Members of the ErbB family of cell surface tyrosine kinase receptors are important targets for cancer treatment because they frequently contribute to the pathogenesis of malignancy. In this issue of the JCI, Fukuoka et al. generate data that suggest that using a tyrosine kinase inhibitor (TKI) against epidermal growth factor receptor (EGFR, also known as ErbB1) may be a novel approach for treating patients with hypercortisolism due to pituitary corticotroph adenomas (Cushing disease). While surgical resection remains the cornerstone of treatment for individuals with such tumors, this study suggests that TKIs could perhaps be used to reduce tumor size prior to surgery or to treat recurrent disease after surgery.

Cushing disease is a condition in which the pituitary gland releases too much adrenocorticotrophic hormone (ACTH), the hormone that stimulates the secretion of cortisol from the adrenal cortex (Figure 1 and ref. 1). Cortisol, which is normally released in response to stress or reduced levels of serum glucocorticoids, regulates blood glucose levels by promoting gluconeogenesis, suppresses the immune system, and accelerates protein metabolism. Hypercortisolism is the hallmark of Cushing disease and causes a diverse array of symptoms, including central obesity, hypertension, hyperglycemia, osteoporosis, and skin and muscle atrophy.

Cushing disease is caused by an adenoma arising from pituitary corticotroph cells. These cells, which are found in the anterior or pituitary, produce ACTH from the precursor proopiomelanocortin (POMC) and then secrete it in response to corticotropin-releasing hormone from the hypotalamus (Figure 1). Treatment options for patients with Cushing disease are essentially limited to surgical resection. However, surgical resection alone has several important limitations (reviewed in ref. 1). First, preoperative studies to localize the tumor are not always definitive, since the majority of pituitary corticotroph adenomas are very small in size (less than 10 mm in diameter). Second, surgical remission rates for larger tumors are relatively low. Finally, postoperative recurrence rates range from 10% to 45%, depending on the size of the initial tumor.

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A new medical therapy for Cushing disease?
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Given the limitations of surgical resection, new medical treatment options are needed for patients with Cushing disease. Clinical trials with a dopamine agonist (2) and a somatostatin analog (3) — which work by limiting tumor secretion of ACTH and subsequent hypercortisolism — have shown some promise, but only in a small proportion of patients. In this issue of the JCI, Fukuoka et al. report data that suggest that targeting the ErbB family member EGFR (also known as ErbB1) could provide a pituitary-targeted medical treatment option prior to or after surgical resection of a pituitary corticotroph adenoma (4).

**Mutations in EGFR in cancer**

Members of the ErbB family are mutated or overexpressed in a variety of human solid tumors, and this has been shown to play an important role in the pathogenesis of these malignancies (5). The intrinsic tyrosine kinase activity of EGFR and ErbB2 is aug-

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**Figure 1**
The hypothalamic-pituitary-adrenal (HPA) axis in healthy controls and patients with Cushing disease. The normal HPA axis is subject to negative feedback regulation by circulating cortisol levels. Cortisol normally regulates carbohydrate, protein, and lipid metabolism and plays a key role in the immune system. In Cushing disease, a pituitary corticotroph adenoma secreting too much ACTH activates the HPA axis, resulting in defective negative feedback and excessive cortisol production. Patients exhibit central obesity, hypertension, hyperglycemia, osteoporosis, and muscle atrophy.

**Figure 2**
Proposed function of the EGFR in pituitary corticotrophs. (A) Relationship between Pomc expression (which encodes a precursor protein that can be cleaved to generate ACTH) and pituitary cell growth mediated by the MAPK pathway. Corticotroph adenomas have aberrant MAPK pathway activation, resulting in pituitary cell growth and increased Pomc expression (4). (B) Use of a TKI reduces corticotroph adenoma growth and Pomc expression, which is mediated by the MAPK signaling pathway.
mented by overexpression or by mutation in many human tumors, and this facilitates tumor growth. Targeting these receptors has therefore been intensively pursued as an important anticancer therapeutic strategy.

Tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib have been developed against EGFR, and they block receptor activity by inhibiting ATP binding to the kinase site. Gefitinib and erlotinib are somewhat effective in the treatment of non–small cell lung cancers that have activating mutations in the kinase domain of EGFR. However, many patients who are initially responsive to these therapeutics subsequently experience tumor recurrence and become refractory to therapy (6).

EGFR and ACTH expression

Although a substantial proportion of pituitary corticotroph adenomas have been shown to express EGFR (7–9), the role of this receptor in the pathogenesis of Cushing disease has not been determined. Fukuoda et al. set out to test the hypothesis that EGFR activation is important in the pathogenesis of pituitary corticotroph adenomas and that gefitinib could inhibit both EGFR activation and tumor growth (4). Remarkably, they showed that gefitinib substantially reduced POMC mRNA expression and ACTH secretion in cell lines derived from human, canine, and mouse pituitary corticotroph adenomas. They further showed that changes at the proximal mouse Pomc promoter mediated this effect in vitro transfection studies and that the effect of EGF on the Pomc promoter was MAPK dependent (Figure 2A).

The ability of gefitinib to suppress Pomc mRNA levels in mouse corticotroph cell cultures correlated directly with an increase in markers of apoptosis and a decrease in cellular proliferation (4). Furthermore, gefitinib also decreased tumor growth and serum ACTH levels in mice allografted with an EGFR-overexpressing mouse corticotroph tumor cell line. The authors therefore concluded that gefitinib is useful in reducing ACTH levels as well as corticotroph cell growth, both in vitro and in vivo. As a result, they suggest a role for TKIs in the treatment of patients with Cushing disease.

A new therapy for Cushing disease?

The work of Fukuoda et al. (4) provides the rationale for a potential new medical treatment option for patients with Cushing disease — using a TKI such as gefitinib prior to surgery, to increase the chance that a large pituitary corticotroph adenoma can be successfully resected, or after surgery, to reduce postoperative recurrence rates (Figure 2B). However, the authors note two limitations to using TKIs for treating patients with Cushing disease (4). First, not all pituitary corticotroph adenomas express EGFR, and those that do not would not be affected by gefitinib. This was evidenced by the authors’ results with their canine model of Cushing disease, in which a few animals were found to be unresponsive to gefitinib because they lacked EGFR expression in their pituitary tumor (4). Second, gefitinib is particularly effective in the clinical setting of tumors bearing the EGFR L858R mutation, which is found in many patients with non–small cell lung cancer (10). Fukuoka et al. point out that it is not clear whether human pituitary corticotroph adenomas harbor this mutation. Other limitations of the strategy come to mind; for example, the effect of gefitinib on ACTH secretion might be dissociated from its effect on tumor cell growth, rendering it less useful for long-term treatment of Cushing disease. Moreover, pituitary corticotroph adenomas treated with gefitinib may develop resistance to the drug by acquiring new mutations in the EGF signaling pathway or by activating signaling from a related family member, such as ErbB3. As noted above, use of this drug in individuals with non–small cell lung cancer suggests that resistance could become a concern (6).

Conclusions

Regardless of the potential clinical limitations, the work of Fukuoda et al. provides a novel candidate approach for treating patients with Cushing disease based on solid mechanistic science (4). It highlights a previously underappreciated pathway regulating Pomc expression (7–9) and provides a rational approach to regulating this pathway in the clinic. More needs to be learned about the effects of TKIs on human pituitary corticotroph adenomas, especially the ability of such drugs to affect tumor cell growth and tumor survival. However, this study provides a strong foundation to investigate the effects of gefitinib in patients with Cushing disease. Physicians caring for these patients will anxiously await the results.

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