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Key genes of vitamin D metabolism and their roles in the risk and prognosis of cancer

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Vitamin D is an essential vitamin for normal human metabolism and plays pivotal roles in various biological processes, such as maintaining calcium and phosphorus balance, regulating immune responses, and promoting cell differentiation while inhibiting proliferation. Vitamin D is obtained through sunlight exposure and diet, and is metabolized into its active form via hydroxylation in liver and kidney. Vitamin D deficiency is linked to various diseases, including skeletal disorders, diabetes, and cardiovascular diseases. Recent epidemiology and oncology research have demonstrated that serum vitamin D level, as well as genetic polymorphisms and expression dysregulation of genes related with vitamin D metabolism, have significantly influences on the incidence and prognosis of various types of cancer, including breast cancer, prostate cancer, liver cancer, gastrointestinal malignancy, and hematologic malignancies. The mechanisms linking vitamin D metabolism dysregulation to malignancy are multifactorial, such as the alteration in cell metabolism, proliferation, differentiation, and tumor microenvironment. These findings suggest potential therapeutic benefits of targeting the vitamin D signaling pathway for the diagnosis and treatment of cancer. However, there is still a lack of clinical applications regarding the knowledge of vitamin D metabolic pathway, and future research is urgently needed to illustrate the underlying mechanisms for the rationale design of clinical trials. Therefore, this review summarizes the metabolic pathways of vitamin D and its association with cancer, highlighting the importance of genetic polymorphisms and expression dysregulation of genes involved in vitamin D metabolism in cancer susceptibility and prognosis.

KEYWORDS

vitamin D, metabolism, cancer, genetic polymorphisms, microenvironment

1 Introduction

Vitamin D, a fat - soluble vitamin, has long been recognized for its crucial role in maintaining bone health by regulating calcium and phosphorus homeostasis (Holick, 2004; Bouillon et al., 2019) However, over the past few decades, an increasing body of research has expanded our understanding of vitamin D beyond its traditional role in skeletal health. This review aims to comprehensively summarize the current knowledge regarding the source,

TABLE 1 Association of vitamin D gene polymorphisms with cancer prognosis.

Gene	Function	Cancer-related research findings
CYP2R1	25-hydroxylase involved in converting vitamin D to 25(OH)D	A/G and A/A: reduce the risk of death in non-small cell lung cancer (Kong et al., 2020) G/A: decreased risk in the colon and rectum (Wen et al., 2021)
CYP27A1	25-hydroxylase involved in converting vitamin D to 25(OH)D	Breast cancer: High expression is associated with a reduced risk of distant recurrence (Inasu et al., 2021) Bladder, Prostate, and Renal cell carcinoma: expression is reduced and act as a tumor suppressor (Baek et al., 2017; Liang et al., 2019) Ovarian and Breast cancer: High expression may promote tumor progression (He et al., 2019; Ma et al., 2020)
CYP3A4	Involved in drug metabolism and chemotherapy resistance	G and G/G: increased the risk of prostate cancer (Zhou et al., 2013) C/T:reduced ability to metabolize multiple cancer drugs (Rodríguez-Antona et al., 2007; Tian and Hu, 2015)
CYP27B1	Converts 25(OH)D to the active form 1,25(OH)2D, essential for VDR signaling	rs10877012: associated with increased risk of colorectal cancer (Latacz et al., 2020) Breast cancer, Non-melanoma skin cancer: low expression is associated with disease progression and recurrence (Nemazannikova et al., 2019; Voutsadakis, 2020)
CYP24A1	Inactivates vitamin D metabolites by 24-hydroxylation, regulating VDR signaling	Breast cancer, Colorectal cancer, Lung cancer, Ovarian cancer: high expression is associated with poor prognosis (Davis et al., 2007; Shiratsuchi et al., 2017) Oral squamous cell carcinoma: low expression is associated with poor prognosis (Nakamori et al., 2024)
VDBP	Binds and transports vitamin D to target tissues	rs7041 and rs4588: associated with risk for lung and colorectal cancer (Maneechay et al., 2015) Hepatocellular carcinoma、 Colorectal cancer: high expression is associated with good prognosis (Muindi et al., 2013; Qin et al., 2024)
VDR	Nuclear receptor regulating calcium-phosphorus homeostasis and tumor suppression	Breast cancer, colorectal cancer , lung cancer: VDR expression was decreased (Marik et al., 2010; Srinivasan et al., 2011) Prostate cancer: rs2107301, rs2238135 were associated with an increased risk of cancer (Holick et al., 2007)

metabolism, and function of vitamin D, as well as its associations with various diseases, with a particular focus on cancer.

The discovery of vitamin D in the early 1920s, initially linked to the prevention of rickets, marked the beginning of a long - standing exploration into its biological functions. Since then, researchers have identified multiple forms of vitamin D, with vitamin D2 and D3 being the most prominent (Dueland et al., 1985; Mau et al., 1998; Houghton and Vieth, 2006; Baur et al., 2020). The human body can synthesize a significant portion of vitamin D through skin exposure to ultraviolet B (UVB) radiation, while the remaining amount is obtained from dietary sources. This dual source of vitamin D contributes to its presence in various tissues and its complex metabolic processes (Reboul et al., 2011; Baur et al., 2020).

Vitamin D metabolism involves a series of enzymatic reactions that convert the inactive forms of vitamin D into its biologically active metabolite, 1,25 - dihydroxyvitamin D [1,25(OH)2D]. Key proteins, such as cytochrome P450 enzymes and the vitamin D - binding protein (VDBP), play essential roles in these metabolic pathways. The active form of vitamin D exerts its functions by binding to the vitamin D receptor (VDR), a ligand - dependent nuclear transcription factor, which then regulates the expression of numerous target genes involved in a wide range of physiological processes (Czogalla et al., 2020).

While the traditional role of vitamin D in bone health remains well - established, emerging evidence has highlighted its involvement in many other physiological and pathological conditions. Vitamin D deficiency has been associated with an increased risk of various diseases, including diabetes, cardiovascular diseases, acute infections, chronic inflammatory diseases, and asthma. These associations suggest that vitamin D may have broader immunomodulatory, anti - inflammatory, and homeostatic functions in the body.

Cancer is one of the most significant public health challenges globally, and understanding its underlying mechanisms and developing effective prevention and treatment strategies are of utmost importance. In recent years, there has been growing interest in the potential role of vitamin D in cancer. Epidemiological studies have reported associations between serum vitamin D levels and the risk of different types of cancer. Additionally, laboratory studies have demonstrated that vitamin D and its metabolites can influence cancer cell proliferation, differentiation, apoptosis, migration, and the interaction between cancer cells and the immune system (Zhang and Naughton, 2010). Furthermore, genetic polymorphisms and abnormal expression of key genes involved in vitamin D metabolism have been linked to cancer risk and prognosis. These findings not only provide insights into the molecular mechanisms underlying the relationship between vitamin D and cancer but also offer potential biomarkers for cancer prediction and new therapeutic targets for cancer treatment.

This review will first detail the source, metabolism, and physiological functions of vitamin D, followed by an in - depth discussion of the diseases associated with vitamin D deficiency. Then, it will explore the associations between vitamin D and different types of cancer, as well as the role of key genes in vitamin D metabolism in cancer. Finally, it will summarize the current state of knowledge and discuss future perspectives for research on vitamin D in the context of human health and cancer.

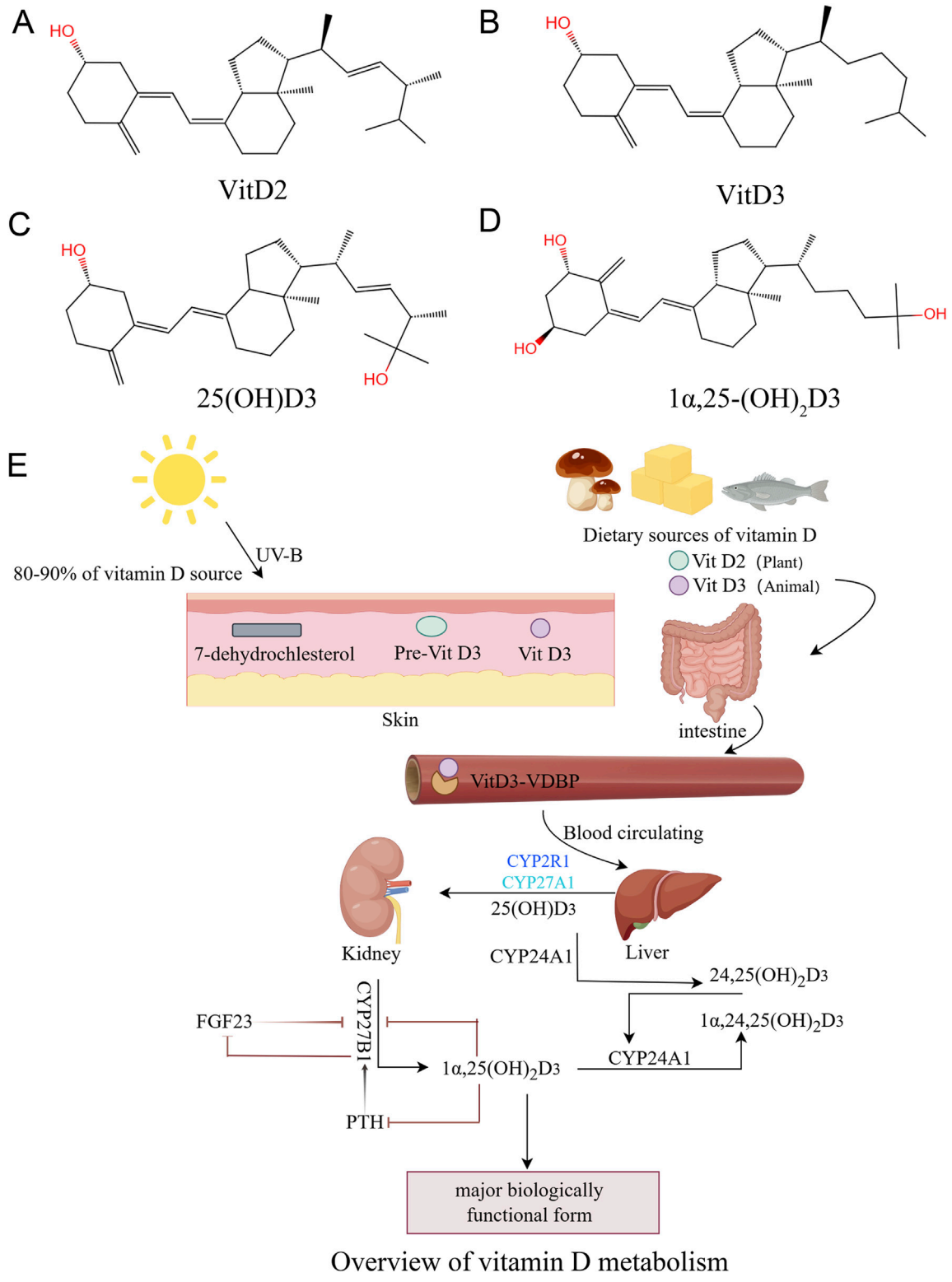

FIGURE 1
The sources and metabolism of vitamin D (overview of vitamin D metabolism). **(A)**: Chemical structure of vitamin D2, **(B)**: Chemical structure of vitamin D3, **(C)**: Chemical structure of 25(OH)D3, **(D)**: Chemical structure of 1α,25-(OH)2D3. **(E)**: Vitamin D3 is mainly produced by the conversion of 7-dehydrocholesterol from sun-exposed skin and food intake.

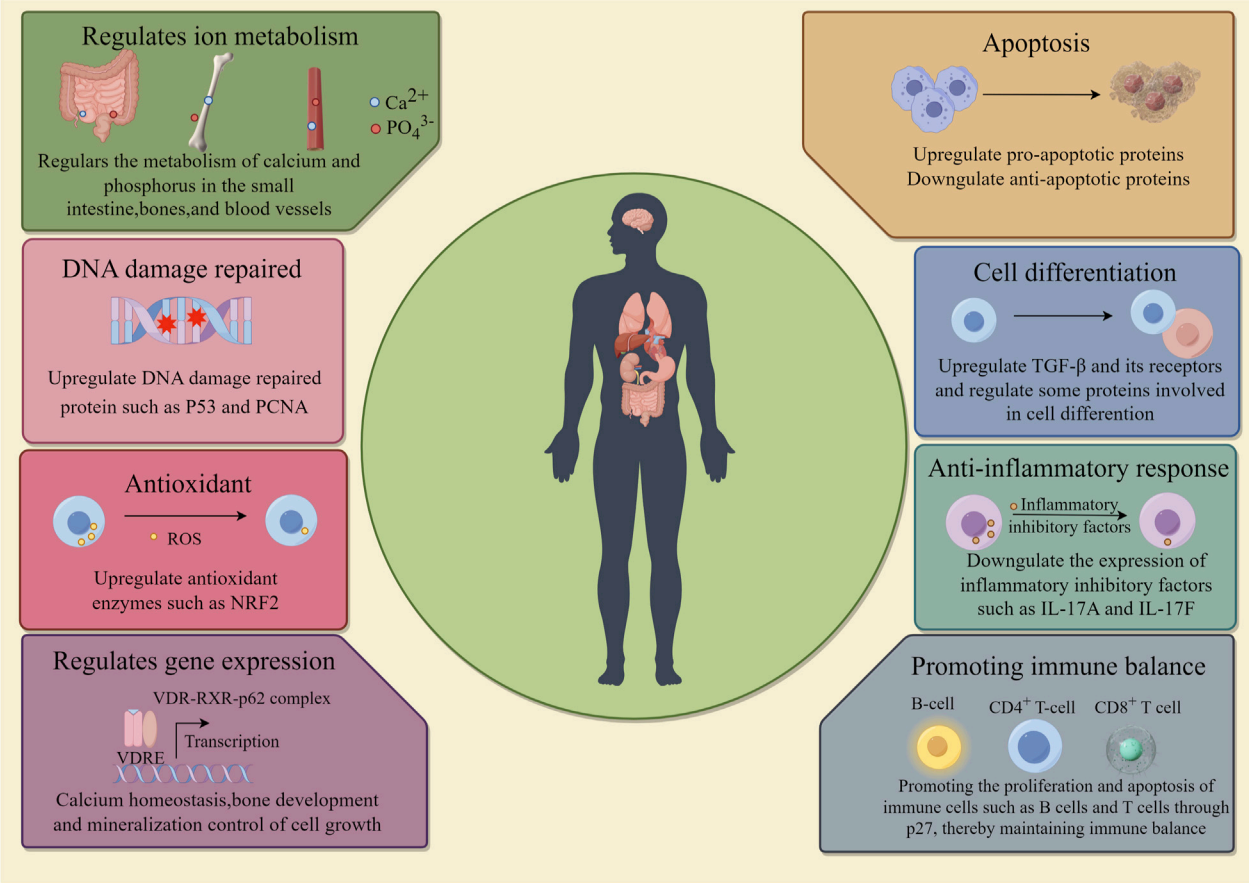

FIGURE 2
Function of vitamin D. The roles of vitamin D in the human body include: regulation of metabolism; DNA repair; Antioxidant; Promoting gene expression, promoting cell apoptosis and differentiation; Anti-inflammatory response; Promote immune balance.

2 Source, metabolism, and function of vitamin D

2.1 The source of vitamin D

In early 1920s, scientists discovered that exposure to sunlight or consumption of ultraviolet-irradiated olive oil could help prevent rickets. Further research led to the identification and naming of the active component responsible for combating rickets as vitamin D (Mccollum et al., 1922). Vitamin D is fat-soluble vitamin that can be categorized into various forms depending on the structure of side chains, such as Vitamin D2, Vitamin D3, Vitamin D4, Vitamin D5, Vitamin D6, and Vitamin D7. Among these, VD2 and VD3 are the primary forms found in plants and animals (Holick, 2023).

Vitamin D2 is produced from ergosterol upon ultraviolet light exposure in plants and fungus, whereas vitamin D3 is converted from 7-dehydrocholesterol upon ultraviolet irradiation in animals. In humans, 80%–90% vitamin D is synthesized in skin, while the rest is obtained from diet such as mushrooms or cod liver oil via chylomicrons and lymphatic vessels in intestine (Dueland et al., 1985; Mau et al., 1998; Houghton and Vieth, 2006; Reboul et al., 2011; Baur et al., 2020).

Both vitamin D2 and D3 would be stored and released from adipose tissues, skeletal muscles, brain, lung, spleen and skin, and they serve the same physiological functions (Holick, 2004; Bouillon et al., 2019). Their catabolism mainly occurs in liver and kidney, with most being excreted through bile in feces, and a portion is also eliminated through urine (Jones, 2008). The general production and metabolic process of vitamin D is summarized in Figure 1.

2.2 Key proteins involved in the metabolism of vitamin D

Vitamin D undergoes 2 rounds of hydroxylation reactions to transform into $1,25(OH)_2D$, the ultimate biologically active form in human, and liver is the principal site for the initial hydroxylation to produce 25(OH)D. A variety of CYP family members with 25-hydroxylase activity have been discovered to date, among which CYP2R1 is considered as the key enzyme for this reaction (Cheng et al., 2004; Thacher et al., 2015). Genetic deletion of CYP2R1 resulted in severe symptoms of vitamin D deficiency in mice, including hypocalcemia, hyperphosphatemia, and osteomalacia (Roizen et al., 2018), and a multicenter genetic association study revealed that a few CYP2R1 genetic polymorphisms were correlated with serum 25(OH)D3 level to varying degrees (Wang et al., 2010). Besides CYP2R1, CYP27A1 also participates in the hydroxylation of vitamin D

with a preference for vitamin D3 over D2 (Pikuleva et al., 1998; Shinkyo et al., 2004), while CYP3A4 primarily catalyzes vitamin D2 as substrate (Aiba et al., 2006). In rats, CYP2C11 also exhibits 25-hydroxylase activity, while it is still unclear whether human possess its homolog (Rahmaniyan et al., 2005).

After initial hydroxylation reaction, 25(OH)D is the main circulating form in serum (Lund and DeLuca, 1966; Mawer et al., 1969; Norlin and Wikvall, 2023), and its serum concentration is often considered as the primary clinical indicator for evaluating vitamin D level (Damasiewicz et al., 2015). The majority of liver-produced 25 (OH)D is released into bloodstream forming complex with Vitamin D Binding Protein (VDBP), a carrier protein which is also produced by hepatocytes. VDBP greatly increases the solubility of vitamin D metabolites and protects them from metabolic degradation, whose serum level sometimes serves as an auxiliary indicator for assessing an individual's vitamin D status during clinical practices (Haddad et al., 1993).

In kidney, 25 (OH)D/VDBP complexes are filtered by the glomerulus and reabsorbed at proximal convoluted tubule. Within tubular cells, 25 (OH)D is released from VDBP complex through lysosomal degradation and transferred to mitochondria (Nykjaer et al., 1999; Nykjaer et al., 2001), where 25 (OH)D is further hydroxylated to 1,25 $(OH)_2D$ by CYP27B1 (Jones et al., 2014). CYP27B1 expression level is highest in kidney, but it is also detectable in other tissues such as epidermis and immune cells, and 1,25 $(OH)_2D$ can still be produced in anephric rats and patients with chronic renal failure, indicating that the activation of vitamin D might not be exclusively limited to kidney (Zehnder et al., 2001). Eventually, 1,25 $(OH)_2D$ is released into bloodstream and binds again to VDBP during its circulation all over the body, but the affinity of VDBP for 25 (OH)D is 10–100 times greater than 1,25 $(OH)_2D$ (Verboven et al., 2002).

CYP24A1 is a key enzyme regulating the circulating concentrations of 1,25 $(OH)_2D$, which constitutes the degradation of the vitamin D molecules into water-soluble calcitroic acids for excretion by catabolizing 25(OH)D and 1,25$(OH)_2D$ into 24-hydroxylated products (24,25 $(OH)_2D$ and 1,24,25$(OH)_3D$) (Li and Tuckey, 2023). CYP24A1 is present in all cells that contain vitamin D receptor (VDR), and its expression is induced by sufficient vitamin D and normal calcium balance, forming a negative feed-back loop to restrict vitamin D functions.

2.3 The physiological functions of vitamin D

Biologically active 1,25 $(OH)_2D$ is recognized by VDR, a ligand-dependent nuclear transcription factor discovered in 1974 (Brumbaugh and Haussler, 1974). Upon 1,25$(OH)_2D$ binding, VDR undergoes phosphorylation at serine 208 within hinge domain (Jurutka et al., 1993; Arriagada et al., 2007), followed by heterodimerization with retinoid X receptor (RXR) at hexametric repeats on Vitamin D Response Elements (VDRE) in promoter regions of target genes (Fretz et al., 2006; Meyer et al., 2006). Then 1,25$(OH)_2D$/VDR/RXR complex recruits either transcriptional co-activators (such as p160 and TIF2) or repressors (such as N-CoR and SMRT) to regulate the expression of target genes (Haussler et al., 1997; Bettoun et al., 2003; Leong et al., 2004; Dhawan et al., 2005; Shri Preethi et al., 2023). Besides nuclear VDR (nVDR), cytoplasmic VDR (cVDR) and membrane VDR (mVDR) have also be reported (Barsony et al., 1997; Zhang Y. et al., 2023). A study on ovarian cancer demonstrated that cVDR level was negatively correlated with overall survival of ovarian cancer patients, while nVDR did not show such prognostic potential (Czogalla et al., 2020). Till now, it is still not thoroughly investigated whether cVDR and mVDR play distinct functions compared to nVDR, especially in a transcription-independent or vitamin D-independent way.

The classic function of vitamin D is to maintain the stability of plasma calcium and phosphorus levels, which are essential for skeletal mineralization, muscle contraction, nerve conduction, as well as other basic functions of cells. 1,25 $(OH)_2D$/VDBP complexes travel all over the body via blood circulation, participating in the regulation of calcium and phosphorus absorption, transfer, and reabsorption (Maestro et al., 2016). In intestinal mucosal cells, 1,25 $(OH)_2D$ acts on nVDR to promote the biosynthesis of calcium-transporting proteins such as TRPV5/6, calbindin-D9k, plasma membrane Ca^{2+}-ATPase1b, and NCX1 (Wongdee and Charoenphandhu, 2015; Xu et al., 2021). Moreover, 1,25 $(OH)_2D$ enhances calcium reabsorption by renal distal tubule by up-regulating the expression of plasma membrane Ca^{2+}-ATPase1b in renal epithelial cells (Glendenning et al., 2000). In osteoblast, 1,25 $(OH)_2D$ facilitates the deposition of calcium and phosphorus in the form of bone salts via up-regulating the expression of ALPL and c-MYC, thus promoting the calcification of bone tissues (Anderson, 1995; Piek et al., 2010; Schwetz et al., 2017).

Other than calcium homeostasis, 1,25$(OH)_2D$ is involved in various other biological processes. For example, 1,25 $(OH)_2D$ exerts a protective effect on genomic integrity by upregulating the expression of proteins associated with DNA damage repair pathway, such as P53 and PCNA (Anapali et al., 2022; Li et al., 2022). Moreover, animal model study showed that vitamin D reduced the severity of cardiac hypertrophy by increasing mitophagy and decreasing apoptosis in aging hearts (Shahidi et al., 2023). Similarly, a study on traumatic brain injury showed that 1,25 $(OH)_2D$ could promote autophagic process and activate NRF2 signaling, thus exhibiting a neuroprotective role (Cui et al., 2021). Another study on dermal wound healing process showed that the combination of vitamin D and low concentration of TGFβ1 synergistically increased gene expression of TGFβ1, connective tissue growth factor, and fibronectin, which enhanced fibroblast migration, myofibroblast formation, and collagen production (Ding et al., 2016). Therefore, vitamin D contributes to tissue hemostasis in various organs beyond skeleton.

Besides solid organs, vitamin D and its metabolites also contribute to the regulation of immune system due to the expression of VDR in various types of immune populations (Provvedini et al., 1983). Many studies have demonstrated that 1,25$(OH)_2D3$ plays a key role in immune-inflammatory suppression. For example, 1,25 $(OH)_2D3$ treatment could induce the production of IL-4 and GATA3 in CD^{4+} T cells in the absence of cytokine stimulation *in vitro* (Boonstra et al., 2001). Furthermore, 1,25 $(OH)_2D3$ can reduce the expression of inflammatory factors such as IL-17A, IL-17F, and IL-22, and decrease the number of $CD4^+$ T cells and memory $CD4^+$ cells in stimulated peripheral blood mononuclear cells from treatment-naive patients with early rheumatoid arthritis (Colin et al., 2010). In patients with intestinal inflammation, 1,25 $(OH)_2D3$ can directly inhibit the

overactivation of $CD8^+$ T cells to maintain intestinal homeostasis (Chen et al., 2014). Additionally, it can reduce the activation of $CD8^+$ T cells by suppressing the secretion of IFN-γ and TNF-α (Lysandropoulos et al., 2011). Recently, Marco Fraga et al. reported that rapid membrane vitamin D signaling promoted a regulatory Th2-like response with CCR8 expression in oral cancer (Fraga et al., 2021).

Other than T cells, 1,25 $(OH)_2D3$ also plays immune-suppressive role in B cells and macrophages. More specifically, 1,25 $(OH)_2D3$ treatment up-regulates the expression of p27 in B cells, which inhibits proliferation and induces apoptosis, as well as reducing the generation of plasma cells and post-switch memory B cells (Chen et al., 2007). Moreover, B cells primed by 1,25 $(OH)_2D3$ show reduced surface CD86, consequently impairing their capacity to activate T cells (Drozdenko et al., 2014). Similar to the observations on B cells, 1,25 $(OH)_2D3$ could downregulate pro-inflammatory mediators such as TNF-α, IL-1α, IL-1β, IL-6 and RANKL, as well as reduce NO production and surface MHC class-II antigens in monocyte-derived macrophages (Xu et al., 1993; Nashold et al., 2000; Neve et al., 2014). Moreover, 1,25 $(OH)_2D3$ also impairs NK cell development and cytotoxic functions in a vitro umbilical cord blood hematopoietic progenitor cell differentiation model (Weeres et al., 2014).

In general, vitamin D mainly contributes to immune homeostasis as an immune-suppressive player, and the association between vitamin D and immune disorders such as autoimmune diseases and immune-suppressive tumor microenvironment warrants further exploration and investigation.

2.4 Diseases related with vitamin D deficiency

2.4.1 Skeletal disorders

A deficiency in vitamin D can lead to impaired calcium absorption and bone mineralization, causing the development of rickets and chondrosis (Liu et al., 2023). Chondrosis can present with bone and joint problems, respiratory problems, and facial and bone deformities, while rickets may also have effects on teeth, hearing and vision. In children, observational studies have demonstrated that a serum level of 25 (OH)D above 50 nmol/L is required to prevent rickets (Yamshchikov et al., 2009). Randomized trials support oral vitamin D supplement of 400 IU/day as the optimal dose for the prevention of nutritional rickets (Specker et al., 1992; Gallo et al., 2013).

2.4.2 Diabetes

Observational studies have shown an inverse association between vitamin D levels and the risk of diabetes (Chiu et al., 2004; Reis et al., 2007; Lu et al., 2009; Afzal et al., 2013; Gong et al., 2024). Multiple mechanisms might be involved in such an association. For example, animal studies have shown that 1,25 $(OH)_2D$ promotes the biosynthesis ability of pancreatic β cells and accelerates the conversion of proinsulin to insulin (Bourlon et al., 1999). *In vitro* experiments also showed that calbindin-D (28k), a transcriptional target of $1,25(OH)_2D$, could prevent the apoptosis of pancreatic β cells via directly inhibiting the activity of caspase-3 (Christakos and Liu, 2004).

2.4.3 Cardiovascular diseases

In vivo and *in vitro* experiments have proved that vitamin D has many cardiovascular effects, such as anti-hypertrophy properties (Kim et al., 2006; Chen et al., 2011), inhibition of cardiomyocyte proliferation, stimulation of smooth muscle cell proliferation (Carthy et al., 1989; Rebsamen et al., 2002; Doran et al., 2008), endothelial growth factor expression (Wong et al., 2008), inhibition of natriuretic peptide release and renin-angiotensin-aldosterone system (Li et al., 2002). However, randomized trials of vitamin D supplementation do not support benefits for cardiovascular health (Hiemstra et al., 2019). More research is required to elucidate the relationship between vitamin D deficiency and cardiovascular diseases.

2.4.4 Acute infection

Vitamin D reduces the risk of microbial infection and death by many mechanisms, including physical barrier, cellular natural immunity, and adaptive immunity (Rondanelli et al., 2018). Laboratory study have showed that 1,25 $(OH)_2D$ reduces the proportion of rotavirus replication *in vivo* and *in vitro* (Zhao et al., 2019). Experimental data have also proved that vitamin D supplementation can reduce the risk of influenza and COVID-19 infection and death (Urashima et al., 2010; Hastie et al., 2020; Ilie et al., 2020). Clinical trial showed that supplementation with 4000 IU/d of vitamin D can reduce dengue virus infection (Martínez-Moreno et al., 2020). Moreover, an analysis of data from 25 randomized controlled trials of vitamin D supplementation for the prevention of acute respiratory infections demonstrated that the overall protective effect was stronger in people with baseline 25 (OH)D concentrations below 25 nmol/L, compared to those with baseline 25 (OH)D concentrations of 25 nmol/L or higher (Li-Ng et al., 2009; Manaseki-Holland et al., 2010; Urashima et al., 2010).

2.4.5 Chronic inflammatory diseases

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that leads to neurodegeneration (Thompson et al., 2018). A prospective study of more than 7 million military personnel in the United States. Military repository found that a lower serum vitamin D level was correlated with a higher risk of MS (Munger et al., 2006). Vitamin D plays an important role in the pathogenesis of MS by participating in the regulation of immune response (Mahon et al., 2003; Lysandropoulos et al., 2011; Grau-López et al., 2012).

Other than MS, vitamin D deficiency is also correlated with a higher risk for chronic inflammatory diseases of liver and intestine. For example, the high prevalence of vitamin D deficiency in patients with autoimmune hepatitis indicates its importance as an immunomodulator (Smyk et al., 2013). Similarly, a study on a cohort of 203 treatment-naïve patients with chronic hepatitis B virus (HBV) demonstrated that low 25(OH)D level was associated with higher HBV replication rate (Farnik et al., 2013). Moreover, *in vitro* experiment demonstrated that vitamin D deficiency promoted the proliferation and activation of hepatic stellate cells, which might contribute to hepatic fibrosis, a common hepatic pathological change resulted from chronic inflammatory diseases (Sun et al., 2021). Besides liver diseases, animals lacking vitamin D diet are more likely to develop experimental colitis due to increased

intestinal permeability (Du et al., 2017). Mechanistic study showed that vitamin D/VDR signaling could induce the expression of *Claudin-2*, a key gene involved the epithelial integrity (Fujita et al., 2008).

2.4.6 Asthma

Low serum 25 (OH)D level has been found to be associated with asthma in both adults and children (Confino-Cohen et al., 2014; Hattangdi-Haridas et al., 2019). In terms of asthma recurrence rates, children with asthma who took vitamin D supplements have significantly lower recurrence rate than those in the placebo group (Korn et al., 2013; Ozturk Thomas et al., 2019). Recent studies have shown that vitamin D has important immunomodulatory effects, which can inhibit airway inflammation (El Abd et al., 2024), improve airway hyperreactivity (Wang et al., 2022), improve airway remodeling, reduce glandular secretion, reduce bronchial smooth muscle cell proliferation, and increase the body's response to hormones (Britt et al., 2016).

3 The association between vitamin D and cancer

Vitamin D participates in the physiological processes of life as a precursor to steroid hormones, and recent studies have found that vitamin D also plays a key role in the prevention and treatment of cancer via regulating cancer cell metabolism, proliferation, differentiation, migration, as well as its dynamic interaction between immune system and tumor microenvironment (Figure 2) (Zhang and Naughton, 2010; Jeon and Shin, 2018; Sheeley et al., 2022; Seraphin et al., 2023).

3.1 Vitamin D and breast cancer

Breast cancer is a common malignant tumor that threatens the life and health of women and its incidence rate ranks first among all types of cancer worldwide (Sung et al., 2021). A population-based case-control study comprising 289 breast cancer cases and 595 matched controls showed that a high level of serum 25 (OH)D significantly reduced the risk of developing breast cancer in premenopausal population in the region of southern Germany (Abbas et al., 2009). Moreover, a meta-analysis on 44,165 cases from 64 studies worldwide demonstrated that a higher serum 25 (OH)D concentration was associated with better prognosis for breast cancer patients (Vaughan-Shaw et al., 2017).

A number of hypotheses have been proposed to explain the relationship between vitamin D and breast cancer carcinogenesis in a variety of cell lines and animal models (Ooi et al., 2010). As demonstrated by several *in vitro* studies on breast cancer cell lines, 1,25 $(OH)_2D$ influences multiple signaling pathways, such as RAS/MEK/ERK pathway and AMPK pathway, thus inducing differentiation, cell cycle blockage and apoptosis in both normal and malignant breast cells, as well as inhibiting cell proliferation and angiogenesis (LaPorta and Welsh, 2014; Zheng et al., 2019). Moreover, vitamin D is able to inhibit invasion and metastasis of breast cancer cells by decreasing N-cadherin and vimentin expression in breast cancer cells while upregulating the expression of E-cadherin (Blasiak et al., 2020). Interestingly, 24,25 $(OH)_2D3$, which is often considered as a functionally inactivated vitamin D metabolite, could also exhibits anti-cancer properties in ER^+ breast cancer cells, but not in ER^- breast cancer cells, suggesting that the anti-cancer effect of 24,25 $(OH)_2D3$ may be ER-dependent (Verma et al., 2021).

In animal experiments, a study on a rat mammary hyperplasia model revealed that nipple diameter, height, and mammary thickness decreased with increasing vitamin D dosage, and the expression of estrogen receptor alpha (ERα) and progesterone receptor (PR) in tissues also declined with increasing vitamin D dosage. Immunocompromised mice bearing MCF-7 breast cancer xenografts showed significant tumor shrinkage (>50%) after ingestion of a vitamin D3-supplemented diet (5000 IU/kg) compared with a control diet (1000 IU/kg) (Swami et al., 2012). Mice with higher vitamin D levels were more immune resistant to transplanted cancers and responded better to checkpoint blockade-based cancer immune therapy, which was related to the action of vitamin D on gut microbiota particularly *Bacteroides fragilis* (Giampazolias et al., 2024). Moreover, Esma Karkeni et al. reported that vitamin D supplement could decrease tumor growth by increasing tumor infiltrating $CD8^+$ T cells in a murine orthotopic breast cancer model fed with normal diet. Interestingly, such protective effect of vitamin D would be reversed in high-fat diet conditions, suggesting the involvement of other metabolism factors in this process (Karkeni et al., 2019).

3.2 Vitamin D and prostate cancer

Prostate cancer is one of the most common tumors in men, and its incidence rate ranks second in male malignant tumors (Sung et al., 2021; Wei et al., 2021). Haojie Li et al. reported that Men with a low serum vitamin D status and a less active VDR genotype were at approximately two-fold higher risk for prostate cancer than men with the active VDR allele and a high serum 5 (OH)D3 in a prospective study involving 18 years of follow-up of 14,916 men initially free of diagnosed cancer in United States (Li et al., 2007). However, Yonghua Xu et al. conducted a meta-analysis of 21 observational studies on cohorts of various countries, and found that men with a high level of serum 25 (OH)D had a significantly increased risk of prostate cancer (Xu et al., 2014). These controversial epidemiological observations suggest that vitamin D might play complicated roles in prostate cancer.

However, vitamin D and its metabolites mostly exhibit anti-proliferative effects against prostate cancer in laboratory studies. For example, 1,25 $(OH)_2D3$ reduces the expression of anti-apoptotic proteins and induces insulin-like growth factor binding protein (IGFBP3), thus leading to apoptosis in prostate cancer cell lines (Boyle et al., 2001; Guzey et al., 2002; Washington and Weigel, 2010). Similarly, 1,25 $(OH)_2D3$ reduces the expression of cyclooxygenase-2 (COX-2) and 5-prostaglandin dehydrogenase (15-PGDH), two critical enzymes involved in the metabolism of prostaglandin, which consequently inhibits proliferation of prostate cancer cells. (Moreno et al., 2005).

3.3 Vitamin D and liver cancer

Hepatocellular carcinoma (HCC) is the third most lethal malignant tumor in the world (Sung et al., 2021; Wu et al., 2022;

Jiang et al., 2023), and an increasing number of studies have found that there is an indirect relationship between serum vitamin D levels and the risk of HCC (Markotić et al., 2022). For example, Veronika Fedirko et al. reported that in a European population cohort study of 204 cases, individuals with serum vitamin D levels below a certain threshold (25(OH)D < 75 nmol/L) had a significantly increased risk for HCC compared to those with higher levels (Fedirko et al., 2014).

In vitro studies have shown that 1,25 $(OH)_2$D3 inhibits the proliferation of HCC cell lines by multiple mechanisms, such as induction of apoptosis and cell cycle blockage at G1 phase (Chiang et al., 2011; Wang et al., 1996). Besides directly acting on the proliferation of HCC cells, vitamin D also exerts synergistic anti-HCC effects with existing drugs. For example, astemizole enhanced the anti-tumor effect of Vitamin D in HCC both *in vitro* and *in vivo* (Xu et al., 2018). Additionally, vitamin D is an anti-fibrotic agent which can inhibit collagen expression, which also contributes to the suppression of HCC development and progression (Chen et al., 2016).

3.4 Vitamin D and the cancer of gastrointestinal tract

As a key transcriptional factor regulating calcium absorption, VDR expression is high in gastrointestinal tract, especially intestine, and a number of research have demonstrated that vitamin D/VDR signaling axis exerts regulatory functions in the malignant transformation of colon and stomach. For example, an epidemiological investigation showed an inverse relationship between solar radiation (latitude) and colorectal cancer (CRC) mortality and incidence in the United States, indicating that vitamin D might be a protective factor for CRC (Garland and Garland, 1980; Sui et al., 2018; Chen et al., 2019; Zou Y. et al., 2024). Numerous *in vitro* and *in vivo* studies have demonstrated that 1,25 $(OH)_2$D could not only inhibit proliferation, but also induce epithelial differentiation, apoptosis, and detoxification metabolism by regulating the expression of target genes such as CST5 and JMJD3 in CRC cells (Alvarez-Díaz et al., 2009; Pereira et al., 2011). Moreover, vitamin D inhibits Wnt signaling by blocking cross-talk between tumor epithelial cells and their microenvironment. Specifically, VDR downregulates the expression of β-catenin, cyclin D1 and LEF-1 *in vitro*, and xenografts established by VDR-overexpressing SW480 cells shows suppression of tumor growth and decreased expression of β-catenin, cyclin D1 and LEF-1 (Yu et al., 2023). Vitamin D also inhibits the nuclear translocation of β-catenin by downregulating the expression of Wnt ligands (Wnt1 and Wnt3a), which further reduces the expression of the downstream target gene cyclin D1 (Zou M. et al., 2024). Vitamin D also represses the cell cycle regulator MYC gene directly and indirectly through the Wnt/β-catenin pathway (Liu et al., 2008). A recent study reported that acidosis, a common feature of CRC microenvironment, could induce VDR nuclear exportation, which tuned down the VDR-dependent anti-malignant signaling and consequently led to phenotypic transformation towards CRC stem cell (Hu et al., 2020).

Similar to CRC, many studies have demonstrated that vitamin D and its metabolites exert protective effects against gastric cancer. Analysis of serum 25 (OH)D level in gastric cancer patients have demonstrated that both clinical stage and lymph node metastasis classification are significantly inversely associated with vitamin D level (Ren et al., 2012). Bao et al. found that 1,25 $(OH)_2$D3 treatment induced apoptosis in gastric cancer cells *in vitro* (Bao et al., 2013). Vitamin D acts through the hedgehog signaling pathway and reduces cell viability by inhibiting the expression of many hedgehogs signaling target genes in gastric cancer cells, including Patched1 and Gli1 (Baek et al., 2011). Moreover, functional VDR elements have been identified in the promoters of phosphatase and tensin homologues (PTEN), a potent tumor suppressor, suggesting that vitamin D may be involved in the regulation of PTEN expression (Bao et al., 2013). Vitamin D significantly promotes apoptosis in undifferentiated gastric malignant cells (especially hCG-27) (Ren et al., 2012). Recent studies have revealed that vitamin D plays a role in modulating the expression of various genes associated with extracellular matrix remodeling, which may impede the progression of gastric cancer by regulating the extracellular matrix microenvironment. Specifically, vitamin D decreases the expression of profibrotic factors, including TGFB1 and SERPINE1, as well as collagen types I and III, and other collagen isoforms, while it also increases the expression of antifibrotic factors such as BMP7, MMP8, and follistatin. These effects suggest that vitamin D could potentially prevent the progression of gastric cancer by balancing the pro-fibrotic and anti-fibrotic factors within extracellular matrix (Artaza and Norris, 2009).

3.5 Vitamin D and hematologic malignancy

Hematological malignancies are myeloid and lymphatic tumors caused by disruption of normal hematopoietic function. They are classified into several common subtypes, generally consisting of leukemia, multiple myeloma, non-Hodgkin lymphoma, and Hodgkin lymphoma (Zhang N. et al., 2023). 1,25 $(OH)_2$D3 has anti-proliferative, pro-apoptosis, and pro-differentiation effects in hematologic malignancies, such as leukemia and lymphomas (Kozielewicz et al., 2016). In addition, 1,25 $(OH)_2$D3 also reduces the production of pro-inflammatory cytokines such as IFN-γ, TNF-α and IL-17, which are known to be associated with the development of inflammation (Peruzzu et al., 2022). In leukemia and lymphoma cells, 1,25 $(OH)_2$D3 reduces the activation of oncogenic JAK/STAT pathway (Olson et al., 2017). Particularly in myeloid leukemia cells, 1,25 $(OH)_2$D3 treatment promotes the differentiation of the predominantly neutrophilic myeloid cell lineage, while leading to a reduction in the proliferation and an enhancement in the monocyte-macrophage differentiation pathway, which may be related to the upregulation of the transcription factor CEBPD (Marchwicka and Marcinkowska, 2018).

4 The association between key genes of vitamin D metabolism and cancer

The relationship between vitamin D deficiency and cancer risk has received widespread attention. Genetic polymorphisms and abnormal expression of vitamin D metabolizing enzymes are strongly associated with cancer risk and prognosis (Table 1), and

these findings provide new perspectives on cancer prevention and treatment, and may contribute to the development of new therapeutic strategies (Bergadà et al., 2014).

4.1 CYP2R1, CYP27A1, and CYP3A4

CYP2R1, CYP27A1 and CYP3A4 are 3 major 25-hydroxylases responsible for the initial hydroxylation to convert vitamin D to 25 (OH)D, and their genetic polymorphisms have been found associated with different risks for developing certain types of cancer.

Kong et al. analyzed the correlation between CYP2R1 rs10741657 and the prognosis of 542 Asian non-small cell lung cancer patients by multivariate Cox regression model, and they found that the A/G and A/A carriers displayed a lower risk of death than G/G carriers (A/G vs. G/G, HR = 0.79, 95% CI: 0.61–1.03; A/A vs. G/G, HR = 0.69; 95% CI: 0.46–0.97; $p = 0.033$) (Kong et al., 2020). Parallelly, Jing Wen et al. conducted a meta-analysis covering 23,780 cancer cases and 27,307 controls on 3 SNPs of CYP2R1 (rs10741657 G/A, rs12794714 G/A, and rs2060793 G/A) and did not identify significant correlation with overall cancer risk, but further stratified analyze revealed that CYP2R1 rs12794714-G/A SNP was associated with a significantly lower risk of colorectal cancer (A vs. G: OR = 0:866, 95% CI: 0.753–0.997, p = 0.046) (Wen et al., 2021).

Li-Ping Zhou et al. investigated the association between CYP3A4*1B (rs2740574A > G) polymorphism in a meta-analysis involving 3,810 cancer patients and 3,173 healthy controls, and they discovered that G allele and G/G genotype were associated with increased risk of cancers (allele model: OR = 1.24, 95 %CI: 1.09–1.42, p = 0.001; recessive model: OR = 1.77, 95 %CI: 1.30–2.41, p < 0.001; homozygous model: OR = 1.72, 95 %CI: 1.19–2.47, p = 0.004). Meanwhile, cancer type subgroup analyses showed that the G allele and G carrier (A/G + G/G) had significantly increased risk of prostate cancer, but not with breast cancer, leukemia, or other cancers, while ethnicity subgroup analysis showed that G/G genotype might increase the risk of cancer among African populations, but not Caucasian or Asian population. This study indicated G allele and G/G genotype polymorphism in the CYP3A4 gene might be associated with an increased risk of cancers, particularly prostate cancer in African population (Zeigler-Johnson et al., 2004; Zhou et al., 2013).

Other than cancer susceptibility, CYP3A4 also plays a key role in chemotherapy resistance, and a drug metabolism study on 108 cancer patients demonstrated that CYP3A4*22 carriers (rs35599367 C > T) exhibited reduced erythromycin N-demethylation activity by 40%, highlighting the importance of considering CYP3A4 polymorphisms in cancer treatment to maximize efficacy and to avoid unpredictable adverse events (Elens et al., 2013).

Besides genetic polymorphisms, alterations in gene expression level also have influences on the activity of vitamin D 25-hydroxylases, consequently changing an individual's cancer susceptibility and responses to therapies. For example, high CYP27A1 expression is associated with a reduced incidence of distant recurrence-free survival events in breast cancer (Inasu et al., 2021). Similarly, expression of CYP27A1 is reduced in clinical specimens in bladder cancer, prostate cancer and renal cell carcinoma, and restoration of its expression is able to inhibit the proliferation of these cancer cell lines, indicating its potential role as a tumor suppressor (Riecanský and Plachá, 1983; Alfaqih et al., 2017; Baek et al., 2017; Liang et al., 2019; Zhang X. et al., 2022). Interestingly, CYP27A1 and CYP2R1 expressions are higher in endometrial carcinoma compared to normal endometrium, but they are still inversely with the proliferation marker Ki67, and vitamin D treatment reduces cell viability and colony number *in vitro*, suggesting that CYP27A1 and CYP2R1 are beneficial factors for endometrial carcinoma patients in consistence with previous observations (Bergadà et al., 2014). However, recent studies on tumor infiltrating myeloid cells led to opposite understanding regarding the role of CYP27A1 in carcinogenesis. Specifically, Sisi He et al. reported that high CYP27A1 expression was associated with shortened progression-free survival for ovarian cancer patients, and the expression of CYP27A1 was critical for the infiltration of monocytic myeloid derived suppressor cells to support tumor growth in an ovarian cancer mouse model (He et al., 2019). In consistence with the observation in ovarian cancer, Liqian Ma et al. reported that CYP27A1 was highly expressed in myeloid cells, and breast cancer metastasis was reduced after myeloid specific knockout of CYP27A1 in mice, suggesting that CYP27A1 axis in myeloid cells played an oncogenic role in breast cancer (Ma et al., 2020).

The researches on CYP3A4 expression in cancer are mainly focused on drug resistance. For example, a study on multidrug resistance-associated proteins demonstrated that CYP3A4 overexpression would lead to the acquisition of doxorubicin resistance in human prostate cancer LNCaP, osteosarcoma MG-63, and chondrosarcoma SW-1353 cells (Tian and Hu, 2015; Ohya et al., 2023). Similarly, expression of CYP3A4 and P-glycoprotein (MDR1) correlates with poor clinical response in peripheral T-cell lymphoma (PTCL), and high CYP3A4 expression correlates with lower complete remission rates, suggesting its role in predicting therapeutic responses to standard PTCL chemotherapy (Rodríguez-Antona et al., 2007).

4.2 CYP27B1

The cytochrome enzyme CYP27B1 converts the major circulating metabolite of vitamin D, 25 (OH)D, to the active form of 1,25 (OH)D, a process that is essential for its function as VDR ligand. The relationship between polymorphisms in CYP27B1 and cancer susceptibility has been extensively studied, although the results have been inconsistent. Certain single nucleotide polymorphisms (SNPs) in CYP27B1 may decrease enzyme activity [e.g., R107H (rs28934604), A129T (rs58915677), S356N (rs13377933) and V374A (rs2229103)], whereas certain variants [e.g., V166L (rs58915677)] may increase enzyme activity (Jacobs et al., 2013). In colorectal cancer (CRC), CYP27B1 is expressed at sites in intestinal cells that are capable of converting vitamin D pro-vitamin to an active form that affects colon cancer risk. For example, rs10877012 polymorphism in the promoter region of CYP27B1 gene affects balance between vitamin D3 metabolites in circulation, and G/T and T/T populations showed a weaker correlation between serum 25(OH)D3 and $1,25(OH)_2D3$ concentrations compared to G/G population

(Marques Vidigal et al., 2017). Maria Latacz et al. investigated the association between the rs10877012 (T/G) polymorphism in the CYP27B1 gene and CRC susceptibility and identified a significant association between the presence of T allele and CRC incidence (OR = 2.94; 95%CI: 1.77–4.86; $p < 0.0001$), suggesting the impaired vitamin D metabolism might be a risk factor for CRC (Latacz et al., 2020).

Besides polymorphisms, expression level of CYP27B1 has potential implications in the prognosis for a variety of cancers. Loss of CYP27B1 expression and molecular defects may lead to reduced VDR signaling and correlate with disease progression and recurrence in many types of solid tumors such as breast cancer and non-melanoma skin cancer (Nemazannikova et al., 2019; Voutsadakis, 2020). Moreover, a study on ovarian cancer showed that loss of CYP27B1 expression was mediated by EZH2, a histone methyltransferase catalyzing the trimethylation of histone H3 lysine 27 (H3K27me3) (Huo et al., 2020).

4.3 CYP24A1

CYP24A1, known as 25-hydroxyvitamin D-24-hydroxylase, is a mitochondrial enzyme that regulates the activity level of VDR signaling by performing hydroxylation at 24′position to produce inactive vitamin D metabolites. Recent studies have shown that CYP24A1 plays an important role in the development and progression of many cancers, and abnormalities in its expression level are closely related to the biological behavior of tumor (Sakaki et al., 2014; Sheng et al., 2019; Zeng et al., 2022).

CYP24A1 expression is generally higher in cancer tissues compared to normal tissues, which also correlates with aggressive diseases and poor prognosis. For example, in breast cancer, high expression of CYP24A1 is associated with tumor progression, and amplification of CYP24A1 locus at 20q is an adverse prognostic factor for recurrence free survival in ER^+ breast cancer (Davis et al., 2007; Zhalehjoo et al., 2017). Similar correlation between CYP24A1 expression and poor prognosis has also been observed in colorectal cancer, lung cancer and ovarian cancer (Shiratsuchi et al., 2017; Lin et al., 2024). However, Yuna Nakamori et al. recently discovered that low expression levels of CYP24A1 promoted oncogenic progression in oral squamous cell carcinoma (OSCC) and were significantly associated with poor prognosis in patients with this malignancy, indicating that CYP24A1 might play a tumor-suppressive role in OSCC (Nakamori et al., 2024).

Other than expression level, CYP24A1 gene variants are also correlated with cancer susceptibility. For example, Ying Wei reported that CYP24A1-rs4809957 SNP was associated with an increased risk of breast cancer (allele A: OR = 1.27, 95% CI: 1.03–1.55, $p = 0.024$; A/A vs. G/G: OR = 1.80, 95% CI: 1.15–2.82, $p = 0.010$; recessive model: OR = 1.70, 95% CI: 1.12–2.58, $p = 0.012$) (Wei et al., 2019). J J Oh et al. evaluated the association between 21 SNPS in CYP24A1 and prostate cancer risk in Korean male population, and identified 5 CYP24A1 variants (rs2248461, OR = 0.63; rs2248359, OR = 0.65; rs6022999, OR = 0.65; rs2585428, OR = 0.46; rs4809959, OR = 0.52) were significantly negatively associated with prostate cancer risk after multiple comparisons by a method of false discovery rate (Oh et al., 2014).

In pre-clinical cancer therapy research, CYP24A1 inhibitors are able to reduce the breakdown of 1,25 (OH)2D and enhance its anti-tumor effect, and show potential therapeutic value. For example, CYP24A1-specific inhibitor VID400, anti-CYP24A1 analogues ED-71 (Eldecalcitol) and MART-10 have exhibited potent biological effects in both *in vitro* and *in vivo* studies, including inhibition of cancer cell growth and induction of apoptosis (Sakaki et al., 2014).

4.4 VDBP

Vitamin D binding protein (VDBP), also known as group-specific complement or Gc protein, is an important component of the endocrine system responsible for stabilizing and transporting vitamin D to target tissues, thereby having an indispensable function in regulating calcium homeostasis and bone mineralization.

Wanwisa Maneechay et al. reported that the minor allele frequencies of rs7041 (G) and rs4588 (A) were 0.32 and 0.24, respectively, and rs7041 (TG/GG) was associated with lung cancer risk (OR = 1.78, 95% CI: 1.05–3.03) in Thailand. Further subgroup analysis revealed that minor-allele genotypes of rs7041 (TG/GG) was associated with colorectal cancer among males older than 60 years, while the minor-allele genotypes of rs4588 (CA/AA) was associated with colorectal cancer among males younger than 60 years. SNP combinations (rs7041-rs4588) analysis showed that the TT-CA combination had a significant protective association with lung cancer (OR = 0.44, 95% CI: 0.22–0.85) (Maneechay et al., 2015). Moreover, the proportion of subjects with low serum vitamin D (<20 ng/mL) was significantly higher in those harboring CA or AA genotypes of rs4588 (41.7%) compared to the CC genotype (15.5%, $p < 0.01$) (Maneechay et al., 2015).

Expression of VDBP is also associated with a variety of diseases, including a variety of cancers such as breast, prostate, pancreatic, lung, colorectal, basal cell carcinoma, and cutaneous melanoma (Francis et al., 2021; Filigheddu et al., 2024). Specifically, elevated VDBP expression is associated with a good prognosis in HCC, and it may act as an important prognostic biomarker in HCC (Qin et al., 2024). Similarly, higher levels of VDBP are associated with improved overall and overall survival in colorectal cancer (Muindi et al., 2013).

4.5 VDR

Nuclear steroid receptor VDR is not only essential in maintaining calcium-phosphorus homeostasis, but also plays a key role as a tumor suppressor effects in many types of solid tumors (Voutsadakis, 2020).

Reduced expression of VDR has been observed in many types of cancer, including breast cancer and colorectal cancer. Specifically, methylation of exon 1a in VDR gene is significantly higher (65% of CpGs methylated) compared with normal breast tissue (15%) (Marik et al., 2010). Similarly, Malini Srinivasan et al. have shown that the high expression of VDR in the nucleus of lung cancer is associated with a good prognosis (Srinivasan et al., 2011). Moreover, CpG methylation level in VDR gene is negatively correlated with CRC risk, indicating that VDR might play tumor-suppressive role in CRC (Wang et al., 2023). Another research by Yongguo Zhang et al. have showed that overexpression of VDR inhibits invasion and promotes apoptosis of CRC cells, whereas loss of VDR results in a decreased level of

Claudin-5 and an increased number of malignant foci in CRC mouse model (Zhang Y. et al., 2022).

In addition, specific polymorphisms in VDR gene have been associated with prostate cancer risk in studies of prostate cancer. In the genotype analysis, men who are homozygote for the rare allele for VDR SNP rs2107301 had a 2.5-fold higher risk of prostate cancer compared with those who are homozygote for the common allele (95% CI: 1.52–4.00; p = 0.002). Furthermore, men who are homozygote for the rare allele for the VDR SNP rs2238135 have a 2-fold higher risk of prostate cancer compared with those who are homozygote for the common allele (95% CI: 1.17–3.26; p = 0.007 (Holick et al., 2007).

VDR-coregulator inhibitor PS121912 could amplify 1,25 $(OH)_2$D3-induced growth inhibition and apoptosis in multiple cancer cell lines at sub-micromolar concentrations. Mechanistically, the combination of PS121912 and 1,25 $(OH)_2$D3 reduces the presence of SRC2 and enriches the occupancy of corepressor NCoR at the promoter site of VDR target genes. Transcription factors E2F1 and E2F 4 are also downregulated by the combination of PS121912 and 1,25 $(OH)_2$D3, thus in turn reducing the transcription levels of cyclin A and D and arresting cancer cells in the S or G2/M phase (Sidhu et al., 2014).

On the other hand, VDR is closely related to obesity. In terms of adipogenesis, 1,25 $(OH)_2D_3$ exerts different effects in mice and humans through VDR, which can not only inhibit adipogenesis in mice, but also increase the activities of adipogenesis-related enzymes and PPARγ in humans. In terms of gene polymorphism, VDR gene is highly polymorphic, including Bsm I, Apa I, Taq I, Fok I, Tru 9I, Eco RV and other single nucleotide polymorphisms (Gupta et al., 2024). The variations of these genes have been confirmed to be associated with the susceptibility to obesity in different ethnic populations such as Europe, America and Asia. It increases the risk of obesity and is associated with other diseases. Obesity affects vitamin D metabolism and reduces serum 1,25 $(OH)_2D_3$ level, which involves the sequestration and volume dilution of cholecalciferol by fat, changes in vitamin D metabolic enzymes in adipocytes, and the influence of genetic factors such as VDR mutation. Low levels of 25 $(OH)_2D_3$ may play an important role in the development of obesity-related cancers.

5 Conclusions and perspectives

In conclusion, vitamin D metabolism has substantial influences on human health. As a highly accessible clinical index and oral supplementation, it has been widely used for the prevention and treatment of skeletal disorders for decades. Epidemiologic studies on the correlation between serum vitamin D concentration and cancer risks, genome-wide association study on the status of vitamin D-metabolic genes, as well as laboratory analysis on cancer models have all indicated a potential involvement of vitamin D metabolism in the carcinogenesis and cancer treatment. However, the clinical benefits of vitamin D supplement for cancer treatment has not been thoroughly investigated with clinical trials. In recent years, many nutritionists have joined in oncology department as we start to reveal the importance of nutrient metabolism in cancer treatment, we would expect more real-world data originated from carefully designed clinical trials in this field.

Author contributions

SZ: Investigation, Project administration, Data curation, Writing – review and editing, Software, Formal Analysis, Conceptualization, Writing – original draft, Methodology. LZ: Writing – original draft, Investigation, Formal Analysis, Writing – review and editing, Methodology, Conceptualization, Data curation. YW: Software, Investigation, Project administration, Validation, Writing – original draft. YH: Data curation, Formal Analysis, Writing – review and editing, Conceptualization. JY: Funding acquisition, Resources, Supervision, Writing – original draft. JC: Funding acquisition, Writing – review and editing, Resources, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
$24,25(OH)_2D_3$	24,25-dihydroxyvitamin D_3
$1,24,25(OH)_3D$	1,24,25-trihydroxyvitamin D
CNS	central nervous system
CRC	colorectal cancer
HCC	hepatocellular carcinoma
HBV	hepatitis B virus
IFN-γ	interferon-γ
IL	interleukin
JAK/STAT	Janus kinase/signal transducer and activator of transcription
MS	multiple sclerosis
mVDR	membrane vitamin D receptor
nVDR	nuclear vitamin D receptor
OSCC	oral squamous cell carcinoma
PR	progesterone receptor
PTCL	peripheral T-cell lymphoma
PTEN	phosphatase and tensin homologues
RAS/MEK/ERK	rat sarcoma/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase
RXR	retinoid X receptor
SMRT	silencing mediator for retinoid and thyroid hormone receptors
SNP	single nucleotide polymorphism
TGFβ1	transforming growth factor β1
TNF-α	tumor necrosis factor-α
TRPV5/6	transient receptor potential vanilloid 5/6
VDRE	vitamin D response element
VDBP	vitamin D binding protein
VDR	vitamin D receptor
25-OHase	25-hydroxylase
1α-OHase	1α-hydroxylase
24-OHase	24-hydroxylase
CYP	cytochrome P450
CYP2R1	cytochrome P450 family 2 subfamily R member 1
CYP27A1	cytochrome P450 family 27 subfamily A member 1
CYP3A4	cytochrome P450 family 3 subfamily A member 4
CYP27B1	cytochrome P450 family 27 subfamily B member 1
CYP24A1	cytochrome P450 family 24 subfamily A member 1
ALPL	alkaline phosphatase liver/bone/kidney
AMPK	adenosine 5′-monophosphate-activated protein kinase
Ca2+-ATPase1b	calcium-transporting ATPase 1b
CCR8	C-C chemokine receptor type 8
c-MYC	cellular-myelocytomatosis
COX-2	cyclooxygenase-2
Dicer	dicer ribonuclease III
DHCR7	7-dehydrocholesterol reductase
FAS	fatty acid synthase
FGF	fibroblast growth factor
GLUT4	glucose transporter 4
GATA3	GATA binding protein 3
hedgehog	hedgehog signaling pathway
HIF-1α	hypoxia-inducible factor 1-alpha
IGFBP3	insulin-like growth factor binding protein 3
JNK	c-Jun N-terminal kinase
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated protein kinase
MDR1	multidrug resistance protein 1
NCX1	sodium/calcium exchanger 1
NCoR	nuclear receptor corepressor
NO	nitric oxide
p160	steroid receptor coactivator-1
PCNA	proliferating cell nuclear antigen
PKC	protein kinase C
PPARγ	peroxisome proliferator-activated receptor gamma
PTEN	phosphatase and tensin homolog
SERPINE1	serpin family E member 1
SOC	store-operated calcium
TIF2	transcription intermediary factor 2
TRPV5/6	transient receptor potential vanilloid 5/6
Wnt	wingless-related integration site