ACTA ABP BIOCHIMICA POLONICA

Vol. 67, No 1/2020
1–5
https://doi.org/10.18388/abp.2020_2905

Review

Vitamin D in autoimmune bullous diseases*

Stefan Tukaj✉

Department of Molecular Biology; Faculty of Biology; University of Gdańsk; Gdańsk, Poland

Numerous epidemiological studies have suggested a link between vitamin D deficiency and the development of various autoimmune diseases, including diabetes mellitus type 1, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis or systemic lupus erythematosus. More recently, such a link has been also proposed for autoimmune bullous diseases (AIBD). This is a relatively rare and potentially life-threatening, organ-specific group of inflammatory skin diseases characterized by the presence of tissue-bound and circulating autoantibodies against various molecules present in desmosomes (in pemphigus diseases) or hemidesmosomes (in pemphigoid diseases). In addition to the well-known role of vitamin D in calcium and phosphate homeostasis, the hormonally active vitamin D metabolite, 1,25-dihydroxyvitamin D_3 (calcitriol), exerts potent effects on cellular differentiation and regulation of immune responses *via* binding to the vitamin D receptor present in most cells of the immune system. Since cells of both, the innate and adaptive immune systems, are known to be relevant in AIBD, the role of vitamin D analogues in the treatment of patients with these disorders deserves much attention. This mini-review summarizes recent epidemiological and experimental studies on vitamin D involvement in the autoimmune bullous diseases.

Key words: calcitriol; $1,25(OH)_2D_3$; vitamin D; 25(OH)D; autoimmune bullous diseases.

Received: 05 November, 2019; revised: 09 January, 2020; accepted: 29 January, 2020 available on-line: 12 February, 2020

✉e-mail: stefan.tukaj@biol.ug.edu.pl
***Acknowledgments of Financial Support**: This study was supported by the Polish National Science Centre (NCN) grant no. 2017/25/B/NZ6/00305.
Abbreviations: AIBD, autoimmune bullous diseases; $1,25(OH)_2D_3$, 1α,25-dihydroxyvitamin D_3; 25(OH)D, 25-hydroxyvitamin D_3; VDR, vitamin D receptor; APC, antigen presenting cell; IVIG, intravenous immunoglobulin; PV, pemphigus vulgaris; PF, pemphigus foliaceus; BP, bullous pemphigoid; EBA, epidermolysis bullosa acquisita; COL17, collagen type XVII; COL7, collagen type VII

VITAMIN D: PRODUCTION, METABOLISM, AND MECHANISMS OF ACTION

In a canonical metabolic pathway, the cholesterol-derived vitamin D is present in two major forms: ergocalciferol (D_2) and cholecalciferol (D_3), the latter being synthesized in the skin upon sunlight exposure (UV radiation) and converted to 25-hydroxyvitamin D_3 [25(OH)D; calcidiol] and 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D$, calcitriol] in the liver and kidneys, respectively, by the vitamin D-25-hydroxylase (CYP2R1 and CYP27A1) and the 25(OH)D-1α-hydroxylase (CYP27B1) (Holick *et al.*, 2011; Bikle, 2014). Active form of vitamin D_3 [$1,25(OH)_2D$] binds to the vitamin D binding protein (DBP) in circulation and is delivered to the target tissues, such as the intestine, bone and kidneys, to regulate the calcium and phosphate homeostasis (Bikle, 2012). In addition, $1,25(OH)_2D$ is also synthesized locally in the epidermis and various immune cells (Bikle, 2012; 2014). Alternatively, vitamin D_2 and D_3 can be supplemented by a balanced diet of plant and animal origin, respectively. Vitamin D, whether produced in the skin from 7-dehydrocholesterol or absorbed from the diet, must be activated first to 25(OH)D and then to $1,25(OH)_2D$ (Bikle, 2014). Nevertheless, numerous agencies and scientific organizations highly recommend vitamin D supplementation to maintain health and prevent development of metabolic, cancerous, and immune-related diseases (Pludowski *et al.*, 2018). Recent studies have revealed that the vitamin D metabolites can be also synthetized and activated through a CYP11A1-driven non-canonical metabolic pathway (Slominski *et al.*, 2012; Slominski *et al.*, 2014a; Slominski *et al.*, 2015a; Slominski *et al.*, 2015b).

While 25(OH)D is the major (inactive) circulating form of vitamin D, commonly used as a serological indicator to evaluate the vitamin D status in patients (Holick *et al.*, 2011), calcitriol represents the biologically active vitamin D metabolite which serves as the primary ligand for the vitamin D receptor (VDR) expressed in the bone, gastrointestinal tract, skeletal muscle or skin, as well as in various immune cells, including dendritic cells, monocytes/macrophages or lymphocytes (Yang *et al.*, 2013; Mazzaferro *et al.*, 2014; Mostafa & Hegazy 2015). The $1,25(OH)_2D$/VDR complex binds to the vitamin D response elements (VDREs) in the genome to activate or suppress transcription of hundreds of genes in a cell-specific manner. In general, the functions of vitamin D analogues are characterized as genomic, i.e. mediated through VDR transcriptional effects inside the cell nucleus, and non-genomic, when VDR induces rapid signaling, including the ability to stimulate calcium transport across the plasma membrane (Bikle, 2014).

Apart from the classic role of vitamin D in the calcium and phosphate homeostasis, many in vivo studies have shown that active vitamin D metabolites regulate several physiological processes, such as the cell proliferation, differentiation, and immune modulation. Active vitamin D metabolites display immunomodulatory activity manifested by reduction in the antigen presenting cells' (APC) activity or pro-inflammatory T helper 1 (Th1) and T helper 17 (Th17) frequencies, as well as expansion of the T- and B-regulatory cells (Takeda *et al.*, 2010; Bikle, 2014; Alhassan Mohammed *et al.*, 2017; Tukaj *et al.*, 2018).

In addition, it has been proven that CYP11A1-derived vitamin D metabolites serve as ligands for VDR or can act as inverse agonists on retinoic acid orphan receptors (ROR) α and γ (Slominski *et al.*, 2014b; Slominski *et al.*, 2017), which are known to play key roles in regulation of the immune and metabolic pathways. More recently,

the top signaling pathways for CYP11A1-driven analogues, such as 20,23$(OH)_2$D, were linked to activation of the aryl hydrocarbon receptor (AhR), representing an alternative receptor to VDR (Slominski *et al*., 2018). It is worth to mention that despite the importance of UVB radiation in the 25-hydroxyvitamin D_3 synthesis, this radiation is also a key agent that induces DNA damage in the skin. Both, 1,25$(OH)_2$D and CYP11A1-derived vitamin D analogues, protect the epidermal keratinocytes against UVB-induced damage *via* activation of the Nrf2-dependent antioxidant response and p53-phosphorylation, as well as by induction of the DNA repair system (Chaiprasongsuk *et al*., 2019). In addition, both - the classical 1,25$(OH)_2$D and non-calcemic CYP11A1-driven analogues, exert anti-inflammatory effects on keratinocytes by inhibiting the nuclear factor-κB (NF-κB) activity (Janjetovic *et al*., 2009; 2010; Tukaj *et al*., 2016).

Because regulatory effects of vitamin D analogues on proliferation and differentiation have been also confirmed for cells outside the immune system, topical application of vitamin D analogues has been considered and approved for the treatment of psoriasis - one of the most common chronic inflammatory skin disease which affects approximately 2% of the general human population (Umar *et al*., 2018). In addition, some reports indicate that topically applied vitamin D analogues are also effective in vitiligo (Xing & Xu, 2012). Because skin is the main source of vitamin D in our body (approximately 90%) and most of the available data point to this vitamin's significant impact on the health of skin and other organs (Mostafa & Hegazy 2015), the potential impact of hypovitaminosis D on the development of dermatological diseases, including autoimmune bullous skin diseases, deserves special attention.

AUTOIMMUNE BULLOUS DISEASES

Autoimmune bullous diseases (AIBD) are characterized by the presence of tissue-bound and circulating autoantibodies that are directed against different structural molecules present in the skin and adjacent mucous membranes. AIBD are divided into three different subgroups, such as the pemphigoid, pemphigus, and dermatitis herpetiformis, the last being the cutaneous manifestation of the celiac disease with autoantibodies directed against the tissue and the epidermal transglutaminase (Witte *et al*., 2018). Pemphigus is a group of autoantibody-mediated autoimmune diseases of the skin and oral mucosa, in which the loss of cell adhesion (acantholysis) causes blisters and erosions. Patients with pemphigus are characterized by the presence of autoantibodies directed against desmoglein 1 and desmoglein 3, which are cell-cell adhesion molecules found in desmosomes in the epidermis. There are two major subtypes of pemphigus diseases: pemphigus vulgaris (PV) and pemphigus foliaceus (PF), the first being the most common form of pemphigus (Kasperkiewicz *et al*., 2017). While the etiology of pemphigus diseases is largely unknown, the genetic and environmental risk factors have been proposed. Both, the PV and PF are frequently associated with other (auto) inflammatory diseases, such as psoriasis, neurological and psychiatric disorders or some malignancies. In the case of PV, genetic risk factors include either HLA alleles DRB1*04:02 and DQB1*05:03 or non-HLA genes, i.e. DSG3, TAP2, IL6, and ST18. In addition, environmental risk factors, in particular use of penicillamine and captopril, as well as exposure to pesticides, metal vapor, UV, ionizing radiation, burns, undergoing surgery or stressful life events have been noted. In genetically susceptible individuals, the autoimmune reaction is driven by autoreactive T and B lymphocytes. Autoreactive T cells are educated by antigen presenting cells (APC) that present Dsg peptides *via* HLA class II molecules. Consequently, autoreactive T helper cells specific for Dsg molecules drive generation of autoreactive B cells and secretion of the tissue-bound and circulating autoantibodies to Dsg (Kasperkiewicz *et al*., 2017; Schmidt *et al*., 2019). Pemphigus can be treated with systemic corticosteroids and adjuvant therapies, including immunosuppressive agents, intravenous immunoglobulin (IVIG) and plasmapheresis. In addition, rituximab, a monoclonal antibody against the CD20 molecule (B cells' marker), is another promising therapeutic option (Kasperkiewicz *et al*., 2017).

Pemphigoid is another well-defined subgroup of AIBD that is characterized by the presence of tissue-bound and circulating autoantibodies directed against different structural molecules present in hemidesmosomes at the cutaneous basement membrane (Schmidt & Zillikens 2013). Bullous pemphigoid (BP), where autoantibodies to BP180 (collagen type XVII or COL17) and BP230 are observed, is the most common autoimmune subepidermal blistering disorder, whose incidence, similarly to other autoimmune diseases, is constantly increasing (Witte *et al*., 2018). By contrast, epidermolysis bullosa acquisita (EBA), a subepidermal blistering disease with autoantibodies to type VII collagen (COL7), is one of the rarest AIBD, with an incidence rate of 0.2–0.5 per million per year (Vorobyev *et al*., 2017). The etiology of pemphigoid seems to be unclear, nevertheless either environmental or genetic risk factors have been described. Numerous data found an association between pemphigoid and other immunological disorders, including psoriasis (Schmidt & Zillikens; 2013; Ohata *et al*., 2015). In addition, BP has been strongly associated with neurological disorders, including cognitive impairment, Parkinson's disease, stroke, epilepsy or multiple sclerosis (Schmidt & Zillikens; 2013). Several trigger factors, such as penicillin, vancomycin, gentamycin, trauma, burns, radiotherapy, UV-radiation, vaccination and contact allergy to metals have been described (Schmidt & Zillikens; 2013; Vorobyev *et al*., 2017). In addition, an association between HLA-DQB1*0301 and BP or mucous membrane pemphigoid (MMP), as well as the risk allele HLA-DRB1*15:03 or association between HLA-DR2 and EBA, have been reported (Schmidt & Zillikens; 2013; Kasperkiewicz *et al*., 2016). The majority of studies concerning the pathophysiology of pemphigoid are based on experimental animal models and numerous evidences pointed to pathogenic importance of both, the local and systemic innate and adaptive autoimmune responses against structural proteins of the dermal–epidermal junction (Schmidt & Zillikens; 2013; Kasperkiewicz *et al*., 2016).

As in the case of pemphigus, the pemphigoid diseases can be controlled medically by using corticosteroids, high-doses of IVIG, rituximab, plasmapheresis, and immunoadsorption (Schmidt & Zillikens 2013; Koga *et al*., 2019).

VITAMIN D STATUS IN THE AUTOIMMUNE BULLOUS DISEASES

Several epidemiological studies demonstrated that the vitamin D deficiency leads to an increased prevalence of autoimmune diseases, such as the multiple sclerosis, diabetes type 1, rheumatoid arthritis or systemic lupus

Table 1. Vitamin D status in *p*atients with AIBD

Patients (No.)	25(OH)D levels (mean ± S.D.) in patients *vs* corresponding controls (*p*-value)	Hypovitaminosis D in patients (%)	References
PV (n=13)	12 ± 4.4 *vs* 22.2 ± 11.7 ng/mL (p=0.012)	62	Marzano *et al*., 2012
BP (n=15)	9·6 ± 7.2 *vs* 22.6 ± 18.7 ng/mL (p=0.022)	73	Marzano *et al*., 2012
BP (n=12)	32.4 ± 16.9 *vs* 32.6 ± 16.2 nmol/L (n. s.)	83	Tukaj *et al*., 2013
PV (n=35)	13.9±8.3 *vs* 22.2±11.1 ng/mL (p<0.001)	48.6	Marzano *et al*., 2015
BP (n=32)	9.5±7.7 *vs* 22.4±14.9 ng/mL (p<0.0001)	75	Marzano *et al*., 2015
PV (n=34)	74.2 ± 53.1 *vs* 89.7 ± 29.5 nmol/L (p=0.008)	50	El-Komy *et al*., 2014
PV (n=30)	11.1±5.8 *vs* 12.1±9.2 ng/ml (n. s.)	100	Joshi *et al*., 2014
PV (n=32)	11.79 ± 1.55 *vs* 20.69 ± 2.79 ng/ml (p=0.009)	Not available	Zarei *et al*., 2014
Pemphigus (n=52)	Not available	78.8	Moravvej *et al*., 2016
BP (n=31)	29.3 ± 17.3 *vs* 34.9 ± 19.4 nmol/L (p=0.246)	86.7	Sarre *et al*., 2016
EBA (n=22)	Not available	73	Tukaj *et al*., 2018

Vitamin D status in patients with pemphigus vulgaris (PV), bullous pemphigoid (BP), and epidermolysis bullosa acquisita (EBA). In one case, the authors presented data concerning the vitamin D status in pemphigus patients without subdivision into PV and pemphigus foliaceus. There is no data available on vitamin D status in other rare pemphigus variants, such as the paraneoplastic pemphigus, pemphigus vegetans, pemphigus erythematosus or herpetiform pemphigus and pemphigoid diseases, such as the mucous membrane pemphigoid, pemphigoid gestationis, linear IgA disease, anti-laminin-γ1-pemphigoid, anti-p200 pemphigoid or lichen planus pemphigoides. According to the International Endocrine Society, the 25(OH)D serum concentrations of 20–29 ng/ml and below 20 ng/ml have been defined as vitamin D insufficiency and deficiency, respectively (Holick *et al*., 2011). The 25(OH)D values are presented in two unit forms, i.e. nmol/L or ng/mL. To convert nmol/L to ng/mL, the values should be divided by 2.5.

erythematosus (Yang *et al*., 2013, Dankers *et al*., 2017). More recently, the role of vitamin D has been also investigated in AIBD and the emerging evidence suggests an increased frequency of vitamin D deficiency/insufficiency in patients with pemphigus and pemphigoid, such as the PV and BP or EBA, respectively (Marzano *et al.,* 2012 and Marzano *et al.,* 2015; Tukaj *et al.,* 2013; El-Komy *et al.,* 2014; Joshi *et al.,* 2014; Zarei *et al.,* 2014; Moravvej *et al.,* 2016; Sarre *et al*., 2016; Tukaj *et al*., 2018) (Table 1). In addition, in some reports, lower concentrations of 25(OH)D have been associated with AIBD activity, pointing towards a possible causative role of hypovitaminosis D in the disease process (Zarei *et al.,* 2014; Marzano *et al.,* 2015; Moravvej *et al.,* 2016). The role of vitamin D deficiency in AIBD, however, is still a matter of debate because other studies have found no difference in the 25(OH)D levels between patients and healthy subjects, possibly due to concomitantly observed low vitamin D levels in the corresponding controls and/or limited number of patients and controls involved in the study (Tukaj *et al.,* 2013; Joshi *et al.,* 2014; Moravvej *et al.,* 2016; Sarre *et al*., 2016).

EXPERIMENTAL THERAPIES USING VITAMIN D ANALOGUES IN THE AUTOIMMUNE BULLOUS DISEASES

The efficacy of vitamin D supplementation in experimental models of arthritis, lupus, multiple sclerosis, encephalomyelitis, diabetes type 1, and atherosclerosis has been confirmed in various studies (Deluca & Cantorna, 2001; Takeda *et al*., 2010; Dankers *et al*., 2017). Moreover, several clinical trials have been performed to investigate the therapeutic value of vitamin D supplementation in multiple sclerosis, rheumatoid arthritis, Crohn's disease, type I diabetes, and systemic lupus erythematosus (Dankers *et al*., 2017). While patients with the autoimmune bullous skin diseases suffer from vitamin D deficiency (Marzano *et al.,* 2012 and Marzano *et al.,* 2012 2015; Tukaj *et al.,* 2013; El-Komy *et al.,* 2014; Joshi *et al.,* 2014; Zarei *et al.,* 2014; Moravvej *et al.,* 2016; Sarre *et al*., 2016; Tukaj *et al*., 2018), a direct link between hypovitaminosis D and the development of autoimmune bullous diseases has not been proven.

It is hypothesized that binding of bullous pemphigoid (BP)-specific IgG autoantibodies to BP180 initiates the Fc receptor-independent events leading to the excessive expression and secretion of pro-inflammatory IL-6 and IL-8 from basal keratinocytes (Schmidt *et al*., 2000; Schmidt & Zillikens, 2013). Activation of complement at the dermal–epidermal junction (DEJ), together with the mast cells' degranulation and inflammatory chemokines result in the infiltration of inflammatory cells, including granulocytes, in the upper dermis. The reactive oxygen species (ROS) and matric metalloproteinases (MMP) released by the activated granulocytes induce dermal-epidermal splitting and blister formation (Schmidt & Zillikens, 2013). We have recently found that bullous pemphigoid (BP) IgG-induced IL-6 and IL-8 secretion from

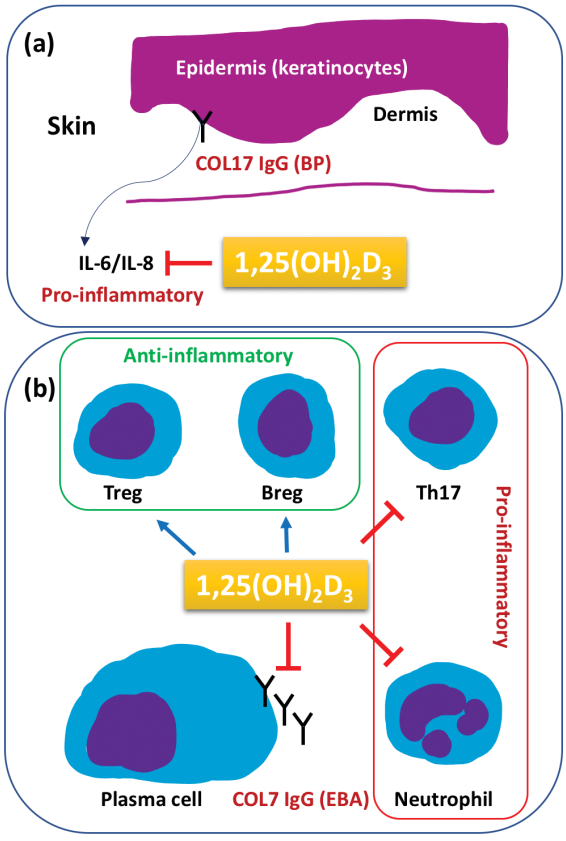

Figure 1. Pathophysiology and the experimental therapy of AIBD.
(**a**) 1,25(HO)$_2$D$_3$ (calcitriol) inhibits secretion of the pro-inflammatory cytokines induced by bullous pemphigoid (BP) anti-COL17 IgG in a human keratinocyte culture. (**b**) 1,25(HO)$_2$D$_3$ promotes expansion of disease-regulating immunosuppressive cells (Treg and Breg), attenuates secretion of pathogenic anti-COL7 IgG, as well as down-regulates neutrophil activity and inhibits proinflammatory Th17 cell population in a mouse model of epidermolysis bullosa acquisita (EBA).

the human keratinocytes HaCaT cells was reduced in the presence of calcitriol *via* inhibition of STAT3 phosphorylation and NF$\varkappa$B activity (Tukaj *et al.*, 2016) (Fig. 1a). Effectiveness of the calcitriol treatment was confirmed *in vivo* by using a well-established EBA mouse model which offers an elegant tool to study the pathogenesis of autoantibody-induced and immune cell-mediated blistering, as well as enables investigators to identify new therapeutic targets for EBA and other AIBD (Bieber *et al.*, 2016; Kasperkiewicz *et al.*, 2016). We have found for the first time that orally administrated calcitriol modulated the clinical course of experimental EBA through induction of the T and B regulatory cells, as well as down-regulation of neutrophil activity and blockade of proinflammatory Th17 cell population (Tukaj *et al.*, 2018). Because both, the immunosuppressive Treg and Breg, or proinflammatory Th1, Th17, and neutrophils are associated with the AIBD development (Hammers *et al.*, 2011; Tukaj *et al.*, 2014; Tukaj *et al.*, 2018; Bieber *et al.*, 2017a; Bieber *et al.*, 2017b; Chakievska *et al.*, 2019), targeting these cell populations is an important therapeutic approach in the described disorders (Fig. 1b).

CONCLUSION

Despite growing understanding of AIBD pathogenesis, treatment of this group of skin disorders remains challenging. This is because of frequent relapses, numerous side effects due to corticosteroid usage, or simply due to lack of effective treatment (Koga *et al.*, 2019; Izumi *et al.*, 2019). In addition, the incidence of AIBD is constantly increasing (Witte *et al.*, 2018), and therefore there is a growing urgency for discovering an effective treatment or prophylactic regimen in order to reduce the incidence of these autoimmune disorders. Despite the usage of topical vitamin D analogues in the treatment of autoimmune skin conditions, such as psoriasis and vitiligo (Xing & Xu, 2012; Umar *et al.*, 2018), there is a limited number of epidemiological and experimental studies on vitamin D involvement in the autoimmune bullous diseases. This requires further research and clinical trials involving the pemphigus and pemphigoid patients. In fact, several case reports have described that the Hailey-Hailey disease, also known as a familial benign chronic pemphigus, can be successfully controlled with vitamin D analogues applied either orally or topically (Bianchi *et al.*, 2004; Rajpara & King, 2005; Megna *et al.*, 2019). Finally, because there are many case reports describing the coexistence of AIBD and psoriasis (Ohata *et al.*, 2015), the role of topically applied vitamin D analogues in the treatment of these disorders needs to be properly evaluated.

REFERENCESS

Alhassan Mohammed H, Saboor-Yaraghi AA, Mirshafiey A, Vahedi H, Shiri-Shahsavar MR, Mousavi Nasl Khameneh A (2017) Immunomodulatory and immunosuppressive roles of 1α,25(OH)2D3 in autoimmune diseases. *Scand. J. Immunol.* **85**: 95–103. https://doi.org/10.1111/sji.12512

Bianchi L, Chimenti MS, Giunta A (2004) Treatment of Hailey-Hailey disease with topical calcitriol. *J. Am. Acad. Dermatol.* **51**: 475–476. https://doi.org/10.1016/j.jaad.2003.10.668

Bieber K, Witte M, Sun S, Hundt JE, Kalies K, Dräger S, Kasprick A, Twelkmeyer T, Manz RA, König P, Köhl J, Zillikens D, Ludwig RJ (2016) T cells mediate autoantibody-induced cutaneous inflammation and blistering in epidermolysis bullosa acquisita. *Sci. Rep.* **6**: 38357. https://doi.org/10.1038/srep38357

Bieber K, Sun S, Witte M, Kasprick A, Beltsiou F, Behnen M, Laskay T, Schulze FS, Pipi E, Reichhelm N, Pagel R, Zillikens D, Schmidt E, Sparwasser T, Kalies K, Ludwig RJ (2017a) Regulatory T cells suppress inflammation and blistering in pemphigoid diseases. *Front Immunol.* **8**: 1628. https://doi.org/10.3389/fimmu.2017.01628

Bieber K, Koga H, Nishie W (2017b) *In vitro* and *in vivo* models to investigate the pathomechanisms and novel treatments for pemphigoid diseases. *Exp. Dermatol.* **12**: 1163–1170. https://doi.org/10.1111/exd.13415

Bikle DD (2012) Vitamin D and bone. *Curr. Osteoporos. Rep.* **10**: 151–159. https://doi.org/10.1007/s11914-012-0098-z

Bikle DD (2014) Vitamin D metabolism, mechanism of action, and clinical applications. *Chem Biol.* **21**: 319–329. https://doi.org/10.1016/j.chembiol.2013.12.016

Chaiprasongsuk A, Janjetovic Z, Kim TK, Jarrett SG, D'Orazio JA, Holick MF, Tang EKY, Tuckey RC, Panich U, Li W, Slominski AT (2019) Protective effects of novel derivatives of vitamin D3 and lumisterol against UVB-induced damage in human keratinocytes involve activation of Nrf2 and p53 defense mechanisms. *Redox Biol.* **24**: 101206. https://doi.org/10.1016/j.redox.2019.101206

Chakievska L, Holtsche MM, Künstner A, Goletz S, Petersen BS, Thaci D, Ibrahim SM, Ludwig RJ, Franke A, Sadik CD, Zillikens D, Hölscher C, Busch H, Schmidt E (2019) IL-17A is functionally relevant and a potential therapeutic target in bullous pemphigoid. *J. Autoimmun.* **96**: 104–112. https://doi.org/10.1016/j.jaut.2018.09.003

Dankers W, Colin EM, van Hamburg JP, Lubberts E (2017) Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential. *Front. Immunol.* **7**: 697. https://doi.org/10.3389/fimmu.2016.00697

Deluca HF, Cantorna MT (2001) Vitamin D: its role and uses in immunology. *FASEB J.* **14**: 2579–2585. https://doi.org/10.1096/fj.01-0433rev

El-Komy MH, Samir N, Shaker OG (2014) Estimation of vitamin D levels in patients with pemphigus vulgaris. *J. Eur. Acad. Dermatol. Venereol.* **7**: 859–863. https://doi.org/10.1111/jdv.12179

Hammers CM, Bieber K, Kalies K, Banczyk D, Ellebrecht CT, Ibrahim SM, Zillikens D, Ludwig RJ, Westermann J (2011) Complement-fixing anti-type VII collagen antibodies are induced in Th1-polarized lymph nodes of epidermolysis bullosa acquisita-susceptible mice. *J. Immunol.* **10**: 5043–5050. https://doi.org/10.4049/jimmunol.1100796

Izumi K, Bieber K, Ludwig RJ (2019) Current Clinical Trials in Pemphigus and Pemphigoid. *Front Immunol.* **10**: 978. https://doi.org/10.3389/fimmu.2019.00978

Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **96**: 1911–1930. https://doi.org/10.1210/jc.2011-0385

Janjetovic Z, Zmijewski MA, Tuckey RC, DeLeon DA, Nguyen MN, Pfeffer LM, Slominski AT (2009) 20-Hydroxycholecalciferol, product of vitamin D3 hydroxylation by P450scc, decreases NF-kappaB activity by increasing IkappaB alpha levels in human keratinocytes. *PLoS One.* **4**: e5988. https://doi.org/10.1371/journal.pone.0005988

Janjetovic Z, Tuckey RC, Nguyen MN, Thorpe EM Jr, Slominski AT (2010) 20,23-dihydroxyvitamin D3, novel P450scc product, stimulates differentiation and inhibits proliferation and NF-kappaB activity in human keratinocytes. *J. Cell Physiol.* **223**: 36–48. https://doi.org/10.1002/jcp.21992

Joshi N, Minz RW, Anand S, Parmar NV, Kanwar AJ (2014) Vitamin D deficiency and lower TGF-β/IL-17 ratio in a North Indian cohort of pemphigus vulgaris. *BMC Res. Notes.* **7**: 536. https://doi.org/10.1186/1756-0500-7-536

Kasperkiewicz M, Sadik CD, Bieber K, Ibrahim SM, Manz RA, Schmidt E, Zillikens D, Ludwig RJ (2016) Epidermolysis bullosa acquisita: from pathophysiology to novel therapeutic options. *J. Invest. Dermatol.* **136**: 24–33. https://doi.org/10.1038/JID.2015.356

Kasperkiewicz M, Ellebrecht CT, Takahashi H, Yamagami J, Zillikens D, Payne AS, Amagai M (2017) Pemphigus. *Nat. Rev. Dis. Primers.* **3**: 17026. https://doi.org/10.1038/nrdp.2017.26

Koga H, Prost-Squarcioni C, Iwata H, Jonkman MF, Ludwig RJ, Bieber K (2019) Epidermolysis bullosa acquisita: the 2019 update. *Front. Med. (Lausanne)* **5**: 362. https://doi.org/10.3389/fmed.2018.00362

Marzano AV, Trevisan V, Eller-Vainicher C, Cairoli E, Marchese L, Morelli V, Beck-Peccoz P, Crosti C, Chiodini I (2012) Evidence for vitamin D deficiency and increased prevalence of fractures in autoimmune bullous skin diseases. *Br. J. Dermatol.* **167**: 688–691. https://doi.org/10.1111/j.1365-2133.2012.10982.x

Marzano AV, Trevisan V, Cairoli E, Eller-Vainicher C, Morelli V, Spada A, Crosti C, Chiodini I (2015) Vitamin D and skeletal health in autoimmune bullous skin diseases: a case control study. *Orphanet. J. Rare. Dis.* **10**: 8. https://doi.org/10.1186/s13023-015-0230-0

Mazzaferro S, Goldsmith D, Larsson TE, Massy ZA, Cozzolino M (2014) Vitamin D metabolites and/or analogs: which D for which patient? *Curr. Vasc. Pharmacol.* **12**: 339–349. https://doi.org/10.2174/1570161113119990024

Megna M, Scalvenzi M, Russo D, Timoshchuk EA, Costa C, Santoianni P (2019) Hailey-Hailey disease successfully treated with vitamin D oral supplementation. *Dermatol. Ther.* **32**: e12767. https://doi.org/10.1111/dth.12767

Moravvej H, Mozafari N, Younespour S (2016) Serum 25-hydroxy vitamin D level in patients with pemphigus and its association with disease severity. *Clin. Exp. Dermatol.* **41**: 142–147. https://doi.org/10.1111/ced.12733

Mostafa WZ, Hegazy RA (2015) Vitamin D and the skin: Focus on a complex relationship: A review. *J. Adv. Res.* **6**: 793–804. https://doi.org/10.1016/j.jare.2014.01.011

Ohata C, Ishii N, Koga H, Fukuda S, Tateishi C, Tsuruta D, Furumura M, Hashimoto T (2015) Coexistence of autoimmune bullous diseases (AIBDs) and psoriasis: A series of 145 cases. *J. Am. Acad. Dermatol.* **73**: 50–55. https://doi.org/10.1016/j.jaad.2015.03.016

Pludowski P, Holick MF, Grant WB *et al.* (2018) Vitamin D supplementation guidelines. *J. Steroid. Biochem. Mol. Biol.* **175**: 125–135. https://doi.org/10.1016/j.jsbmb.2017.01.021

Rajpara SM, King CM (2005) Hailey-Hailey disease responsive to topical calcitriol. *Br. J. Dermatol.* **152**: 816–817. https://doi.org/10.1111/j.1365-2133.2005.06489.x

Sarre ME, Annweiler C, Legrand E, Martin L, Beauchet O (2016) Association between bullous pemphigoid and hypovitaminosis D in older inpatients: Results from a case-control study. *Eur. J. Intern. Med.* **31**: 25–28. https://doi.org/10.1016/j.ejim.2016.02.004

Schmidt E, Reimer S, Kruse N, Jainta S, Bröcker EB, Marinkovich MP, Giudice GJ, Zillikens D (2000) Autoantibodies to BP180 associated with bullous pemphigoid release interleukin-6 and interleukin-8 from cultured human keratinocytes. *J. Invest. Dermatol.* **115**: 842–848

Schmidt E, Zillikens D (2013) Pemphigoid diseases. *Lancet* **381**: 320–332. https://doi.org/10.1016/S0140-6736(12)61140-4.

Schmidt E, Kasperkiewicz M, Joly P (2019) Pemphigus. *Lancet.* **394**: 882–894. https://doi.org/10.1016/S0140-6736(19)31778-7

Slominski AT, Kim TK, Shehabi HZ, Semak I, Tang EK, Nguyen MN, Benson HA, Korik E, Janjetovic Z, Chen J, Yates CR, Postlethwaite A, Li W, Tuckey RC (2012) *In vivo* evidence for a novel pathway of vitamin D_2 metabolism initiated by P450scc and modified by CYP27B1. *FASEB J.* **26**: 3901–3915. https://doi.org/10.1096/fj.12-208975

Slominski AT, Kim TK, Shehabi HZ, Tang EK, Benson HA, Semak I, Lin Z, Yates CR, Wang J, Li W, Tuckey RC (2014a) *In vivo* production of novel vitamin D_2 hydroxy-derivatives by human placentas, epidermal keratinocytes, Caco-2 colon cells and the adrenal gland. *Mol. Cell. Endocrinol.* **383**: 181–192. https://doi.org/10.1016/j.mce.2013.12.012

Slominski AT, Kim TK, Takeda Y, Janjetovic Z, Brozyna AA, Skobowiat C, Wang J, Postlethwaite A, Li W, Tuckey RC, Jetten AM (2014b) RORα and ROR γ are expressed in human skin and serve as receptors for endogenously produced noncalcemic 20-hydroxy- and 20,23-dihydroxyvitamin D. *FASEB J.* **28**: 2775–2789. https://doi.org/10.1096/fj.13-242040

Slominski AT, Li W, Kim TK, Semak I, Wang J, Zjawiony JK, Tuckey RC (2015a) Novel activities of CYP11A1 and their potential physiological significance. *J. Steroid. Biochem. Mol. Biol.* **151**: 25–37. https://doi.org/10.1016/j.jsbmb.2014.11.010

Slominski AT, Kim TK, Li W, Postlethwaite A, Tieu EW, Tang EKY, Tuckey RC (2015b) Detection of novel CYP11A1-derived secosteroids in the human epidermis and serum and pig adrenal gland. *Sci. Rep.* **5**: 14875. https://doi.org/10.1038/srep14875

Slominski AT, Kim TK, Hobrath JV, Oak ASW, Tang EKY, Tieu EW, Li W, Tuckey RC, Jetten AM (2017) Endogenously produced nonclassical vitamin D hydroxy-metabolites act as "biased" agonists on VDR and inverse agonists on RORα and RORγ. *J. Steroid. Biochem. Mol. Biol.* **173**: 42–56. https://doi.org/10.1016/j.jsbmb.2016.09.024

Slominski AT, Kim TK, Janjetovic Z, Brożyna AA, Żmijewski MA, Xu H, Sutter TR, Tuckey RC, Jetten AM, Crossman DK (2018) Differential and overlapping effects of 20,23(OH)-D3 and 1,25(OH)-D3 on gene expression in human epidermal keratinocytes: identification of ahr as an alternative receptor for 20,23(OH)-D3. *Int. J. Mol. Sci.* **19**: 3072. https://doi.org/10.3390/ijms19103072

Takeda M, Yamashita T, Sasaki N, Nakajima K, Kita T, Shinohara M, Ishida T, Hirata K (2010) Oral administration of an active form of vitamin D3 (calcitriol) decreases atherosclerosis in mice by inducing regulatory T cells and immature dendritic cells with tolerogenic functions. *Arterioscler. Thromb. Vasc. Biol.* **30**: 2495–503. https://doi.org/10.1161/ATVBAHA.110.215459

Tukaj S, Schmidt E, Recke A, Ludwig RJ, Zillikens D, Tukaj C, Kasperkiewicz M (2013) Vitamin D status in patients with bullous pemphigoid. *Br. J. Dermatol.* **168**: 873–874. https://doi.org/10.1111/bjd.12037

Tukaj S, Tiburzy B, Manz R, de Castro Marques A, Orosz A, Ludwig RJ, Zillikens D, Kasperkiewicz M (2014) Immunomodulatory effects of heat shock protein 90 inhibition on humoral immune responses. *Exp. Dermatol.* **23**: 585–590. https://doi.org/10.1111/exd.12476

Tukaj S, Grüner D, Tukaj C, Zillikens D, Kasperkiewicz M (2016) Calcitriol exerts anti-inflammatory effects in keratinocytes treated with autoantibodies from a patient with bullous pemphigoid. *J. Eur. Acad. Dermatol. Venereol.* **30**: 288–292. https://doi.org/10.1111/jdv.12929

Tukaj S, Bieber K, Witte M, Ghorbanalipoor S, Schmidt E, Zillikens D, Ludwig RJ, Kasperkiewicz M (2018) Calcitriol treatment ameliorates inflammation and blistering in mouse models of epidermolysis bullosa acquisita. *J. Invest. Dermatol.* **138**: 301–309. https://doi.org/10.1016/j.jid.2017.09.009

Umar M, Sastry KS, Al Ali F, Al-Khulaifi M, Wang E, Chouchane AI (2018) Vitamin D and the pathophysiology of inflammatory skin diseases. *Skin Pharmacol. Physiol.* **31**: 74–86. https://doi.org/10.1159/000485132

Vorobyev A, Ludwig RJ, Schmidt E (2017) Clinical features and diagnosis of epidermolysis bullosa acquisita. *Expert Rev. Clin. Immunol.* **13**: 157–169. https://doi.org/10.1080/1744666X.2016.1221343

Witte M, Zillikens D, Schmidt E (2018) Diagnosis of autoimmune blistering diseases. *Front Med. (Lausanne)* **5**: 296. https://doi.org/10.3389/fmed.2018.00296

Xing C, Xu A (2012) The effect of combined calcipotriol and betamethasone dipropionate ointment in the treatment of vitiligo: an open, uncontrolled trial. *J. Drugs. Dermatol.* **11**: e52–e54

Yang CY, Leung PS, Adamopoulos IE, Gershwin ME (2013) The implication of vitamin D and autoimmunity: a comprehensive review. *Clin. Rev. Allergy Immunol.* **45**: 217–226. https://doi.org/10.1007/s12016-013-8361-3

Zarei M, Javanbakht MH, Chams-Davatchi C, Daneshpazhooh M, Eshraghian MR, DE-Rakhshanian H, Djalali M (2014) Evaluation of Vitamin D status in newly diagnosed pemphigus vulgaris patients. *Iran J. Public Health.* **43**: 1544–1549. PMCID: PMC4449504