EGFR Induces E2F1-Mediated Corticotroph Tumorigenesis

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Introduction

- Increased EGFR expression is associated with aggressive pituitary tumor.
- However, the role that EGFR plays in tumorigenesia has not been clearly elucidated.
- Since there is no small animal model of Cushing disease that has corticotroph adenoma phenotypic characteristics with upregulated HPA axis, we generated EGFR induced corticotroph adenoma mouse model, manifesting aggressive Cushing disease.

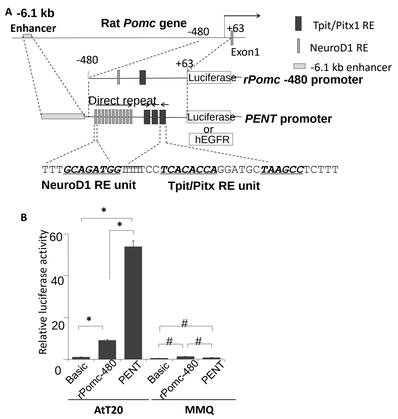

Figure 1. Construct of rPOMC enhancer/promoter.

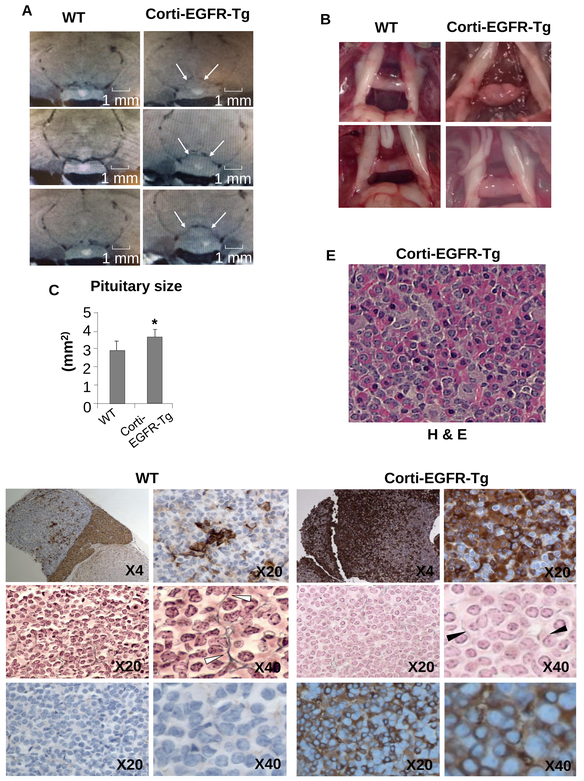

Figure 3. ACTH-secreting pituitary tumorigenesis in corti-EGFR-Tg mice.

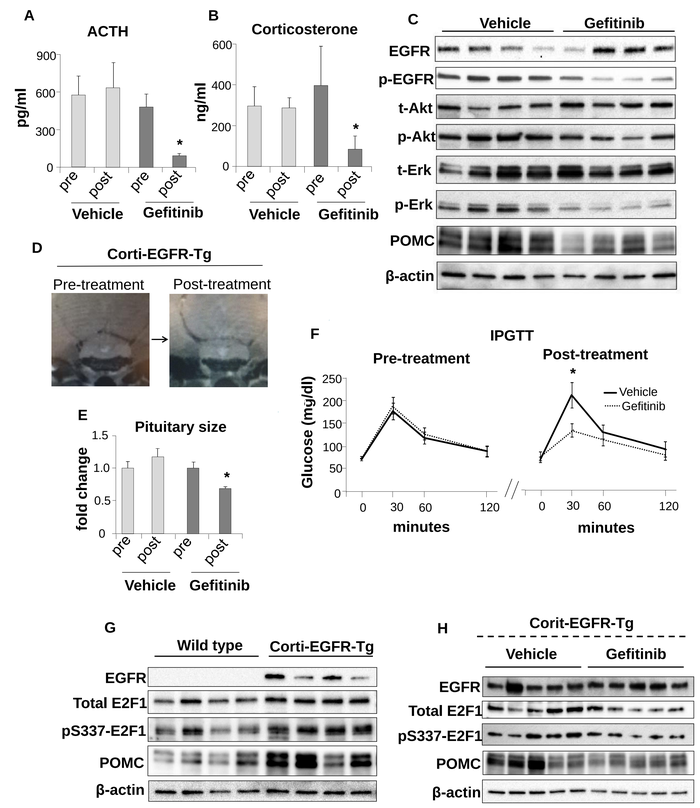

Figure 5. Effect of Gefitinib treatment in corti-EGFR-Tg mice and detection of E2F1.

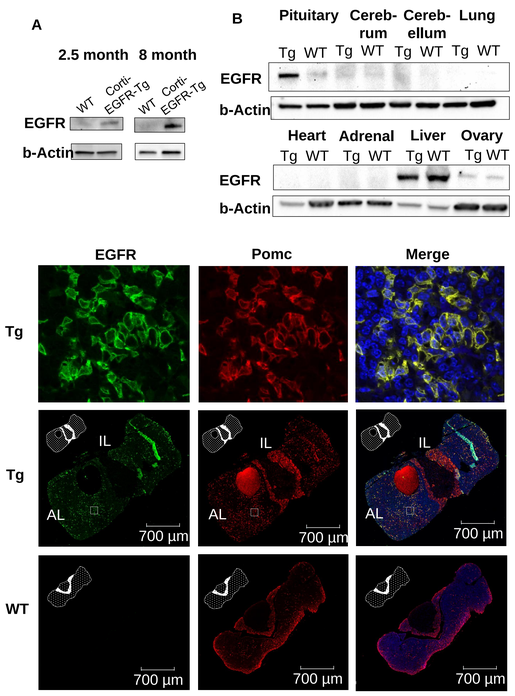

Figure 2. Expression of hEGFR in corti-EGFR-Tg mice

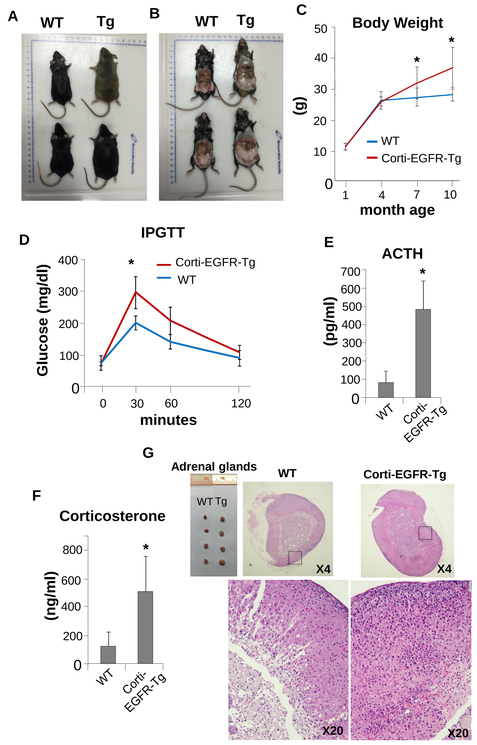

Figure 4. Tumor phenotypes of corti-EGFR-Tg mice.

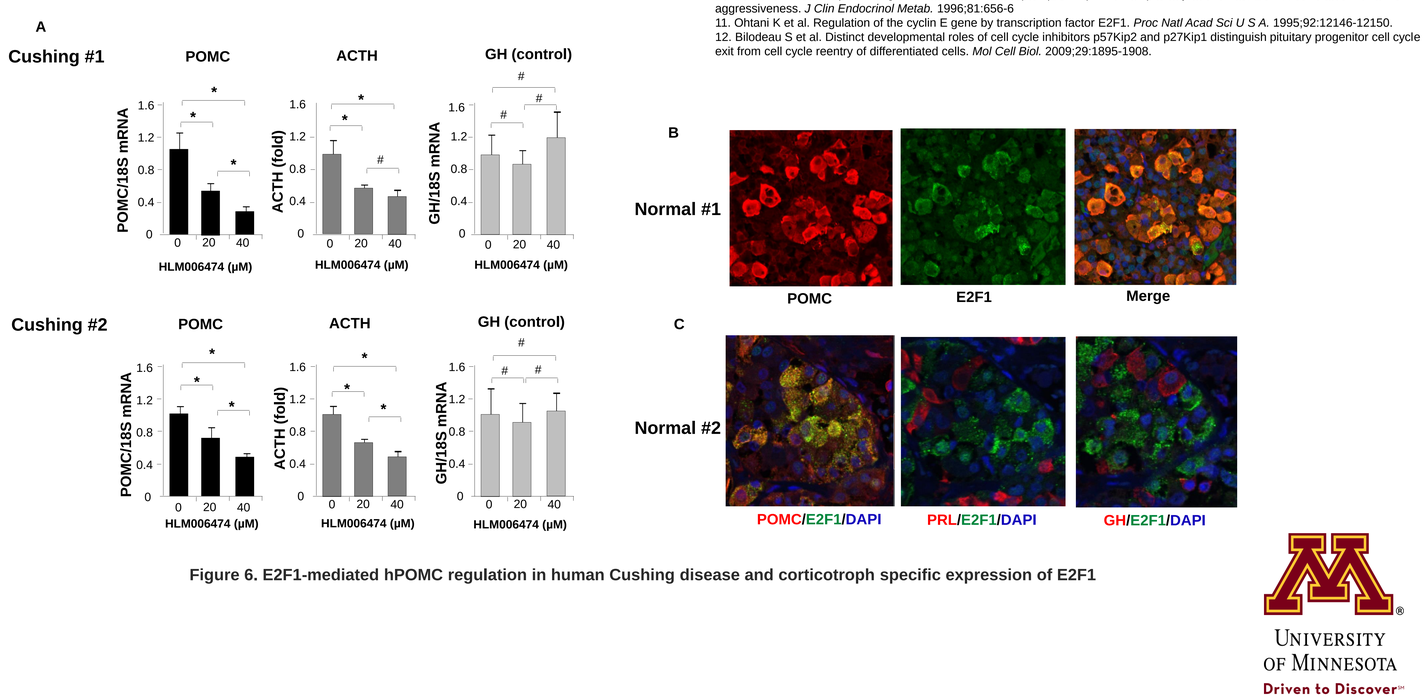

Figure 6. E2F1-mediated hPOMC regulation in human Cushing disease and corticotroph specific expression of E2F1

Discussion

- We present an EGFR-Tg mouse model that recapitulates biochemical and pathologic features of human Cushing disease.
- Corticotroph adenoma is histologically similar to Crooke's cell adenoma, a clinically aggressive pituitary Cushing disease subtype.
- Our findings suggest that EGFR activity is mediated by corticotroph-specific E2F1.
- However, it remains unclear how E2F1 pathways are induced through EGFR signaling in corticotrophs. Possible mechanisms include MAPK, JNK1, and p38 pathways, or that EGFR may enhance pituitary E2F1-mediated transcription in pituitary cells.
- E2F1 and pS337-E2F1 upregulate *POMC* gene expression in pituitary cells, and that E2F1 and pS337-E2F1 expression are, in turn, induced by EGFR.
- E2F1 was preferentially expressed in corticotrophs rather than in somatotrophs or lactotrophs in normal human pituitary tissue. The role of selective E2F1 expression in nontumorous normal pituitary is not known.

Conclusion

The evidence presented here shows that corticotroph EGFR signaling upregulates E2F1-mediated induction of the POMC and ACTH seen in Cushing disease and may play a role in corticotroph tumorigenesis. Blocking EGFR signaling leading to disrupted E2F1 regulation of POMC expression may be a potential therapeutic target.

References

1. Stenzel-Poore MP et al. Development of Cushing's syndrome in corticotropin-releasing factor transgenic mice. *Endocrinology.* 1992;130:3378-3386.
2. Liu NA et al. Targeting zebrafish and murine pituitary corticotroph tumors with a cyclin-dependent kinase (CDK) inhibitor. *Proc Natl Acad Sci U S A.* 2011;108:8414-8419.
3. Theodoropoulou M et al. Expression of epidermal growth factor receptor in neoplastic pituitary cells: evidence for a role in corticotropinoma cells. *J Endocrinol.* 2004;183:385-394.
4. Fukuoka H et al. EGFR as a therapeutic target for human, canine, and mouse ACTH-secreting pituitary adenomas. *J Clin Invest.* 2011;121:4712-4721.
5. Araki T et al. E2F1-mediated human POMC expression in ectopic Cushing's syndrome. *Endocr Relat Cancer.* 2016;23:857-870.
6. George DH et al. Crooke's cell adenoma of the pituitary: an aggressive variant of corticotroph adenoma. *Am J Surg Pathol.* 2003;27:1330-1336.
7. Ma Y et al. A small-molecule E2F inhibitor blocks growth in a melanoma culture model. *Cancer Res.* 2008;68:6292-6299.
8. Melmed S. Mechanisms for pituitary tumorigenesis: the plastic pituitary. *J Clin Invest.* 2003;112:1603-1618.
9. Low MJ et al. Post-translational processing of proopiomelanocortin (POMC) in mouse pituitary melanotroph tumors induced by a POMC-simian virus 40 large T antigen transgene. *J Biol Chem.* 1993;268:24967-24975.
10. LeRiche VK et al. Epidermal growth factor and its receptor (EGF-R) in human pituitary adenomas: EGF-R correlates with tumor aggressiveness. *J Clin Endocrinol Metab.* 1996;81:656-6
11. Ohtani K et al. Regulation of the cyclin E gene by transcription factor E2F1. *Proc Natl Acad Sci U S A.* 1995;92:12146-12150.
12. Bilodeau S et al. Distinct developmental roles of cell cycle inhibitors p57Kip2 and p27Kip1 distinguish pituitary progenitor cell cycle exit from cell cycle reentry of differentiated cells. *Mol Cell Biol.* 2009;29:1895-1908.