MINERAL METABOLISM

Gene silencing for PTH suppression

A novel approach to the treatment of secondary hyperparathyroidism has shown promise in *in vitro* and *in vivo* studies conducted by investigators at Tokai University in Japan. "We expect that RNA interference could reduce the need for calcimimetics and/or vitamin D3 supplementation, and allow easier postoperative control of PTH [parathyroid hormone]," says lead researcher Genta Kanai.

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Patients undergoing dialysis in Japan tend to survive for longer than those in the US or Europe; as a result, they are more likely to develop complications such as secondary hyperparathyroidism. The high prevalence of this condition in the Japanese dialysis population spurred the researchers to seek a novel means of suppressing excessive PTH production without the need for surgical or chemical ablation of the parathyroid glands.

RNA interference is a physiologic mechanism by which a short length of 'interfering' RNA triggers the degradation or obstructs the synthesis of a particular messenger RNA molecule. Since the discovery of this process, attention has been focused on its potential for therapeutic exploitation.

Kanai and colleagues showed that transfection with a double-stranded, small, interfering RNA (siRNA) against PTH led to a dose-dependent suppression of hormone secretion in monolayer cultures of cells obtained from the parathyroid glands of patients with secondary hyperparathyroidism. However, parathyroid cells rapidly deteriorate in monolayer culture; therefore, the investigators also created novel three-dimensional 'spheroid' aggregates of these cells to investigate the long-term effects of RNA interference. siRNA-transfected spheroids exhibited marked suppression of PTH secretion for more than 50 days. Finally, the team transplanted human parathyroid cells into the livers of athymic (nude) mice to demonstrate that hydrodynamic delivery of anti-PTH siRNA caused dose-dependent inhibition of PTH secretion *in vivo*.

Kanai cautions that hydrodynamic delivery of siRNA could have adverse cardiovascular effects in humans. "We are currently developing another delivery method, in which gels containing siRNA and transfection reagents are injected into the inside and surroundings of parathyroid glands in a manner similar to percutaneous ethanol therapy," he adds.

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Original article Kanai, G. *et al.* Suppression of parathyroid hormone production *in vitro* and *in vivo* by RNA interference. *Kidney Int.* **75**, 490–498 (2009).