Endocrine functions of vitamin D

The name “vitamin D” for the fat-soluble secosteroid cholecalciferol implies that humans need to take up this molecule via their diet since their own catabolism may not be able to produce it. In contrast, at UV-B (290–315 nm) exposure human skin is able to synthesize vitamin D on the basis of the cholesterol precursor 7-dehydrocholesterol. Thus, insufficient exposure to sunlight in populations living at Northern latitudes and/or primarily indoors made the vitamin D status of many individuals dependent on diet, such as fatty fish, and cod oil supplementation. This led to the misleading classification of the molecule as a vitamin. Vitamin D itself is biologically inert, but its metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D, also referred to as calcitriol) is a high-affinity ligand of the transcription factor vitamin D receptor (VDR). The nuclear receptor VDR is expressed in the majority of human tissues and cell types, in particular in peritubular gland, parathyroid gland, small intestine, colon, kidney, skin and many cell types of the immune system, and controls the transcription of in total more than 1000 genes. Thus, vitamin D is a pre-hormone that via its hormonal metabolite 1,25(OH)2D has endocrine regulatory functions on a larger number of physiological processes, many of which are discussed in the 14 review articles of this Special Issue.

The issue starts with a reflection how bioinformatic analysis of recently obtained large-scale data, such as chromatin immunoprecipitation sequencing (ChIP-seq) of VDR in various cellular systems, genome-wide association studies for multiple common diseases or whole genome sequencing of more than 10,000 cancer patients, can provide an unbiased view on the physiological impact of vitamin D signaling (Campbell, 2017). The article concludes that vitamin D and its receptor are implicated in bone biology and the function of the immune system, but there is no indication that VDR is directly involved in tumorigenesis. Large-scale data are also discussed in the following review (Carlberg, 2017) but with focus on the epigenome, i.e. on the packaging of the genome within chromatin, and its impact on vitamin D-regulated gene expression. The integration of a larger set of genome- and transcriptome-wide data that were all obtained under identical conditions in human monocytes (THP-1) proposes a model of epigenomic vitamin D signaling that may serve also for other tissues and cell types: i) in the absence of 1,25(OH)2D VDR binds to a limited number of chromatin loci, ii) ligand stimulation increases VDR binding both in number of loci as well as in strength, iii) pioneer transcription factors support the access of VDR to genomic DNA, iv) vitamin D stimulation and VDR binding increase chromatin accessibility at several thousand sites, v) as a consequence of which the binding of the chromatin organizing transcription factor CTCF and its formation of topologically associating domains is modulated. Taken together, vitamin D significantly affects the epigenome of its target tissues before and while the transcriptome is stimulated. A third review on the mechanistic actions of VDR focuses on the structural aspects of vitamin D endocrinology (Rochel and Molnar, 2017). The analyses of crystal structures of VDR, the vitamin D transport protein DBP and the vitamin D metabolizing enzymes CYP2R1 and CYP24A1, provide atomic scale insight on the mechanisms of vitamin D signaling on the level of protein structure. This structural perspective nicely complements the bioinformatic and epigenomic views on the endocrinology of vitamin D and provides mechanistic explanations on a number of vitamin D-associated diseases, such as hereditary vitamin D-resistant rickets.

The evolutionary oldest and probably still prime physiological action of vitamin D endocrinology, the control of calcium homeostasis, is discussed next (Fleet, 2017). Vitamin D regulates serum calcium within a very narrow range by coordinating the action of small intestine, kidney, bone and parathyroid gland, tissues in which largest VDR expression is found. In turn, aging, growth, pregnancy and menopause as well as dietary calcium intake modulate the production of 1,25(OH)2D and by this the activity of VDR in multiple tissues. The main purpose of calcium homeostasis is to assure sufficient calcium delivery for bone mineralization, as discussed by the following review (van Driel and van Leeuwen, 2017). Since bone is a dynamic tissue in equilibrium between resorption of its extra-cellular matrix by macrophage-type osteoclast and its formation by osteoblasts, bone maintenance is critically dependent on vitamin D and other hormones, such as parathyroid hormone and glucocorticoids. Osteoblasts are the key cell type in human bone mineralization and they are stimulated by 1,25(OH)2D. VDR expression levels change during the osteoblast differentiation process, which is of critical impact for the network of VDR target genes in these cells. The following two reviews discuss another important physiological function of vitamin D, the modulation of the immune system, i.e. its gene regulatory effects on cells of the innate (monocytes, macrophages and dendritic cells) and adaptive immune system (B and T lymphocytes). A number of key mediators of immune signaling, such as cytokines and membrane proteins, are primary and secondary vitamin D target genes, but interestingly also many members of metabolic pathways, such as enzymes and transporters, are VDR targets in immune cells (Vanhersen et al., 2017). The metabolic states of immune subsets are very dynamic and vitamin D appears to be a key regulator of this immune-metabolism. The insight that cellular metabolism shapes the phenotype of immune cells allows a more detailed understanding of the role of vitamin D in inflammation and autoimmune diseases and their possible therapy. Inflammatory bowel disease (IBD), in particular its sub-form Crohn's disease, is one of these chronic diseases, the conditions of which were shown to be improved by vitamin D supplementation (Dimitrov and White, 2017). Vitamin D target genes encoding for pattern recognition receptors, anti-
microbial peptides and cytokines in innate immune cells located within the intestine are involved in sensing microbiota, in preventing their overgrowth and in enhancing the intestinal barrier function. In parallel, vitamin D stimulates the differentiation of T cells into a tolerogenic phenotype. This demonstrates that immune-modulatory effects of vitamin D on the innate and adaptive immune system are critical for barrier integrity in the gut and its microbial load and composition.

Three review articles connect the endocrinology of vitamin D with cellular growth. The double function of vitamin D in small intestine and colon, i.e. absorption of calcium and barrier function, emphasizes its critical role in gut physiology and homeostasis (Barbachano et al., 2017). In turn, vitamin D deficiency is associated with an increased risk of colorectal cancer. This suggests that vitamin D and its synthetic analogues have the potential to prevent and/or treat this common type of cancer, a finding that is supported by bioinformatic analysis of large-scale tumor data (Campbell, 2017). The cell growth regulatory potential of vitamin D was first discovered with another very common type of cancer, breast carcinoma (Welsh, 2017). VDR is expressed in normal mammary gland and in many human breast cancer cell lines. However, although there is pre-clinical evidence that vitamin D supplementation affects breast cancer development and progression, clinical trials could not yet support this claim. Since skin is the site of vitamin D production, while in turn UV exposure can cause DNA damage, vitamin D endocrinology of this organ evolved to prevent carcinogenesis (Reichrath et al., 2017). Mechanistically this effect can be explained, at least in part, by the functional interference of VDR with members of the p53 family of tumor suppressors.

The next review discusses the initially rather unexpected function of vitamin D on reproduction (Lorenzen et al., 2017). VDR is expressed in reproductive organs, such as testis and uterus, and modulates the production and release of reproductive hormones, such as testosterone (converted to 80% to estradiol) and testicular peptide hormones, into circulation. This suggests that vitamin D is beneficial for male and female fertility. Interestingly, also during pregnancy vitamin D plays an important role (Hollis and Wagner, 2017). Circulating 1,25(OH)2D levels drastically increase in early pregnancy, probably in order to boost the immune system of both mother and fetus. Vitamin D metabolism during pregnancy is clearly different and vitamin D supplementation protocols for mothers need to be adapted.

The last two reviews link vitamin D endocrinology with the brain and aging. Vitamin D acts as neurosteroid and has a significant role in brain development, neurotransmission and neuroprotection (Cui et al., 2017). Most of these functions are mediated via the regulation of VDR target genes, but some very rapid responses seem to be based on non-nuclear localization of VDR. These regulatory effects of vitamin D are linked to brain ontogeny as well as to functional neurochemical and behavioral outcomes. Vitamin D deficiency during brain development can lead to schizophrenia and autism and in elderly persons it is associated with cognitive impairment and neurodegeneration. The latter is in part due to the fact that during aging vitamin D metabolism and activity changes (de Jongh et al., 2017). This includes reduced intestinal calcium uptake and lower expression of VDR and vitamin D metabolizing enzymes. Thus, appropriate vitamin D supplementation of elderly has positive effects on fracture risk, number of falls and physical function.

In summary, the 14 review articles of this Special Issue present the wide physiological impact of vitamin D endocrinology ranging from the tight control of calcium homeostasis and bone formation to the modulation of innate and adaptive immunity. Vitamin D endocrinology affects chronic inflammatory diseases, cancer, fertility and neurodegeneration and needs to be appropriately triggered by vitamin D supplementation during pregnancy as well as in aging.

References

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