Consideration of possible effects of vitamin D on established cancer, with reference to malignant melanoma
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INTRODUCTION

Vitamin D₃ status in the body is dependent on the amount of vitamin D₃ consumed in the diet or synthesised in the skin following sun exposure. Vitamin D₃ requires activation and is hydroxylated twice, classically, first in the liver to produce 25(OH)D₃ by 25 hydroxylation and then primarily in the kidney or in immune cells such as macrophages and dendritic cells where the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) converts 25(OH)D₃ to the active form 1α,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃). The amount of...
1,25(OH)\(_2\)D\(_3\) produced in the kidney is tightly regulated by serum calcium, parathyroid hormone and 25(OH)D\(_3\) levels and controls the homeostasis of extracellular fluid (ECF) levels of calcium and phosphate (Morris & Anderson, 2010). The pathway controlling the activation of vitamin D is shown in Figure 1.

An alternative pathway for producing biologically active D\(_3\)-hydroxyderivatives is via CYP11A1 which hydroxylates the side chain of vitamin D\(_3\) at carbons 17, 20, 22 and 23 to produce at least 10 other metabolites, with 20(OH)D\(_3\), 20,23(OH)\(_2\)D\(_3\), 20,22(OH)\(_2\)D\(_3\), 17,20(OH)\(_2\)D\(_3\) and 17,20,23(OH)\(_3\)D\(_3\) being the main products (Slominski, Kim, et al., 2012; Slominski, Kim, et al., 2015; Slominski, Kim, Li, et al., 2014; Slominski, Kim, Shehabi, et al., 2014; Slominski, Li, et al., 2015). Intermediates are detectable in serum. (Jenkinson et al., 2021; Slominski, Kim, et al., 2015) CYP11A1 is also expressed in the immune system and skin (Slominski, Kim, Shehabi, et al., 2014; Slominski, Tuckey, et al., 2020) and its metabolites have anti-melanoma activities (Slominski, Brożyna, et al., 2018; Slominski, Janjetovic, et al., 2012). However, CYP11A1 does not act on 25(OH)D\(_3\) (Slominski, Kim, Li, et al., 2014). Therefore, it is unlikely that these biologically active D3-hydroxyderivatives are important when considering administration of oral vitamin D\(_3\) which is rapidly metabolised to 25(OH)D\(_3\) in the liver.

1,25(OH)\(_2\)D\(_3\) is a ligand for the vitamin D receptor (VDR) which acts in combination with the retinoid X receptor (RXRA) to regulate transcription of many genes by binding to vitamin D receptor response elements, (VDREs) in the gene. There are also alternative nuclear receptors for vitamin D hydroxyderivatives with their own response elements (Slominski, Chaiprasongsuk, et al., 2020) including retinoic acid receptor-related orphan receptors (RORx (NR1F1) and ROR\(_\gamma\) (NR1F3)) (Slominski, Kim, Takeda, et al., 2014), the aryl hydrocarbon receptor (AhR) (Slominski, Kim, et al., 2018) and the liver X receptor beta (LXR\(_\beta\)) (Slominski et al., 2021). There are reports of these receptors suppressing tumour progression, e.g. in MM LXR\(_\beta\) (Pencheva et al., 2014; Zhang, Jiang, Zhang, et al., 2014), AhR (Contador-Troca et al., 2015) and ROR\(_\alpha\) and ROR\(_\gamma\) (Brozyna et al., 2016) (note vitamin D3 hydroxyproducts are reverse agonists of ROR\(_\alpha\) and ROR\(_\gamma\); Slominski et al., 2017; Slominski, Kim, Takeda, et al., 2014) but they can also have a tumour promoting effect e.g. LXR\(_\beta\) (Nelson et al., 2013), AhR (Su et al., 2013). As mentioned above the relevant hydroxy product here is 1,25(OH)\(_2\)D\(_3\) which is a ligand of these alternative receptors, but we were unable to find evidence of an effect on tumour growth or anti-tumour immunity of these receptors with 1,25(OH)\(_2\)D\(_3\) as ligand. A further point of uncertainty is whether these receptors persist after the VDR in advanced cancer, loss of signalling being central to our argument about a possible deleterious effect of vitamin D\(_3\) supplements in advanced cancer. We will therefore concentrate on VDR signalling.

The classic roles of vitamin D\(_3\) are the regulation of calcium uptake, calcium homeostasis, bone metabolism, cell growth, division and differentiation. The last two are potentially beneficial in controlling tumour cell growth. However, the expression of VDR has been identified in many tissues in different cell types and the action of 1,25(OH)\(_2\)D\(_3\) has important implications for regulating the immune system, where most cells express VDR, potentially influencing tumour immune surveillance.

Prediagnostic vitamin D\(_3\) status has a well-documented protective effect on the development and subsequent progression of cancer, reviewed by Grant (2018). Post-diagnosis serum 25(OH)D\(_3\) levels have shown an inverse relation with progression in a number of cancers (Vaughan-Shaw et al., 2017). An interpretation of this is that vitamin D\(_3\) has a beneficial effect on established cancer (Newton-Bishop et al., 2009; Nurnberg et al., 2009). The National Institute for Health and Care Excellence (NICE) recommendations on vitamin D\(_3\) and MM are to measure 25(OH)D\(_3\) levels at diagnosis in secondary care in all patients with MM and to give those, whose levels are thought to be suboptimal, advice on vitamin D\(_3\) supplementation

**FIGURE 1** Vitamin D metabolism pathway. In the skin, 7-dehydrocholesterol is converted into pre-vitamin D\(_3\) by UV light and then modified into vitamin D\(_3\). The dietary or therapeutic sources of vitamin D are transported in the blood by means of vitamin D binding proteins and are hydroxylated in the liver into 25-hydroxyvitamin D\(_3\). 25(OH)D\(_3\) is further hydroxylated in the renal tubules into 1,25 dihydroxyvitamin D\(_3\), the active form of the hormone. 1,25(OH)\(_2\)D\(_3\) can also be synthesised in extra renal tissues and cells where it usually acts on local cells as a paracrine or intracrine factor. The amount of 1,25(OH)\(_2\)D\(_3\) produced in the kidney is tightly regulated by serum calcium, parathyroid hormone and 25(OH)D\(_3\) levels which control the homeostasis of extracellular fluid (ECF) levels of calcium and phosphate.
and monitoring in line with local policies and NICE guidelines on vitamin D3 (The National Institute for Health and Care Excellence, 2015; Nice Guideline NG14 July 2015 Melanoma: Assessment and Management).

We consider possible beneficial or deleterious effects of vitamin D3 administration in established cancer and the possible circumstances dictating a positive or negative effect on outcome. First, we discuss basic determinants of cancer outcome that is, intrinsic tumour aggressiveness, in terms of cancer cell growth, differentiation and migration; associated inflammation; anti-tumour immune response and angiogenesis, and the likely impact of vitamin D3 status and the integrity of VDR signalling in the tumour. We then consider the experimental in vivo, epidemiological and clinical evidence of the effect of vitamin D3 in cancer.

2 | POSSIBLE MECHANISMS OF AN EFFECT OF VITAMIN D3 ON CANCER

2.1 | Inhibition of tumour cell growth

Vitamin D3 has a well-known inhibitory effect on cell growth, through anti-proliferative, pro-apoptotic and anti-cell migratory activity as reviewed by Fleet et al. (2012), Samuel & Sitrin (2008). The effects of vitamin D3 on growth are mediated by the action of 1,25(OH)2D3 on the intracellular VDR, which is a transcription factor. In vitro studies show that vitamin D3 inhibits growth in some malignant cell lines (Fleet et al., 2012), including MM (Colston et al., 1981) and promotes differentiation (Samuel & Sitrin, 2008). Moreover, inhibition of experimental carcinogenesis by dietary vitamin D3 supplementation and 1,25(OH)2D3 administration has been demonstrated in vivo in animal models (Beaty et al., 1993; Wood et al., 1983).

These beneficial effects are largely the result of nuclear VDR signalling (Carlberg & Campbell, 2013). Using low nuclear VDR concentration as a marker of defective VDR signalling, 1,25(OH)2D3 fails to disrupt growth and produce cell death in culture (Hutchinson et al., 2018). Moreover, in tumours with known outcome, histological evidence of low nuclear VDR is associated with progression and metastasis (Brozyna et al., 2011, 2014; Hutchinson et al., 2018).

2.2 | Suppression of inflammation

Inflammation has been long recognized as oncogenic but, more importantly here, a promoter of tumour progression (Mantovani et al., 2008), including metastasis (Mantovani, 2009). There is evidence, experimental and observational, that vitamin D3 suppresses inflammation. Vitamin D3 downregulates macrophages in terms of recruitment (Riek et al., 2014) and inflammatory cytokine production (Guillot et al., 2010) such as C-reactive protein (CRP), interleukin (IL) IL1A, IL1B, IL6, IL8, tumour necrosis factor (TNF), while upregulating anti-inflammatory cytokines such as IL10 (Guillot et al., 2010). The growth hormone midkine (MDK) is involved in leukocyte recruitment to the sites of inflammation and expression of proinflammatory cytokines and the expansion of regulatory T-cells as reviewed by Weckbach et al. (2011). A suggested proinflammatory mechanism is the known upregulation of nuclear factor kappa B kinase (NF-kB) (Cerezo-Wallis et al., 2020). Other relevant effects of MDK in cancer are promotion of angiogenesis (Muramaki et al., 2003), up-regulation of integrin mediated cell migration (osteoblast-like cells) and, through Notch2 binding, induction of epithelial mesenchymal transition (EMT) (immortalized HaCaT keratinocytes). There are no reports of an effect of vitamin D3 on MDK in cancer, but this seems feasible as higher levels of MDK are reported in vitamin D deficiency (Serinkan Cinemre et al., 2016). NF-KB is a key transcription factor involved in inflammatory cell differentiation and inflammatory cytokine expression (Li et al., 2017). The VDR physically interacts with Inhibitor of NF-KB subunit Beta (IKKβ) to block NF-KB activation (Chen et al., 2013). In addition, observational studies in healthy individuals have shown an inverse relation between serum 25(OH)D3 and inflammatory markers (Liefgaard et al., 2015). Thus, there is good evidence that vitamin D3 is anti-inflammatory which would be expected to be beneficial in all stages of cancer and irrespective of tumour VDR signalling.

2.3 | Suppression of anti-tumour immunity

Anti-tumour immunity is a very important determinant of cancer outcome as evidenced by the success of recent immune-based therapies (Menon et al., 2016). Vitamin D3 has been reported to enhance anti-tumour immunity by increasing the number of tumour associated immunocytes, via tumour VDR suppression of Wnt-beta catenin signalling (Muralidhar et al., 2019). There is significant evidence showing that Wnt-beta catenin signalling blocks immune recognition of the tumour at all stages, including tumour antigen release, antigen presentation, T-cell priming, activation and infiltration as well as tumour cell elimination (see Figure 2; Luke et al., 2019). However, this is an indirect effect of vitamin D3 and would appear dependent on intact intra tumour VDR signalling. Defective VDR signalling would therefore be associated with reduced numbers of immunocytes, which however, unlike the tumour, would retain sensitivity to vitamin D3. Considering direct effects of vitamin D3 on immunocytes, most immunocytes, including dendritic cells (DCs), CD4+ T cells (T4), CD8+ T cells (T8), γδT cells and macrophages, express the VDR (Baeke et al., 2010; Chen et al., 2005; Hewison et al., 2003; Kreutz et al., 1993; Veldman et al., 2000). Vitamin D3 has many direct suppressive effects on immune cells, as evidenced by its protective effect against auto-immune disease (Goldberg, 1974; Hypponen et al., 2001; Mathieu et al., 1992). When considering the tumour/immunity relationship, the term immunoediting (Dunn et al., 2002) is used. This describes a triphased immunological response to tumours comprising phases of elimination, equilibrium and escape, reviewed by Mittal et al. (2014). In the elimination phase, there is host
immunological attack on the tumour, in the equilibrium phase, there is balance between tumour proliferation and immune suppression, while in the escape phase, there is suppression of anti-tumour immunity allowing the tumour to progress.

2.3.1 Elimination phase

The elimination phase (Mittal et al., 2014) involves innate and adaptive immunity. Critical elements are IFNG secretion and cytolytic capacity of immune cells. An important early source of IFNG is γδ T cells (Gao et al., 2003), other sources being natural killer cells (NK) and T cells, antigen-specific effector T-helper type 1 (Th-1), T8 cytotoxic T-cells (CTLs) and natural killer T cells (NKT) cells. IFNG increases tumour cell immunogenicity, by upregulating components of the major histocompatibility complex (MHC) class I protein and promotes maturation of dendritic cells (DCs), generation of Th1 cells and CTLs and activates cytolicidal activity in macrophages. Tumour cells are killed by CTLs, NK, NKT, γδT cells and macrophages, mechanisms including apoptosis inducing molecules (Fas cell surface death receptor ligand (FASLG), TNF superfamily member 10 (TNFSF10)) and cytolytic molecules (granzyme, reactive oxygen species [ROS]). The immune reaction is triggered by expression of ‘stress’ induced tumour haptons, loss of inhibitory molecules on the tumour and expression of tumour antigens, in context of MHC class I and II molecules (Th-1 and CTLs respectively) or CD1D (NKT cells). An effect of vitamin D₃ on IFNG in this situation is not reported but 1,25(OH)₂ D₃ is known to inhibit IFNG produced by Vγ9Vδ2 T cells (Chen et al., 2005), differentiating NK cells (Weeres et al., 2014), Th1 cells (Staeva-Vieira & Freedman, 2002), CTLs (Jeffery et al., 2009) and peripheral blood mononuclear cells (PBMCs; Ragab et al., 2016).

In innate immunity, NK cells are activated by tumour expression of stress-inducible ligands structurally related to MHC class I, MHC Class I polypeptide-related sequence (MIC) MICA and MICB (Lopez-Soto et al., 2015), recognized by NK cell activation receptors such as killer cell lectin-like receptor K1 (KLRK1). Moreover, killer-cell
immunoglobulin-like inhibitory receptors respond to MHC class 1 on the tumour cell, the absence of which, through malignant transformation or CTL activity, results in NK cell activation. NK cells lyse tumour cells via granzyme and TNFSF10 and FASLG, secrete cytokines, primarily Th-1 type cytokines such as IFNG, TNF and granulocyte/monocyte colony-stimulating factor (CSF2) which facilitate the activation of T cells and other innate immune mediators (Walzer et al., 2005). The effect of vitamin D₃ on NK cells in cancer is not reported but 1,25(OH)₂D₃ reduced perforin-mediated cytotoxicity of activated NK cells (from patients with recurrent pregnancy loss), by decreasing activating NK receptors and increasing inhibitory NK cell receptors (Ota et al., 2015). However, vitamin D₃ increases NK activity in lean mice (Lee et al., 2018).

γδ T cells, reviewed by Zhao et al. (2018), are activated by metabolites of the mevalonate pathway (phosphoantigens), accumulated by transformed cells (Gober et al., 2003), and also by stress-induced autophagolysosomes of the mevalonate pathway (phosphoantigens), accumulated by transformed cells (Gober et al., 2003), and also by stress-induced autophagolysosomes. γδ T cells are a common form of γδ T cells and have direct cytolytic activity involving perforin/granzyme, TNFSF10 and FASLG and produce IFNG and TNF and have direct cytolytic activity involving perforin/granzyme, TNFSF10 and FASLG and produce IFNG and TNF.

In experimental autoimmune encephalomyelitis (EAE), 1,25(OH)₂D₃ is protective through an effect on NKT cells expansion and IFNG production (Chen et al., 2005). Natural killer T cells (NKT) (reviewed by Nair & Dhodapkar (2017)) have, in general, an αβ T-cell receptor (TCR) of limited diversity responding to extrinsic and intrinsic lipid antigen presented in relation to CD1D, a non-polymorphic MHC 1-like molecule. CD1D can be expressed by antigen presenting cells (APCs) and tumour cells, but not usually solid tumours including MM. Type I NKT (invariant NKT) cells are mainly reported to invoke an anti-tumour immune response (Nair & Dhodapkar, 2017). Increased frequency of type I NKT cells in blood and in the tumour infiltrate are favorable prognostic indices (Nair & Dhodapkar, 2017). Anti-tumour type 1 cell activity can involve direct tumour lysis, recruitment and activation of other innate and adaptive immune cells by initiating Th1 cytokine cascade, and regulation of recruited immunosuppressive cells in the tumour microenvironment (TME). In experimental autoimmune encephalomyelitis (EAE), 1,25(OH)₂D₃ is protective through an effect on NKT type 1 cells, possibly involving IL4 (Waddell et al., 2015) and this would suggest 1,25(OH)₂D₃ induces immunosuppressive activity in these cells (Dankers et al., 2016).

Macrophages polarized to M1 macrophages by inflammatory cytokines, IFNG and TNF, secrete inflammatory cytokines, IL6, IL12 and TNF, activating T cells and lyse cancer cells. Macrophages polarized to M2 phenotype have regulatory and wound-healing properties. Regulatory M2 macrophages have anti-inflammatory properties and are important in resolving inflammation, producing the immunosuppressive cytokine IL10 while wound-healing M2 macrophages respond to immune complexes, prostaglandins, apoptotic cells and IL10 to produce IL4 and arginase activity to stimulate collagen synthesis. 1,25(OH)₂D₃ may polarize macrophages to M2 phenotype as described below (Liu et al., 2021).

In acquired anti-tumour immunity, there is activation of tumour antigen-specific Th-1 cells, by tumour antigen presented by either APCs or directly by MHC class II expressing tumour cells. IL12, produced by tumour antigen activated APCs, and IL2 are major drivers of the Th-1 response, IFNG is a major effector and CTLs and macrophages the effector cells. 1,25(OH)₂D₃ is reported to polarize T4 cells away from Th1 toward Th-2 phenotype (Slota et al., 2011). Moreover, there is evidence 1,25(OH)₂D₃ downregulates Th-1 IFNG production in the presence of IL2 (Staeva-Vieira & Freedman, 2002). In addition, 1,25(OH)₂D₃ may downregulate the Th-1 response by downregulation of DCs. In vitro, addition of 1,25(OH)₂D₃ to DCs caused, through inhibition of NF-κB, inhibition of differentiation and maturation, downregulated expression of MHC-class II, co-stimulatory molecules and IL12 (Dong et al., 2005).

CTLs are activated by TCR binding with tumour antigen bound to MHC Class 1 on tumour cells or on professional APCs (cross presentation) (Mittal et al., 2014). Further activation requires co-stimulatory signals and IL2 induced cell proliferation. CTLs, though expressing VDR, are relatively insensitive to anti-proliferative responses of VDR than CD4+ cells (Iho et al., 1990). However, vitamin D₃ inhibits the secretion of IFNG and TNF by the activated CD8+ cells (Lysandropoulos et al., 2011).

Th-17 cells are reported to have both anti-tumour and tumour promoting actions (Alizadeh et al., 2013; Yousefi et al., 2015). The mechanisms of anti-tumour activity include induction of tumour derived cytokines (CXCL9 and 10) which attract Th-1 cells (Kryczek et al., 2009), and subsequently, CD8+ lymphocytes and NK cells (Asadzadeh et al., 2017). Th-17 also activates NK cells and macrophages to produce IL12 (Jovanovic et al., 1998). VDR blocks binding of the transcription factor NFAT1 to the promoter of the human IL17 gene leading to a decrease in IL17 production in Th17 autoimmunity (Joshi et al., 2011).

Thus, in the absence of tumour VDR signalling, many of the reported immunological effects of vitamin D₃ might oppose the immunological attack on the tumour in the elimination phase including downregulation of IFNG production and downregulated activity of NK cells, γδT cells, Th-1 cells, CTLs and Th-17 cells. It is of note that these are described effects of vitamin D₃ but not confirmed in cancer.

2.3.2 | Equilibrium phase

In this phase, there is a balance between tumour proliferation and apoptosis induced by anti-tumour immunity. The suppressive action of vitamin D₃ on anti-tumour immunity is described above.

2.3.3 | Escape phase

In the escape phase (Dunn et al., 2002; Mittal et al., 2014), the tumour becomes more robust against immunological attack, becomes directly immunosuppressive, recruiting suppressor cells...
conferring further immunosuppression. Tumour resistance is increased through signal transducer and activator of transcription 3 (STAT3), apoptosis inhibiting proteins from the BCL2 family and by loss of expression of tumour antigen. Increased tumorigenesis may result from an increased inflammatory TME, epithelial mesothelial transition (EMT) and downregulation of Cadherin 1 (CDH1) (Mittal et al., 2014). There is downregulation of immunological attack, with suppression of NK cells (Pietra et al., 2012), Th-1 cells and CTLs. The recruited immunosuppressive immunocytes from the bone marrow or periphery include tolerogenic DCs, regulatory T cells (Tregs), M2 macrophages and myeloid-derived suppressor cells (MDSC). Effectors, many secreted/expressed by the tumour and also the above immunocytes, include immunosuppressive molecules, for example, indoleamine-2,3-dioxygenase (IDO), tryptophan-2,3-dioxygenase (TDO), arginase, the programmed death receptor ligand 1 (PD1L), cytotoxic T-lymphocyte-associated protein 4 (CTLA4), galectin-1/3/9 and adenosine; immunosuppressive cytokines, for example, IL10, IL23; growth associated protein 4 (CTLA4), galectin-1/3/9 and adenosine; and chemokines (e.g. CCL2, CXCL1 and CXCL5 (Michielsen et al., 2011).

2.3.4 | Immunosuppressive cells

Tolerogenic DCs have impaired antigen presentation capacity including to CTLs, with suppression of T-cell proliferation and adaptive immune responses, (Tran Janco et al., 2015) and induce Tregs (Chen et al., 2008). As mentioned above, 1,25(OH)2D3 impairs DC maturation and survival, producing tolerogenic DC, an important facet of vitamin D3 immunoregulation (Adorini et al., 2004).

CD4+ Tregs are a highly immuno-suppressive subset of CD4+ T cells, characterized by the expression of the master regulatory transcription factor FoxP3, (Fontenot et al., 2003) and promote tumour progression by suppressing effective antitumor immunity (Sakaguchi et al., 2010). Mechanisms include secretion of CTLA4, IL10, TGFB and granzyme/perforin, consumption of IL2 and adenosine production reviewed in (Sakaguchi et al., 2010). High infiltration of Tregs in tumours is associated with a poor prognosis in various types of cancers including MM (Fridman et al., 1998; Nishikawa & Dong, 2017). The type II cell suppression predominates over type I cells when both are stimulated (Ambrosino et al., 2007). Type II cells tolerate myeloid DCs and induce-MDSCs producing TGFB (mouse model fibrosarcoma). There are no reports of an effect of vitamin D3 on suppressive CD4+ T cells, reviewed by Zhao et al. (2018) comprising γδ T cells, reviewed by Zhao et al. (2018) comprising γδ T cells and Vδ1/Vδ2 T cells, polarized by immunosuppressive cytokines, including IL23, IL1B, IL15, IL17, IL4, IL10, IL36G and TGFB, in the TME, to FOXP3+ γδ Treg cells and γδ T17 cells. γδ Tregs have similar function to αβ Treg cells, inducing DC and T-cell senescence and suppressing naïve and effector T cells. γδ T cells are a major source of IL17 in the TME resulting in increased angiogenesis with MDSC and neutrophil polymorph (PM) recruitment. Vδ1 γδ T cells are particularly potent suppressors, promoting EMT via TGFB, impairing DC maturation and function, and are more powerful inhibitors of T4 cells than αβ Treg cells (Kuhl et al., 2009). Thus, γδ T cells may have an anti-cancer effect as described above or a pro-cancer. A greater Vδ1/Vδ2-ratio has a pro-cancer effect and is increased by IL4 (Zhao et al., 2018). Evidence of a direct effect of vitamin D3 on suppressive γδ T cells is lacking but vitamin D3 is known to upregulate FOXP3 as described above and a suppressive effect might be inferred from known effects on the immunosuppressive cytokines regulating Vγ9Vδ2 polarization and the Vδ1:Vδ2-ratio. 1,25(OH)2D3 is known to upregulate the major suppressor cytokines IL4 (Boonstra et al., 2001), IL10 (Boonstra et al., 2001; Ragab et al., 2016) and TGFB (Cantorna et al., 1998), but also downregulate IL17 (Joshi et al., 2011) and the IL23 pathway (Faraji et al., 2016; Konya et al., 2018).

Type II NKT cells are typically associated with immunosuppression in animal cancer models (Nair & Dhodapkar, 2017). The mechanisms are downregulation of immunosurveillance and upregulation of immunosuppressive elements. Type II NKT cells suppress type I cells, CTLs, through IL13 production via IL4R and STAT6 axis, and conventional T cells inhibiting pro-inflammatory function (Nair & Dhodapkar, 2017). The type II cell suppression predominates over type I cells when both are stimulated (Ambrosino et al., 2007). Type II cells tolerate myeloid DCs and induce-MDSCs producing TGFB (mouse model fibrosarcoma). There are no reports of an effect of vitamin D3 on NKT type II cells in cancer, but it may induce immunosuppressive activity on Type 1 cells as described above.

M1 macrophage activity inhibits cell proliferation and causes tissue damage, whereas M2 macrophages promote cell proliferation and tissue repair (Bain & Mowat, 2014) and are more frequent in tumours (Mantovani et al., 2008). M2 macrophages promote angiogenesis, cell migration and intravasation (Lin & Pollard, 2007) and suppress adaptive immunity by PD1L expression (Gibbons Johnson & Dong, 2017). M2 polarizing factors are hypoxia and acidity of the tumour microenvironment (Colegio et al., 2014), IL4, TGFB and IL10 and CSF2 (Su et al., 2014). Tumour-associated macrophages (TAM) mainly have M2 polarisation and produce immunosuppressive cytokines such as IL10, TGFB and PGE2 and low levels of inflammatory cytokines (IL12, IL1B, TNF and IL6). Ability of TAMs to present tumour-associated antigens is decreased as well as stimulation of the anti-tumour functions of CTLs and NK cells. Vitamin D3 is reported to downregulate M1 and upregulate M2 macrophages in diabetic renal disease (Slota et al., 2011; Zhang, Guo, Song, & Zhou, 2014), and a similar effect might be anticipated in cancer through its known upregulation of immunosuppressive cytokines.

MDSCs, recruited by tumour secreted CSF1 and CSF2, suppress T cells including CD8+, NK cells, DCs and macrophages. However, vitamin D3 opposes these effects by promoting differentiation of immature MDSCs into macrophages and DCs, reported in head and
2.3.5 | Effector mechanisms of the escape phase

IDO and TDO cause accumulation of immunosuppressive tryptophan catabolites, particularly kynurenine, resulting in suppression of NK cells (downregulation of activating receptors and granzyme content; Pietra et al., 2012), and antigen-specific T-cell responses, T-cell apoptosis and increased proliferation of Tregs (Uyttenhove et al., 2003). 1,25(OH)₂D₃ has been shown to upregulate IDO resulting in increase of CD4⁺CD25⁺ Tregs in multiple sclerosis (Correale et al., 2009) and 1,25(OH)₂D₃ induced IDO is a suggested mechanism for downregulation of Th-1 priming and tolerogenic DC upregulation of Tregs (Gorman et al., 2010). Consequently IDO has been suggested as a general target of 1,25(OH)₂D₃ in the immune system (Dankers et al., 2016).

The programmed death receptor ligand 1 (PD1L), activates its receptor PD1 (member of CD28 family) on CD8⁺ T cells and represses TCR-mediated activation and inhibits cell survival, proliferation and cytokine production (Parry et al., 2005). CTLA4, secreted by Tregs, blocks the co-stimulatory signal from B7 on the APC and CD28 on the T4 lymphocyte, CTLA having a greater affinity for B7 molecules than CD28, thus inhibiting T4 effector function (Ribas & Wolchok, 2018).

1,25(OH)₂D₃ upregulates PDL1 and PDL2 and CTLA4 by direct transcriptional induction through the VDR and VDRE (Dimitrov et al., 2017) It has been suggested that elevated vitamin D₃ signalling in humans could suppress anti-tumour immunity via increased PDL1 expression. (Dimitrov et al., 2017) Extracellular adenosine is a physiological negative regulator of inflammation and immunity (Sitkovsky et al., 2004) and is largely produced from adenine nucleotides for example, ATP, by ecto-5'-nucleotidases, CD39 and CD73 (Eckle et al., 2007) Adenosine receptors, A2AR and A2BR are expressed in a wide variety of immune cells (Ohta & Sitkovsky, 2014). Effects include downregulation of T cells (including CD8⁺) (Linnemann et al., 2009); inhibition of T-cell activation (Linnemann et al., 2009) proliferation and effector functions (Ohta et al., 2009), such as cytotoxicity and cytokine production (Raskovalova et al., 2007); inhibition of classical proinflammatory activation of APCs and induction of alternative activation (A2BR) (Ohta & Sitkovsky, 2014), resulting in APCs producing immunosuppressive molecules such as TGFβ, IL10, arginase, IDO and COX2 (Novitskiy et al., 2008). Moreover, adenosine upregulates the number and activity of Tregs (Ohta et al., 2012; Ohta & Sitkovsky, 2014), and induces MDSCs (Ryzhov et al., 2011). 1,25(OH)₂D₃ upregulates adenosine production, via increased expression of CD39 and CD73 on CD4⁺ cells (Mann et al., 2015).

IL10 is a powerful tolerogenic agent, downregulating Th-1 and Th-2 responses, which may be secondary to a direct effect on monocyte–macrophages (Couper et al., 2008). IL10 downregulates MHC class II antigens, and co-stimulatory molecules B71/B72 expression on macrophages. It activates STAT3 and induces enhanced
(a) Tumour-Antigens, MHC class 1
Glycolipid antigens
Phospho-antigens
MIC-B
MIC-A
KLRK1
NKT
CD1D
CD8
γδ T
NK
DC
Activity of cytotoxic cells including INFγ, TNF, IL12, Perforin, Granzyme, FASLG, TNFSF10A

Inflammatory cytokines
CRP, IL1, IL6, IL8, TNF, ROS

CD4
Th1
IL2, IFNG

25(OH)D3
1,25(OH)2D3

IL17, ↑

(b) Loss of tumour-antigens, MHC class 1, KLRK1 ligands, FAS and TNFSF10A
IDO, PD1, adenosine
IFNG, TNF

CYP27B1
DC
CD4
Treg

IDO, IL10, FoxP3, CD39, CD73, CTLA4

Suppression of Th1 and Th17, switch to Th2 and Treg

25(OH)D3
1,25(OH)2D3

PD1, IDO, TDO, CD39, CD73, CSF1, CSF2, IL6, TGFβ and VEGF

Arginase-I, IL4
IL-10, TGFβ, PGE2

Tolerogenic DC
maturation, survival
antigen presentation
IL12, IL23
IDO, Arginase, IL10, PD1, CTLA4

Activate suppressor cells
IL10, IL4, TGFβ, FoxP3, CD73

Suppression of Th1 and Th17, switch to Th2 and Treg

Differentiation of MDSCs to macrophages and DCs

CYP27B1
Macrophage
M2

Macrophage switching
M1 to M2
expression of PD1 and PDL1 on DCs rendering them ineffective (Tran Janco et al., 2015), and is involved in polarizing γδT cells to tolerogenic cells (Zhao et al., 2018). Vitamin D₃ is known to induce tolerogenic DCs and Tregs (Novitskiy et al., 2008; Sakaguchi et al., 2010) and to upregulate the transcription factor GATA3 and TH2 cells (Boonstra et al., 2001), which are the sources of IL-10. TGFB induces DC to stimulate Treg formation (Maldonado & von Andrian, 2010), polarizes FOXP3+ γδTreg cells from Vγ9/Vδ2 T cells (Cassert et al., 2009) and recruits TAM M2 macrophages (Byrne et al., 2008). There are reports of an inverse relationship between vitamin D₃ and TGFB (Aschenbrenner et al., 2001; Isik et al., 2012). However, 1,25(OH)₂D₃ may co-operate with TGFB, in the upregulation of immunosuppressive CD73 and FOXP3 expression and is reported to augment CD4+ expression of various TGFB associated molecules, and to increase bioactive TGFB (Mann et al., 2015).

Thus, in the absence of tumour VDR signalling, many of the reported immunosuppressive effects of vitamin D₃, reported in a non-tumour context, may be relevant to tumour immunity as they would apparently oppose immune suppressive effects on the tumour in the elimination phase, tip the balance in the equilibrium phase towards tumour expansion by downregulating anti-tumour immunity and potentially amplify immunosuppression in the escape phase, having overlapping immunosuppressive activities with some of those of the escape phase. These include the development of immunosuppressive immunocytes, tolerogenic DCs, Tregs and M2 macrophages but possibly not MDSCs and mechanistic similarities, involving IDO, PDL1, CTLA, adenosine, IL10 and TGFB. Figure 3 shows a summary of the direct influence of vitamin D influence on innate and adaptive immunity which may affect the immune response to cancer in the elimination (Figure 3a) and escape phases (Figure 3b) of immunoediting in cancer.

### 2.4 | Angiogenesis

Angiogenesis is necessary for local tumour invasion and metastasis. The VDR is expressed in endothelial cells and vascular smooth muscle cells and vitamin D₃ promotes angiogenesis and VEGF secretion (Cardus et al., 2009; Grundmann et al., 2012). However, in the context of tumours, there is evidence of an anti-angiogenic effect of vitamin D₃ (Ma et al., 2011). In vivo tumour-cell induced angiogenesis is reportedly inhibited by 1,25(OH)₂D₃ and retinoids synergistically (Majewski et al., 1993). Furthermore, in a colon cancer model, 1,25(OH)₂D₃ inhibited angiogenesis, which was associated with reduced VEGF expression in tumours (Iseki et al., 1999).

These opposing effects of vitamin D₃ might be reconciled by the postulate of tumour VDR inhibiting a pro-angiogenic factor secreted by the tumour. Loss of tumour VDR would leave a direct vascular effect of vitamin D₃ unopposed. This would be analogous to the effects of vitamin D₃ on immunity as described above. Furthermore, Wnt beta-catenin signalling is known to promote angiogenesis (Chen et al., 2009).

### 3 | THE REPORTED EFFECT OF VITAMIN D₃ IN CANCER

#### 3.1 | Animal studies—the effect of vitamin D₃/1,25(OH)₂D₃ or vitamin D₃ analogues on cancer xenographs

Several experimental studies with explanted human or mouse cancer tissue have shown that Vitamin D₃ is associated with inhibition of tumour growth (Krishnan et al., 2013; Milczarek et al., 2013; Ooi et al., 2010; Swami et al., 2012; Williams et al., 2016) and metastasis. However, there is also experimental evidence of vitamin D₃ promoting tumour progression with metastasis and decreased survival (Anisiewicz et al., 2018; Cao et al., 2018). It is notable that in the studies showing a beneficial effect, the malignant cells were ‘sensitive’ (in terms of inhibition of proliferation) to the direct action of vitamin D₃ and/or immune deficient models were used (Pawlik et al., 2018; Zhang, Guo, Zhang, et al., 2014). In animals showing a deleterious effect, the tumour was not sensitive in vivo nor in vitro (Pawlik et al., 2018). In these animals, transcription was most prominently upregulated in genes of Tregs and Th-2 cells. In a further study, vitamin D administration was associated with a decrease in Th-1 cells, an increase in MDSCs and decreased transcription of INFγ with increased transcription of TGFB (Cao et al., 2018). Thus, sensitivity to growth inhibitory effects of vitamin D₃, which would imply effective tumour VDR signalling, was associated with a beneficial effect but a deleterious effect, with immunosuppression, if not.

#### 3.2 | Observational studies

##### 3.2.1 | Cancer development

Prediagnostic vitamin D₃ status has an undeniably important protective effect on the development and subsequent progression of a variety of cancers, comprehensively reviewed by Grant (2018). The evidence is largely epidemiological based upon an inverse relation of incidence and/or outcome of a variety of carcinomas with indices of solar UVB exposure (Fleischer & Fleischer, 2016; Garland & Garland, 1980; Garland, Garland, et al., 1990; Garland, White, et al., 1990; Grant, 2002; Zamoiski et al., 2016) including latitude (Grant, 2007) and also modifying issues of dark skin (Grant & Peiris, 2012) and outdoor occupation (Grant, 2012; Pukkala et al., 2009).

##### 3.2.2 | Vitamin D levels and established cancer

A majority of observational studies of post-diagnosis 25(OH)D₃ serum levels have shown an inverse relation with progression in a variety of cancers (Vaughan-Shaw et al., 2017) including MM (Newton-Bishop et al., 2009; Nurnberg et al., 2009). This might
be expected early post diagnosis, these levels being a reflection of prediagnosis levels which would have a formative effect on cancer development, and hence, an effect on cancer progression as found in the prospective studies cited above. Supportive of this, a study which measured serum 25(OH)D₃ soon after diagnosis and also assessed previous sun exposure, through patient diaries, concluded that the ‘measured serum 25(OH)D₃ levels not only reflected the recent sun exposure, but could also be considered to be representative for a period of at least several years’ (Nurnberg et al., 2009). The post-diagnosis findings have been interpreted (Newton-Bishop et al., 2009; Nurnberg et al., 2009) as vitamin D₃ administration having a beneficial effect on established cancer. This is likely to be valid for early developing cancers but, in more advanced cancer, we believe this concept should be tempered by VDR status as discussed above. There are few reports of 25(OH)D₃ levels later during follow-up. One study found that, compared with initial 25(OH)D₃ levels, both decreased and increased later levels were associated with worsened prognosis, which prompted the authors to caution against widespread use of vitamin D₃ supplementation in melanoma patients (Saig et al., 2015). A further study found that blood levels taken after resection of regional nodes, sometimes years after initial diagnosis in stage III MM patients, had no relationship with prognostic indices or survival (Lipplaa et al., 2018).

### 3.3 Intervventional studies

#### 3.3.1 Vitamin D supplements and development and subsequent progression of cancer

Randomized controlled trials on vitamin D supplementation, reviewed by Keum et al. (2019), have shown a variable effect on cancer incidence but a protective effect with larger dose and a more consistent protective effect on subsequent mortality.

#### 3.3.2 1,25(OH)₂D₃ or vitamin D₃ analogue supplements in established cancer

A trial of large dose vitamin D₃ in advanced MM was documented in 2014 (Saw et al., 2014) but results are still awaited. A placebo-controlled trial on vitamin D₃ supplementation (100,000 IU every 50 days for 3 years) for resected Stage II MM patients (MelaViD trial) was posted in 2010 but was terminated in 2017 because of inadequate recruitment (150 patients) and no results were reported (De Smedt et al., 2017). A phase 2 study high- vs low-dose vitamin D₃ plus standard chemotherapy in 139 metastatic colon cancer (CRC) patients showed a significant (p = .04) advantage in progression-free survival (PFS) of high-dose vitamin D₃ (Ng et al., 2019); result of a confirmatory phase 3 trial is awaited. However, a study of 2000 IU/d cholecalciferol vs placebo in patients with alimentary cancer, including CRC, showed no significant effect on 5-year relapse-free survival, (Urashima et al., 2019) and a similar study lasting two years following diagnosis, in metastatic CRC, showed no benefit to overall survival (Antunac Golubic et al., 2018). A retrospective, single institution, study of vitamin D₃ supplementation (‘low dose’) in non-metastatic HER2+ breast cancer reported a prolongation of disease-free survival (Zeichner et al., 2015). However, the same study showed a deleterious effect in larger tumours. Larger or deeper tumours are likely to be more advanced and thus, VDR signalling less likely to be intact (Hutchinson et al., 2018). A pilot study of 16 patients with head and neck SCC being treated with 1.25(OH)₂D₃ during the 3-week interval between cancer diagnosis and surgical treatment (3 cycles of 4 µg of 1.25(OH)₂D₃ for each of 3 sequential days, followed by 4 days) showed a prolongation of time to recurrence in the treated group (p = .04) (Walsh et al., 2010). No further results appear to have been published. A study in low-grade prostate cancer given high dose vitamin D₃ for a year showed improvement compared with historical controls (Marshall et al., 2012). In advanced malignancy, a number of uncontrolled studies have shown modest or no measurable improvement in advanced prostate, pancreatic and hepatic cancer (Beer, Lemmon, et al., 2003; Dalhoff et al., 2003; Evans et al., 2002; Liu et al., 2002; Schwartz et al., 2005) and similarly 1,25(OH)₂D₃ combined with carboplatin in prostate cancer (Beer et al., 2004; Flaig et al., 2006). High-dose 1,25(OH)₂D₃ plus docetaxel showed promising results in prostate cancer (Beer, Ellers, et al., 2003) and was followed by a controlled trial of docetaxel with or without high dose 1,25(OH)₂D₃, which just failed to show a significant effect of the 1,25(OH)₂D₃ arm (Beer et al., 2007). This was followed by a large phase 3 (ASCENT) study which included dexamethasone in both arms and prednisolone in the placebo arm. This trial was halted because of excess deaths in the 1,25(OH)₂D₃ arm (Scher et al., 2011). Thus, there is evidence of some beneficial effect of vitamin D₃, particularly in early disease but also of a deleterious effect, particularly in advanced disease.

### 4 COMMENT

There is evidence for a beneficial effect of vitamin D₃ in the processes involved in cancer, with the suppression of growth and inflammation, enhancement of anti-tumour immunity and suppression of angiogenesis. However, there are differences between the reported effects of vitamin D₃ in cancerous and non-cancerous contexts on immunity and angiogenesis. VDR signalling is of obvious importance in tumour cells but also in inflammatory cells, immunocytes and angiocytes. With loss of tumour cell VDR signalling, vitamin D₃ signalling in other cells in the TME continues and may gain significance. The reported beneficial effect of vitamin D₃ on tumour immunity (Muralidhar et al., 2019) would appear dependent on tumour cell VDR signalling. In the absence of tumour VDR signalling, some beneficial effects of vitamin D₃ that is, the suppression of inflammation and possibly suppression of MDSCs, would be expected to continue but deleterious effects would
seem likely to emerge, with loss of tumour growth suppression, suppression of anti-tumour immunity and possibly upregulation of tumour angiogenesis. Anti-tumour immunity may be particularly important. In cancers, such as MM, where tumour VDR enhances anti-tumour immunity, loss of tumour VDR signalling might be expected to result in opposition of the elimination phase, tipping the equilibrium phase in favour of tumour progression and enhancement of the escape phase by the direct action of vitamin D$_3$ on immunocytes.

Observational studies of early post diagnosis 25(OH)D$_3$ levels have shown a protective effect on progression in a number of cancers. (Newton-Bishop et al., 2009; Nurnberg et al., 2009; Vaughan-Shaw et al. 2017) However, these levels are a likely reflection of prediagnosis levels which are known to have a formative effect on cancer development and progression. Levels taken later in established cancer are infrequently reported and have shown varying associations including a deleterious effect. In animal models, where tumour VDR signalling was apparently defective, vitamin D$_3$ administration decreased survival and increased metastases, associated with downregulation of Th-1 cells and INFG gamma and upregulation of MDSCs and TGFB (Anisiewicz et al., 2018; Cao et al., 2018) and upregulation of transcription of Tregs and Th-2 cells (Pawlik et al., 2018). In advanced human disease (a likely marker of impaired immunocytes. 5126–5136.

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More work is needed on assessing the integrity of tumour VDR signalling in cancer and trials are necessary to assess the safety of vitamin D$_3$ supplementation, including small dose, in tumours with defective VDR signalling. A further treatment possibility is to rectify defective VDR signalling as recently suggested (Muralidhar et al., 2019), and one possibility is through MAPK inhibition (Hutchinson et al., 2018).

**CONFLICT OF INTEREST**

The authors declare no conflict of interest for preparing this manuscript.

**DATA AVAILABILITY STATEMENT**

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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