HIGHLIGHT

A molecular switch for parathyroid cell differentiation

Jens P Berg
Hormone and Central Laboratory, Aker University Hospital, 0514 Oslo, Norway

(Correspondence should be addressed to Jens P Berg; Email: j.p.berg@ioks.uio.no)

Normally, secretion of parathyroid hormone (PTH) from the parathyroid glands is inversely related to the concentration of ionized calcium in the circulation and this plays a crucial role in calcium homeostasis. In primary hypoparathyroidism the patient presents with hypocalcemia, hyperphosphatemia, and absent or low concentrations of PTH. The entity comprises a heterogeneous group of disorders with several genetic causes, which recently was shown to include mutations in the gene for the transcription factor GCMB, a human orthologue of the *glial cells missing (gcm)* gene in *Drosophila* (1).

Neuroectodermal cells in *Drosophila* differentiate into either neurons or glia, which are important for guiding migrating neurons and axons, supporting and sheathing them and regulating the extracellular concentration of ions and neurotransmitters (2). Expression of the *gcm* gene induces differentiation of neuroectodermal cells to glia instead of neurons. Overexpression of the gene increases the number of glia cells and fewer neurons will develop, whereas its inactivation leads to the opposite. The *gcm* gene encodes a transcription factor which is expressed transiently and precedes the expression of every other known glial marker. Two genes closely related to the *Drosophila gcm* gene have been identified in mammals: GCMA and GCMB, which are also denoted GCM1 and GCM2 respectively (3). The tissues where the mammalian genes are expressed indicate that these transcription factors have been assigned new roles during evolution. The GCMA protein is primarily found in the labyrinthine trophoblasts in the fetal part of the placenta. The cells form a layer that is needed for normal exchange of nutrients and gas between the mother and the fetus. Ablation of the *Gcma* gene in mice interrupted the normal development of the layer and resulted in placental failure, whereas no abnormalities were detected in the embryo, particularly in the central nervous system (4). The GCMB gene is expressed in the parathyroid cells. Mice without a functional *Gcmb* gene did not develop parathyroid glands, and became severely hypocalcemic shortly after birth, with a neonatal mortality of 30% (5). The surviving mice had a milder hypocalcemia, were viable, fertile, developed normally, and had low, but measurable serum, levels of PTH. In these mice, an additional source of PTH was identified in the thymus, which expressed low levels of the GCMA protein.

The structure of the *Drosophila* GCM and mammalian GCMA and GCMB proteins is similar and can be functionally divided into DNA-binding and transactivation domains (3). They have similar DNA-binding specificity, but GCMB has a much weaker transactivation potential. Ectopic production of murine GCMA in *Drosophila* can induce glia cell differentiation, whereas GCMB is unable to transform neurons into glia. GCMB has an inhibitory domain including an amino acid sequence (PEST sequence) that is a marker for rapid degradation of the protein. The protein is very labile compared with GCMA, and this is probably the reason why its transcriptional activity is lower (6).

The expression of the GCMB gene is restricted to the parathyroid glands. It was therefore an ideal candidate gene in a study of familial isolated primary hypoparathyroidism by Ding et al. (1). The proband had generalized seizures at 5 weeks old because of hypocalcemia, and serum levels of PTH were undetectable. After treatment of the hypocalcemia, the patient developed normally and did not experience further seizures. The human GCMB gene consists of five exons and is located on chromosome 6p23–24 (7). Genetic analyses showed that the proband was homozygous for an approximately 8 kb deletion spanning from 1901 bp upstream of the initiator codon in exon 1 to the border between intron 4 and exon 4. The parents were heterozygous for the same deletion, but there were no other indications of consanguinity. Carriers of the mutation had no signs of hypoparathyroidism. At 19 months of age, the proband had detectable serum levels of intact PTH, which were at the lower reference limit. Although it cannot be excluded that the patient had PTH that derived from parathyroid remnants, another possibility is that the thymus can serve as an auxiliary source of PTH in humans as in mice. Hyperparathyroidism is in some cases caused by aberrant PTH production in the mediastinum and thymus (8). This has been explained by ectopic migration of a parathyroid gland during development, but detection of PTH in Gcmb knock-out mice and in a patient with GCMB gene mutation supports the observation that ectopic PTH may originate from the thymus itself (9).
The partial deletion of the GCMB gene reported by Ding et al. (1) is the first example of a mutation that leads to isolated agenesis or dysgenesis of the parathyroid glands. Isolated parathyroid agenesis has also been reported in X-linked recessive hypoparathyroidism, which is linked to a 1.5 Mb region on chromosome Xq26–q27. Congenital defects in the development of the parathyroid glands have been associated with several other developmental abnormalities such as the DiGeorge syndrome, the hypoparathyroidism, sensorineural deafness and renal dysplasia syndrome, the hypoparathyroidism, retardation and dysmorphism syndrome, and in more than half of the patients with the Kenny–Caffey syndrome (for references see (10)). Moreover, congenital hypoparathyroidism has been reported in a patient homozygous for a mutation resulting in an inborn error of fatty acid oxidation and in some neuropathies caused by mutations in mitochondrial genes.

In addition to defects in the development of the parathyroid glands, primary hypoparathyroidism can be the result of mutations that impair the synthesis or secretion of PTH (10). Both autosomal recessive and dominant modes of transmission have been demonstrated in patients with hypoparathyroidism caused by PTH gene mutations that interfere with the synthesis of bioactive PTH. The secretion of PTH from the parathyroid glands is regulated by serum Ca²⁺, and has a set point which is lowered by activating mutations in the CASR gene. The gene encodes a calcium receptor, and constitutive activation of the receptor results in hypoparathyroidism, hypocalcemia and hypercalciuria (11).

The report by Ding et al. (1) shows that the GCMB gene is important for normal PTH synthesis in humans and supports the notion that expression of the gene seems to be a switch for normal parathyroid cell development. Increased knowledge of genes that induce the differentiation of parathyroid cells is essential for a potential therapeutic use of modified stem cells in patients with hypoparathyroidism.

References