Hypopituitarism: from molecular diagnoses in patients to functional studies in mice

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Hypopituitarism is generally caused by congenital anomalies in development of the pituitary gland and/or hypothalamus, adult onset adenoma development, or environmental exposures such as traumatic brain injury or cancer treatment. Some children with hypopituitarism have craniofacial abnormalities due to disruption in development of the midline and anterior embryonic structures. Most patients respond to hormone replacement therapy, but some do not, and complications can be life threatening. Molecular diagnosis can be invaluable for predicting therapeutic response, disease progression, and risk for future pregnancies. Most of the causes of congenital hypopituitarism are defects in transcription factors that affect head and/or pituitary gland development, but the majority of cases have no known molecular diagnosis. We seek to identify the genetic causes of hypopituitarism using high throughput DNA sequencing and to understand how lesions in these genes cause organ failure using cell cultures and genetically modified mice. It is our long-term goal to use information about disease pathophysiology to develop useful therapeutics including the possibility of induced pluripotent stem cell replacement therapy. Mutations in the transcription factors POU1F1 and PROP1 cause non-syndromic hypopituitarism and are among the most common known causes of the disorder. Using genetically engineered mice and cell cultures, immunohistochemistry, stem cell colony forming assays, RNA-Seq, ChIP-Seq we determined that mutations in these genes affect pituitary stem cell growth and differentiation. *Prop1* promotes the transition of progenitors into differentiating cells by driving an epithelial to mesenchymal transition-like process. These results advance our understanding of the genetic causes of hypopituitarism and the underlying disease pathophysiology.