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Tissue-Specific Regulatory Effects of Vitamin D and Its Receptor on Calbindin-D28K and Calbindin-D9K

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Abstract

The balance between calcium and vitamin D is essential in mammalian development. Calbindin-D28K (CaBP-28K) and calbindin-D9K (CaBP-9K) are cytosolic vitamin D-dependent calcium-binding proteins that mediate the dynamic equilibrium of vitamin D and calcium, particularly in the absorption of intestinal calcium, in urinary calcium excretion, and in bone formation. However, the precise roles of CaBP-28K and CaBP-9K are not well understood. CaBP-9K/CaBP-28K double-knockout (KO) mice have a normal phenotype under conditions of normal dietary intake of calcium. Conversely, when given a calcium-deficient diet, these double-KO mice have greater reductions in serum calcium levels and bone length than do wild-type mice. In this review, we summarize and interpret the body of literature regarding the relationship of vitamin D and its receptor with CaBP-28K and CaBP-9K in mammals.

Keywords: Calbindin-D28K; Calbindin-D9K; 1,25(OH)₂D₃; VDR; Intestine, Kidney; Bone

Introduction

Calcium is vital to the human body. Calcium ion homeostasis is necessary for cell membrane integrity, excitability of the musculoskeletal system, blood coagulation, secretion of neurotransmitters and hormones, and myocardial contraction [1,2]. Maintenance of the calcium balance requires the cooperation of numerous calcium transport proteins, including transient receptor potential vanilloid type 5 (TRPV5) [3], transient receptor potential vanilloid type 6 (TRPV6) [4], plasma membrane Ca²⁺ ATPase (PMCA) [5], parvalbumins (PVs) [6], calbindin-D9K (CaBP-9K) [7], calbindin-D28K (CaBP-28K), calretinin (CR) [8], and sodium-calcium exchanger 1 (NCX1)

[9,10]. Of these, CaBP-9K and CaBP-28K are the 2 so-called vitamin D-dependent calcium-binding proteins [11,12]. In the modulation of calcium homeostasis, vitamin D, CaBP-9K, and CaBP-28K play important roles [13,14] in the absorption of intestinal calcium, in urinary calcium excretion, and in bone formation.

Literature Review

Association of vitamin D and its receptor with CaBP-9K and CaBP-28K

Many reviews have addressed the vitamin D endocrine system and the mechanisms of action of vitamin D [15-18]. The human body can obtain vitamin D via photosynthesis in the skin or by dietary intake. The active form of vitamin D hormone, 1 α ,25-dihydroxyvitamin D₃ (1,25[OH]₂D₃), binds and activates its receptor (VDR), a nuclear transcription factor [19]. Vitamin D deficiency or a mutation that inactivates VDR can yield rickets and numerous extra-skeletal biologic responses, such as inhibition of progression of colon, breast, and prostate cancer cells; effects on the cardiovascular system; and protection against several autoimmune diseases, including inflammatory bowel disease and multiple sclerosis [20,21]. Supplementation of exogenous vitamin D can reverse rachitic bone to some extent. However, the dosage of vitamin D supplementation is still under debate, in part because the role of vitamin D signaling in calcium handling systems especially in bone is not understood fully.

The cytoplasmic proteins CaBP-9K and CaBP-28K bind Ca²⁺ and are regulated by 1,25(OH)₂D₃. CaBP-28K first was described as a 28-kDa protein in the chicken duodenal mucosa and the rat intestinal mucosa; the protein isolated from the rat intestinal mucosa later was identified as the 9-kDa CaBP-9K [22-24]. These proteins belong to different subfamilies and share little sequence homology, but both involve the EF-hand structural motif. CaBP-28K (human gene symbol, *CALB1*)

belongs to the CALB family of proteins and comprises 6 EF-hand domains; CaBP-9K is a member of the large S100 family (human gene symbol, *S100G*) and is composed of 2 EF-hand domains [25-27]. The CaBP-9K and CaBP-28K genes and cDNA have been cloned by means of reverse transcription and polymerase chain reaction (RT-PCR) [28-30]. CaBP-9K has been found in a variety of tissues, including bone, uterus, placenta, intestine, kidney, and pituitary gland [31-34]. CaBP-28K has been found in bone, kidney, brain, pancreas, intestine, and teeth [35-43].

Vitamin D regulates CaBP-9K and CaBP-28K in a tissue-specific manner. In the intestine and kidney, CaBP-28K and CaBP-9K are dependent on $1,25(\text{OH})_2\text{D}_3$. However, CaBP-9K functions in the uterus, placenta, and lung independently of $1,25(\text{OH})_2\text{D}_3$ [29,44-46], and CaBP-28K is not regulated by $1,25(\text{OH})_2\text{D}_3$ in chick brain tissue [47]. In enamel cells, CaBP-9K is dependent on expression of $1,25(\text{OH})_2\text{D}_3$, whereas CaBP-28K is not [40]. Herein, we review data on the correlation of $1,25(\text{OH})_2\text{D}_3$ and VDR with CaBP-9K and CaBP-28K in the intestine, kidney, and bone to summarize our understanding of the processes of calcium absorption, excretion, and incorporation.

Regulation of CaBP-9K and CaBP-28K in intestinal calcium absorption

Among mammals, the primary source of calcium absorption is dietary intake. Calcium transport in the intestine is considered to occur via 3 pathways. In the duodenum and upper jejunum, transport proceeds primarily via the transcellular pathway [48,49], which involves entry of calcium via an apical calcium channel (TRPV6 or TRPV5), CaBP-9K-facilitated translocation of calcium through the interior of an enterocyte, and basolateral extrusion of calcium by an intestinal plasma membrane pump (PMCA1b or NCX1). Another shuttling process is vesicular calcium transport, in which calcium is sequestered and moved primarily via lysosomes [50-53]. The third process is paracellular transport, which is a mode of rapid, energy-independent, concentration-dependent diffusion that takes place throughout the intestine [54,55]. In the transcellular and vesicular pathways, the regulation of calcium absorption is dependent on $1,25(\text{OH})_2\text{D}_3$ and requires the presence of VDR [56]. The paracellular pathway is neither saturation nor concentration dependent; when the calcium concentration in the intestinal lumen exceeds approximately 2 to 6 mmol/L, paracellular transport is the main mode of absorption [57].

Vitamin D and its receptor are crucial regulators of intestinal calcium absorption [58]. Under conditions of vitamin D deficiency, mice lacking VDR have reduced intestinal calcium absorption [59-62]. With advancements in research regarding intestinal calcium absorption, the roles of CaBP-9K/CaBP-28K and $1,25(\text{OH})_2\text{D}_3$ /VDR have evolved. CaBP-9K has been found mainly in the mammalian (eg, pig) intestine. CaBP-9K is highly expressed in the duodenum; its expression decreases gradually through the intestine and is undetectable in the distal ileum [63,64]. CaBP-9K originally was thought to cooperate with $1,25(\text{OH})_2\text{D}_3$ /VDR in the regulation of intestinal calcium

absorption. In rat intestinal tissue, the -449 and -485 regions of the 5' end of the CaBP-9K gene were found to have a vitamin D-responsive element region (VDRE) [65]. In vitamin D-deficient, VDR-knockout (KO), or 1α -hydroxylase-KO mice, the expression of CaBP-9K in the intestine was significantly decreased, compared with controls [66-68]. Despite the presence of vitamin D, intestinal CaBP-9K mRNA and protein levels were reduced in VDR KO mice [68]. Hence, CaBP-9K transcription is mediated by binding of VDR to the VDRE located within promoter regions. In chickens and mice, low calcium can stimulate the expression of CaBP-9K in the duodenum, and high calcium can inhibit its expression. Moreover, the influence of calcium on intestinal CaBP-9K requires the presence of VDR [69-71].

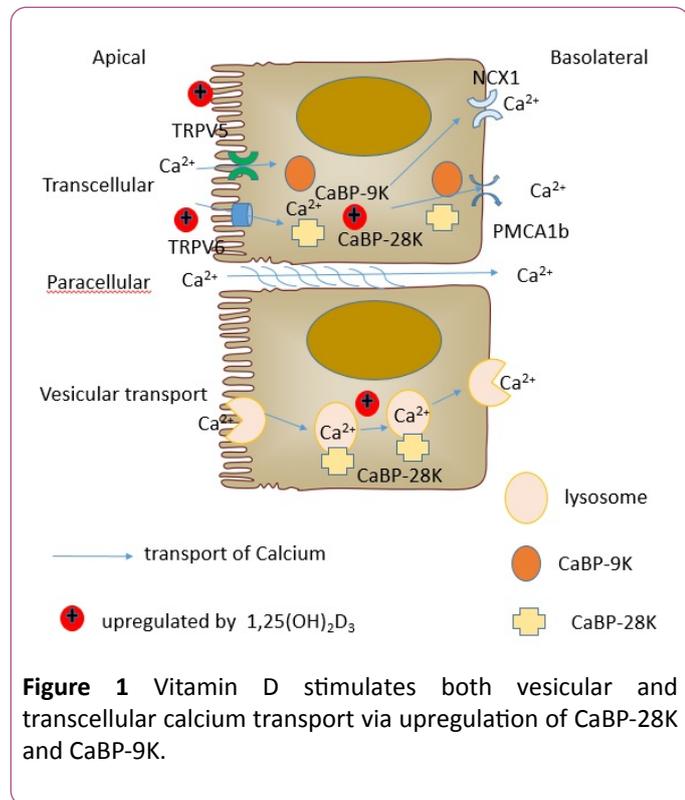
In the human intestine, investigators have determined that CaBP-9K mRNA levels increase with age, vitamin D levels decrease with age, and VDR mRNA levels do not correlate with age [72,73]. Thus, intestinal calcium absorption in humans seems not to depend on a relationship between CaBP-9K and $1,25(\text{OH})_2\text{D}_3$ /VDR. CaBP-9K KO mice have a normal phenotype and can survive for more than 1 year [74]; TRPV6 and PMCA1 are upregulated in these animals, potentially to compensate for the absence of CaBP-9K [75,76]. Thus, CaBP-9K appears to have only a minor role in intestinal calcium absorption, but further clarification of this role should be sought. Few studies have addressed CaBP-28K in the intestine. Although CaBP-28K has been found in the intestine, it occurs at a much lower level than does CaBP-9K. A low calcium concentration can stimulate the expression of CaBP-28K, and elevated calcium inhibits its expression. In the chick duodenum, vitamin D-dependent CaBP-28K is localized in lysosomal vesicles. When vitamin D-deficient chicks are treated with $1,25(\text{OH})_2\text{D}_3$, lysosomes in the intestinal epithelial cells exhibit $1,25(\text{OH})_2\text{D}_3$ -mediated upregulation in calcium content and CaBP-28K expression [77]. Vitamin D has a greater stimulatory effect on calcium uptake than on calcium transport; this phenomenon may be attributed to rapid $1,25(\text{OH})_2\text{D}_3$ -enhanced vectorial calcium absorption during lysosomal transport [52,55] (**Figure 1**).

Calcium absorption in the intestine is complex and involves multiple pathways with numerous contributing factors, including CaBP-9K and CaBP-28K. Transcellular absorption occurs primarily in the duodenum and upper jejunum, whereas paracellular absorption may occur at any intestinal site. Vesicular calcium transport has not been characterized fully. Further research is needed to ascertain how these pathways function in series and/or in parallel to affect optimal calcium absorption in response to the available calcium source and quantity.

Relationship between $1,25(\text{OH})_2\text{D}_3$ /VDR and CaBP-9K/CaBP-28K in the kidney

The amount of calcium excreted in the urine ranges from 100 to 200 mg per day. The renal tubules reabsorb 98% to 99% of calcium as urine is conveyed. The distal tubule is the chief site for regulation of calcium excretion, and reabsorption of calcium in the distal tubule primarily occurs via the transcellular route. Calcium absorption in the kidney

resembles that of the intestine, albeit with different molecular mediators. Specifically, kidney absorption processes include entry of calcium through TRPV5, cytosolic transfer of calcium by binding to CaBP-9K/CaBP-28K, and extrusion of calcium by the Na⁺/Ca²⁺ exchanger (NCX1) and PMCA1b [78-81].

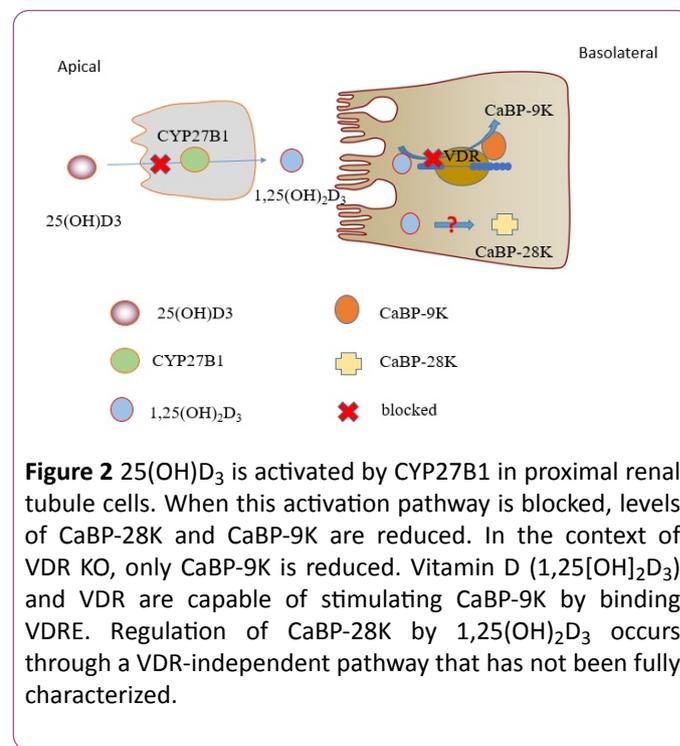


CaBP-9K and CaBP-28K are coexpressed in the distal tubule. Because these factors exhibit potent calcium-binding capacities, CaBP-9K and CaBP-28K have been presumed to be vital for vitamin D-dependent regulation of calcium reabsorption in the kidney. When vitamin D-deficient mice are treated with 1,25(OH)₂D₃, both CaBP-9K and CaBP-28K are upregulated in the kidney [82]. However, in wild-type (WT) mice fed a low-calcium (0.02%) or a high-calcium (2%) diet, the expression of CaBP-9K was increased or decreased, respectively, whereas the expression of CaBP-28K was unaffected. In rats, increased plasma calcium had no effect on the concentration of renal CaBP-28K [83].

The effects of 1,25(OH)₂D₃/VDR on CaBP-9K/CaBP-28K are conditional. In primary renal tubular cells obtained from mice, CaBP-9K is tightly regulated by 1,25(OH)₂D₃ [84]. In rats, the expression of renal CaBP-28K is increased by high levels of 1,25(OH)₂D₃ but is not sensitive to minor changes in 1,25(OH)₂D₃ [83]. In VDR KO mice, investigators found a 90% reduction in renal CaBP-9K (compared with WT mice) but near-normal renal expression of CaBP-28K [66]. In 1 α -hydroxylase KO mice, CaBP-9K and CaBP-28K both are reduced in the kidney [85]. Therefore, vitamin D may control calcium reabsorption in the kidneys by affecting CaBP-28K independently of VDR.

Research regarding the significance of CaBP-9K and CaBP-28K in renal calcium absorption is ongoing. Results of studies involving CaBP-9K KO mice and CaBP-28K KO mice

suggest that CaBP-9K and CaBP-28K are redundant for urinary calcium reabsorption; these KO mice had normal serum calcium levels [86,87]. Other calcium transporters (eg, TRPV5/TRPV6 and PMCA1b) may compensate for CaBP-9K during renal calcium reabsorption in mice [74]. Findings with VDR KO mice and CaBP-9K/CaBP-28K double-KO mice indicate that CaBP-28K does not affect body calcium levels or renal calcium reabsorption; in contrast, CaBP-9K is tightly regulated by 1,25(OH)₂D₃/VDR and plays an important role in renal calcium reabsorption under calcium-deficient conditions [66,88]. When compared with VDR KO mice, VDR/CaBP-28K double-KO mice had higher urinary calcium excretion [89]. CaBP-28K KO mice fed a high-calcium diet were found to have a 2- to 3-fold increase in urinary calcium [90]. Thus, CaBP-28K may play a role in kidney calcium reabsorption by a VDR-independent process (**Figure 2**).



CaBP-9K and CaBP-28K may exert indirect effects on paracellular calcium reabsorption, which is regulated by tight-junction proteins. Specifically, genes that encode tight junctions, such as *ZO-1*, *CLDN1*, *CLDN4*, *CLDN5*, *CLDN10b*, and *CLDN16* can be differently upregulated in mice lacking CaBP-9K, CaBP-28K, or both CaBP-9K and CaBP-28K when the mice are fed a diet deficient in calcium or deficient in both calcium and vitamin D [91]. In the regulation of kidney calcium homeostasis, CaBP-9K and CaBP-28K have complex, potentially important, roles that involve both intracellular and paracellular pathways.

Regulation of CaBP-9K/CaBP-28K by 1,25(OH)₂D₃/VDR in bone

Vitamin D (1,25[OH]₂D₃) has crucial functions in bone calcium homeostasis [92]. Calcium is a major constituent of bone, and bone constitutes the largest source of calcium in the body. Several hypotheses have been proposed regarding the

function of $1,25(\text{OH})_2\text{D}_3/\text{VDR}$ in bone. One is that $1,25(\text{OH})_2\text{D}_3/\text{VDR}$ has bidirectional activities. A physiologically optimal concentration of $1,25(\text{OH})_2\text{D}_3$ may facilitate bone formation, whereas a deficiency or excess of $1,25(\text{OH})_2\text{D}_3$ may limit mineralization. Cyp24a1(25-hydroxyvitamin D-24-hydroxylase)-null mice exhibit intramembranous bone lesions; this defect is absent in Cyp24a1/VDR double-null mice. Hence, elevated $1,25(\text{OH})_2\text{D}_3$ interacting with VDR appears to produce bone defects [93,94]. Under normal conditions, $1,25(\text{OH})_2\text{D}_3/\text{VDR}$ promotes mineralization and can produce anti-rickets effects in skeletal tissues. However, high-dose or prolonged treatment with $1,25(\text{OH})_2\text{D}_3$ can yield bone mineral loss and impaired mineralization [95-97]. Maternal hypervitaminosis D reduces fetal bone mass and mineral acquisition and can be lethal to the neonate [98].

A deficiency in $1,25(\text{OH})_2\text{D}_3$ or the absence of VDR or CYP27B1 (25-hydroxyvitamin D-1 alpha hydroxylase) can lead to the rickets phenotype, characterized by reduced calcium binding in the bone matrix, decreased bone mineral density, and osteomalacia [20,21,67,95,96,99,100]. Proliferation of osteoblast-like osteosarcoma cells is stimulated at physiologic levels of $1,25(\text{OH})_2\text{D}_3$ (0.1 nM) but is hindered at higher doses (10 nM) [97-100]. Hence, physiologic levels of $1,25(\text{OH})_2\text{D}_3$ in bone appear to be tightly regulated such that an optimal level facilitates bone formation, and an imbalance in $1,25(\text{OH})_2\text{D}_3$ serves as an antimineralization signal.

The functions of $1,25(\text{OH})_2\text{D}_3$ and VDR in bone depend on the calcium balance [101]. If VDR is impaired in the intestine or if dietary intake of calcium is low (i.e., a negative calcium balance), VDR signaling in osteogenic cells produces increased bone resorption and impaired bone mineralization; this preserves serum calcium levels. In a mouse model of intestinal VDR deficiency, calcium is significantly mobilized from the bone to preserve normal serum calcium levels; this occurs via upregulation of the ratio of receptor activator of nuclear factor- κ B ligand (RANKL)/osteoprotegerin(OPG) in osteoblasts to increase the generation of osteoclasts [61]. In addition to stimulating bone resorption, $1,25(\text{OH})_2\text{D}_3$ inhibits bone matrix mineralization by upregulating Enpp1, Enpp3, and Ank; these factors increase pyrophosphate, a potent mineralization inhibitor [61,102,103]. If calcium levels are normal or elevated (ie, a positive calcium balance) and serum levels of $1,25(\text{OH})_2\text{D}_3$ are normal, intestinal calcium absorption is facilitated, and sufficient calcium is delivered for mineralization of bone matrix. Hence, the role of VDR signaling in bone cells during positive calcium balance involves maintenance of calcium homeostasis.

The function of $1,25(\text{OH})_2\text{D}_3/\text{VDR}$ in bone cells differs by cell type and stage. For instance, the effect of $1,25(\text{OH})_2\text{D}_3/\text{VDR}$ in bone depends on the osteoblast differentiation stage. VDR signaling in osteoprogenitors and osteoblasts induces osteoclast formation and bone resorption; this negatively regulates bone mass [104]. In mature osteoblasts, VDR increases bone mass by decreasing the ratio of RANKL/OPG and increasing LRP-5 expression [105-107]. VDR signaling in osteocytes may be redundant because VDR inactivation has no

effect on mature osteoblasts or osteocytes in terms of bone mass and mineralization [61]. Because these differentiation stages coexist, the functions of VDR signaling in osteogenic cells are complex and warrant further investigation.

Discussion

CaBP-9K and CaBP-28K have been found in calcium-transporting epithelia and are co-expressed in mineralized tissues—such as ameloblasts, odontoblasts, osteoblasts, and osteocytes—as well as in chondrocytes [12,108-110]. CaBP-28K inhibits the apoptosis of osteoblast cells [111]. The roles of CaBP-9K and CaBP-28K in calcium regulation in vivo have been assessed by means of CaBP-9K KO mice and CaBP-28K KO mice. These KO mice have a phenotype that resembles that of WT mice, and the growth, life span, serum calcium levels, and serum phosphate levels of the KO mice are within normal ranges [87,112].

Results of early studies in this field suggested that CaBP-9K and CaBP-28K were of minor importance in calcium homeostasis because they could be functionally substituted by other calcium transporters. Subsequent findings involving CaBP-9K and CaBP-28K double-KO mice were that the mice appeared normal under conditions of normal dietary intake of calcium; however, under calcium-deficient conditions, the double-KO mice had more decreased serum calcium levels and bone length than did WT mice [88]. More recent work involved VDR/CaBP-D28K double-KO mice. Compared with VDR KO mice, VDR/CaBP-28K double-KO mice exhibit worsened growth retardation, lower body weight, and a more severe rachitic skeletal phenotype. When fed a normal diet, the double-KO mice had lower bone mineral density and a more distorted growth plate, with more osteoid formation in the trabecular region. When both VDR KO mice and VDR/CaBP-28K double-KO mice were fed a high-calcium, high-lactose diet, serum calcium levels were normalized in both the VDR KO and the double-KO mice, whereas skeletal abnormalities were resolved in the VDR KO mice but not in the double-KO mice [89]. The phenotypes of different gene KO mice were showed below (Table 1).

In research involving CaBP-28K KO mice, significantly increased femora and tibia cortical bone volumes were noted (113). These effects resulted from a decrease in the marrow cavity area, significantly decreased endosteal perimeters, and an increased trabecular number, compared with WT mice. CaBP-28K KO mice had stiffer bones, increased failure loads, and a decreased ratio of bone surface to bone volume, compared with WT mice. CaBP-28K KO mice also had decreased serum osteocalcin, which is an indicator of bone formation rate [113]. The increased bone volume and stiffness and decreased bone formation rate among CaBP-28K KO mice indicated that CaBP-28K plays an important role in bone homeostasis [114]. These results demonstrate that CaBP-9K and especially CaBP-28K are vital contributors to bone calcium homeostasis and skeletal mineralization [115]. Advancements in our understanding of calcium balance in bone development

likely will hinge on clarification of the regulatory processes between 1,25(OH)₂D₃/VDR and CaBP-9K/CaBP-28K.

Table 1 The phenotypes of different gene KO mice were showed.

KO-gene	CaBP9K	CaBP28K	vdr	VDR/CaBP28K	CaBP9K/CaBP28K
Serum					
Ca	N	N			N
P	N	N			N
PTH		N			
1,25(OH) ₂ D ₃					
URINE					
Ca	N				
P					
Bone					
Bone length	N	N			N
Cortical bone volume					
Bone marrow cavity area					
Endosteal circumference					
Bone hardness					
Bone load					
Trabecular bone					
Body weight	N	N			N
N: normal ; : down or weaken; : up or enhanced; blank: Unknown					

Conclusion

Vitamin D (1,25[OH]₂D₃) and calcium are maintained in balance, at least in part, by CaBP-9K and CaBP-28K. Intestinal calcium absorption involves participation of CaBP-28K in the vesicular transport pathway, which is regulated by 1,25(OH)₂D₃/VDR but is not well understood.

In maintenance of kidney calcium, CaBP-9K appears to be regulated directly by 1,25(OH)₂D₃/VDR, whereas CaBP-28K participates in calcium regulation via a poorly characterized, 1,25(OH)₂D₃-dependent and VDR-independent manner. In bone, CaBP-28K regulates development of the growth plate and can affect bone formation and mineralization. Additional work involving the relationship of CaBP-9K/CaBP-28K with 1,25(OH)₂D₃/VDR during calcium homeostasis is warranted and may offer insight regarding the diagnosis and treatment of vitamin D- and calcium-imbalance diseases.

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