Gefitinib

A common mechanism for tumour formation is the activation of protein kinases that occur because of inherent chromosomal abnormalities or a somatic mutation. Drugs that inhibit activated protein kinases therefore have been shown to be effective in the treatment of certain cancers.

One of these drugs, gefitinib, was originally designed to inhibit the epidermal growth factor receptor (EGFR) kinase enzyme. The rationale was that EGFR is more abundantly expressed in lung cancer tissue than in surrounding lung tissue; however, it was subsequently found that EGFR expression did not seem to correlate with clinical response to gefitinib. What did seem to correlate was ethnicity: Japanese patients had significantly higher responses to the drug than patients of European ancestry.

Paez and colleagues set out to determine if there was something different about the EGFR in the Japanese patients that was responsible for the higher response. They searched for somatic differences between non-small-cell lung cancer tumours in the 2 populations and found that there were indeed differences. A higher proportion of Japanese patients had mutations in the EGFR — either substitutions or deletions of amino acids — than did the patients of European ancestry. Furthermore, they confirmed that those patients with the mutations were the ones who had a clinical response to gefitinib.

In a follow-up experiment, the researchers performed in vitro experiments, administering gefitinib to non-small-cell lung cancer cell lines. Again they confirmed that those lines with the identified mutations responded to the drug.

The authors concluded that while the initial randomized controlled trials for gefitinib did not reveal any survival advantage for those patients taking the drug, it may be that the drug works only for a select subgroup of patients with non-small-cell lung cancer whose tumours possess the mutations. They suggest that a prospective clinical trial enrolling these patients is necessary to confirm the drug's efficacy. (Paez et al. *Science* Epub 2004 Apr 29) — *Stephen Choi*, CMAJ

Leptin linked to rewiring in brain's feeding circuit

The hormone leptin, which is known to regulate body weight, has been shown to cause rapid rewiring of key neurons in the arcuate nucleus (Arc) of the hypothalamus of mice. Although it is known that leptin acts on the hypothalamus to decrease food intake, Pinto and colleagues revealed in a series of experiments the neural mechanisms that may mediate eating behaviour and body weight.

Leptin regulates the activity of Arc neurons that express the appetite-suppressing peptide proopiomelanocortin (POMC) and other Arc neurons that express the appetite-stimulating neuropeptide Y (NPY). To date, there is no direct evidence showing that leptin has differential effects on these 2 neuron types.

Using transgenic mice that express detectable proteins in POMC and NPY neurons, the authors aimed to study the intrinsic activity of these neurons and their responses to leptin.

By means of immunohistochemistry and electron microscopy, the authors determined that, compared with wild-type mice, leptin-deficient (ob/ob) mice had a significantly greater number of excitatory synapses onto NPY neurons and a significantly greater number of inhibitory synapses onto POMC neurons.

Consistent with this, electrophysiologic testing revealed higher excitatory tone onto NPY neurons and increased inhibitory tone in POMC neurons.

In a placebo-controlled study, the authors found that leptin-deficient mice that were given a single leptin injection exhibited a rapid rewiring of synaptic connections, so that they more closely resembled wild-type mice. These synapse changes were seen several hours before leptin's effect on food intake, and might account for changes in feeding behaviour. In showing that changes in the complex behaviour of appetite may come down to rapid changes in neuronal anatomy, the authors provide important insights into the pathogenesis of obesity. (Pinto et al. *Science* 2004;304:110) — *Marlene Busko*, Montréal

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