocarcinoma, and confirmatory experiments are underway. In light of gross morphological changes that appeared to extend beyond gonadotropes, we performed qPCR analysis of other cell lineages in 6-week-old YAP5SA;GRIC mutants and corresponding controls. *Gh*, *Pomc*, *Prl* and *Tshb* mRNA levels were decreased in pituitaries of mutant animals. In addition, GH and ACTH protein expression, as assessed by immunohistochemistry, was nearly undetectable in pituitaries in mutant animals, suggesting compromised presence or function of somatotropes and corticotropes. To better understand the onset of this pathology, we performed histopathological analysis of YAP5SA;GRIC mutants in early post-natal life. Although pituitaries from 1-day-old mutant animals seemed normal in comparison to controls, we found signs of cellular necrosis and vacuolar degeneration in 1-week-old mutants. Together, our results indicate that constitutively active YAP in murine gonadotropes leads to significant morphological and functional alterations throughout the pituitary.