Vitamin D receptor knock-out mice: the exceptional and the exceptional

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After activation by the active vitamin D metabolite, 1α,25-dihydroxyvitamin D₃, the vitamin D receptor (VDR), a member of the steroid/thyroid/retinoid receptor gene superfamily of transcription factors, regulates the expression of genes in a variety of vitamin D-responsive tissues (1, 2). The VDR consists of two distinct functional parts, an amino-terminal DNA-binding domain with two zinc fingers (which determine DNA specificity) and a carboxy-terminal ligand-binding domain. While classic vitamin D targets include bone, kidney, and intestine, where it acts to maintain serum calcium levels and to build and preserve bone (1), compelling evidence has emerged in recent years that vitamin D is also critical for epidermal differentiation, hematopoiesis and the immune system (3, 4). While VDR point mutations in humans (most commonly in the DNA-binding domain, less frequently in the ligand-binding domain) and vitamin D deficiency (following experimental malnutrition) in animals have revealed some insights into the role of the vitamin D system, the molecular basis for the interaction of 1α,25-dihydroxyvitamin D₃ with the VDR and the structure–function relationship of the VDR have remained unclear.

Using gene targeting to generate VDR-deficient mice, two independent studies have now simultaneously provided intriguing details about the impact of the VDR (5, 6). The first study, conducted by Yoshizawa et al. (5), ablated exon 2 of the VDR gene, which encodes the first zinc finger of the DNA-binding domain, whereas the second study, conducted by Chun Li et al. (6), ablated a VDR fragment spanning exons 3–5, which encode, among others, the second zinc finger of the DNA-binding domain. Homozygous littermates from both studies displayed a phenotype that closely resembles vitamin D-dependent rickets (VDDR) type II in humans, including marked rickets and osteomalacia, elevated levels of, and resistance to 1α,25-dihydroxyvitamin D₃, pronounced hypocalcemia, profound secondary hyperparathyroidism resulting from compensatory hyperparathyroid hyperplasia, failure to thrive, and short stature due to abnormalities of the growth plate (5, 6). In addition, total alopecia (5, 6) developed with dilated hair follicles and formation of dermal cysts (6), a symptom that is variably found in some kindreds with VDDR II, but not in patients with rickets due to dietary vitamin D deficiency. However, there were some striking differences between the two studies. While the VDR (exon 3–5)-deficient mice were viable, fertile, and displayed no additional developmental abnormalities when examined at 70 days of age (6), VDR (exon 2)-deficient mice had dysmorphic features with a flat face and a short nose, and a lethality rate (precipitated by weaning) of 50% at 70 days of age, and 100% after 155 days of age respectively (5). In contrast, uterine hypoplasia due to impaired folliculogenesis (absence of mature graafian follicles) in the ovaries of VDR (exon 2)-deficient female mice was observed. Increase of uterine weight following treatment with estrogen indicated that the uterus remains responsive to estrogen, and that the primary defect in VDR (exon 2)-deficient mice occurs at the level of follicle maturation (5).

Thus, the major achievement of the two studies is to provide a valuable animal model of a rare human disease with important clinical implications, and a model to study the actions of vitamin D in vivo. However, the fact that uterine hypoplasia, infertility and early lethality are present in one study (5), but neither in the other (6) nor in human VDDR II, requires future studies. These would have to clarify whether the product of exon 2 of the VDR is crucial for survival or whether the targeting vector used for ablation of exon 2 of the VDR also ablated other gene products that are crucial for normal development of the female reproductive tract and survival. A recent study described a patient with VDDR II due to a novel mutation in the VDR ligand-binding domain (exon 8) which leads to decreased affinity for 1α,25-dihydroxyvitamin D₃ (7). Intriguingly, this patient also had total lipodystrophy and a persistent Müllerian duct syndrome with rudimentary uterus and fallopian tubes, which in view of the remote chance of occurring independently, also hints at a role of the VDR in female reproduction. Thus, within a few months, animal models to study the molecular basis of two distinct inborn errors of bone metabolism, VDDR type I (8, 9) and II (5, 6), have become available. It seems endocrinologists will soon know more about the molecular basis of the vitamin D system and, as a free gift, will encounter even more surprises.
References


