The parathyroid gland is a low turnover, discontinuously replicating tissue composed of cells that rarely undergo mitoses [1, 2]. The quiescent parathyroid cells, however, retain their potential to divide in response to growth stimuli, including the onset of renal failure, low calcium, high phosphorus, or vitamin D deficiency [2]. In patients with renal failure, parathyroid glands initially grow diffusely and polyclonally. In advanced stages of parathyroid hyperplasia, the cells in the nodules transform monoclonally and proliferate aggressively [3]. Nodular hyperplasia constitutes the more severe form of secondary hyperparathyroidism. Neither the mechanisms triggering the initial increase in proliferating activity nor those resulting in changes in growth pattern are completely elucidated.

Recent studies in 5/6 nephrectomized rats have implicated elevations in transforming growth factor-alpha (TGF-α) expression in the increased proliferating activity of parathyroid cells in early renal failure [4]. High dietary phosphorous intake further enhances parathyroid levels of TGF-α and therefore, proliferation rates [4]. Prevention of the increases in TGF-α and induction of parathyroid levels of the cyclin-dependent kinase inhibitor p21 by high dietary calcium, phosphorus restriction, or vitamin D therapy mediate their effects in attenuating or completely counteracting the growth-promoting signals triggered by uremia [4, 5]. The relative contribution of either mechanism to arrest parathyroid growth remains unclear.

High calcium and vitamin D are efficient in controlling parathyroid levels of TGF-α and its downstream-growth signal, cyclin D1, in an experimental model of early uremia [5]. This finding suggests a role for the progressive reduction in the levels of the calcium-sensing receptor (CaSR) and the vitamin D receptor (VDR) in the worsening of proliferating activity in patients with advanced renal failure. In fact, higher cyclin D1 expression occurs in nodular hyperplasia compared to diffuse hyperplastic glands [3]. However, neither the increase in cyclin D1 expression nor the reduction in CaSR is a key determinant of the switch to the more aggressive nodular growth. Studies in transgenic mice targeted to specifically overexpress cyclin D1 in the parathyroids conclusively demonstrated the importance of cyclin D1 in parathyroid growth [6]. Similar to parathyroid adenomas in humans, these mice slowly develop large hyperplastic glands and in some cases adenomatous glands. However, in nodular hyperplasia in humans, different from parathyroid adenomas, no correlation exists between levels of cyclin D1 and mitogenic activity. More important, these studies in mice [6] and recent studies in uremic rats [7] also indicated that reduced CaSR in the parathyroid glands followed rather than caused the hyperplasia.

Studies by Tokumoto et al [8], in this issue of Kidney International, present the impaired induction of the expression of the cyclin-dependent kinase inhibitors p21 and p27 by the VDR as a pathogenic mechanism for nodular parathyroid growth in renal failure. Examination of nodular hyperplastic parathyroid tissue from 23 patients demonstrated a strong direct correlation between VDR levels and parathyroid content of the cyclin-dependent kinase inhibitors p21 and p27. More important, the lower the parathyroid levels of VDR and cyclin-dependent kinase inhibitors, the higher the markers of proliferating activity and the size of the nodular gland. The lack of an association between parathyroid levels of p21 and p53, the main regulator of p21 expression, suggested a direct induction of p21 by the VDR as a potential mechanism. The lack of a parathyroid cell line and the diffuse pattern of parathyroid hyperplasia in uremic rats, however, prevent from conclusive validation of the proposed model, which emerges solely from simultaneous assessment of parathyroid expression of VDR and cell-cycle regulators in nodular human parathyroid glands. Nevertheless, the findings by Tokumoto et al further our understanding on the pathogenesis of the abnormalities in parathyroid cell replication that could help improve therapeutic strategies to avoid the more severe form of secondary hyperparathyroidism. Their results support the findings from studies in early uremia in rats on the importance of vitamin D induction of parathyroid p21 expression in regulating the rate of parathyroid cell proliferation [5]. In addition to confirming the association between a reduction in p27 and hyperplastic growth in secondary hyperparathyroidism [9], their demonstration of vitamin D-dependent regulation of p27 in the parathyroids suggests an additional mechanism for the resistance to the antiproliferative effects of the sterol in nodular hyperplasia. In aggressive carcinomas, where growth is driven exclusively by TGF-α activation of signaling by its receptor, the epidermal growth factor receptor (EGFR), increases in p27 are mandatory.

Key words: TGF-α, hyperplasia, cyclin-dependent kinase inhibitors, p21, p27, uremia, calcium-sensing receptor, vitamin D receptor

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for the efficacy of anti-EGFR therapy [10]. The demonstrated efficacy of vitamin D in preventing the increases in parathyroid TGF-α [5] and the reported strong correlation between parathyroid VDR and p27 levels suggest that vitamin D treatment inhibits parathyroid growth not only by reducing TGF-α expression but also the downstream growth signaling from the EGFR. The ability of vitamin D therapy to prevent parathyroid VDR-down-regulation in uremia [11] suggests that early interventions with the sterol could avoid activation of the autocrine TGF-α/EGFR growth loop and therefore, nodular growth.

ADRIANA S. DUSSO
St. Louis, Missouri, USA

Correspondence to Adriana S. Dusso, Ph.D., Research Associate, Professor, Renal Division, Campus Box 8126, 660 S. Euclid, St. Louis, MO 63110 USA.
E-mail: adusso@im.wustl.edu

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