



# The physiology of vitamin D—far more than calcium and bone

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Vitamin D is a molecule displaying an important physiological impact. Average human diet is neither rich in vitamin D<sub>2</sub> (of plant origin) nor in vitamin D<sub>3</sub> (of animal origin). Therefore, humans have to rely on the endogenous production of vitamin D<sub>3</sub> in UVB exposed skin. This process was an important evolutionary driver for skin lightening after our ancestors decided some 100,000 years ago to move North out of Africa toward Asia and Europe (Juzeniene et al., 2009). Did this happen only to extract calcium efficiently from our diet and to keep our bones strong?

Vitamin D<sub>3</sub> exerts most, if not all, of its physiological effects via its metabolite 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>), which acts as a nuclear hormone, since it is the only high affinity ligand for the transcription factor vitamin D receptor (VDR). VDR is expressed in the majority of human tissues and cell types, i.e., at far more places than needed for calcium homeostasis and proper bone formation. The aim of this Research Topic is to explore the physiology of vitamin D from the perspective of the genome-wide distribution of VDR-binding sites in cells as different as B lymphocytes, monocytes, macrophages, colon cancer cells, and hepatic stellate cells (Tuoesmäki et al., 2014). The choice of these cell types as experimental models is already a clear indication that the physiology of vitamin D involves also actions on the adaptive and innate immune system and on cancer cells.

This Research Topic starts with an overview on the recently explored genome-wide locations of VDR and their link to the accessibility of chromatin and its 3-dimensional organization (Carlberg, 2014). This genomic view is extended by a structural view on the interaction of the VDR with DNA, natural and synthetic ligands and co-regulatory proteins (Molnar, 2014). The VDR-mediated genome-wide actions of vitamin D result in a change of the transcriptome in all VDR expressing tissues and cell types. Taking all human tissues together this does not only affect thousands of protein-coding mRNAs but also a comparable number of non-coding RNAs (Campbell, 2014). The signal transduction of the lipophilic molecule 1,25(OH)<sub>2</sub>D<sub>3</sub> is straightforward, since it reaches the VDR directly in the nucleus. Nevertheless, vitamin D signaling functionally interacts with a number of other signal transduction pathways, many of which start with receptors at the cell membrane (Larriba et al., 2014). The introductory section of this Research Topic is complemented by a view on the epigenome-wide effects of vitamin D, such as DNA methylation and histone modifications (Fetahu et al., 2014).

The general physiological function of vitamin D is to keep us healthy by promoting strong bones, properly functioning muscles and a potent immune system. When weather and season allows, we can keep our vitamin D levels up through endogenous production during carefully dosed exposure to sunlight (Reichrath et al., 2014). However, at winter above latitudes of 40° North or below 40° South insufficient amounts of UVB radiation pass the atmosphere. This implies that at least during winter we have to consider vitamin D as an essential micronutrient that we should supplement via fortified food compounds, such as milk and margarine, or appropriately dosed pills (Bendik et al., 2014). Both sun exposure in summer and supplementation during winter should keep our vitamin D status on an optimal level, which most likely is individual for each of us (Carlberg et al., 2013). Under these conditions cells of our innate and our adaptive immune system, such as monocytes and macrophage as well as B and T lymphocytes, can take maximal benefit from the gene regulatory potential of vitamin D (Chun et al., 2014).

In addition to the cells of the immune system VDR is expressed in most other tissues that origin from mesenchymal cells, such as bone (Van De Peppel and Van Leeuwen, 2014), myocytes (Polly and Tan, 2014), and adipose tissue (Mutt et al., 2014). This demonstrates that the well-known role of vitamin D in bone extrapolates to skeletal muscle and fat.

Most common diseases, such as type 2 diabetes, cancer and autoimmune diseases, are associated with chronic inflammation. Inflammation is mediated by tissue-associated macrophages, dendritic cells, and T lymphocytes, in which vitamin D has important gene regulatory functions (Wöbke et al., 2014). This may also be a key mechanism for the beneficial effects of vitamin D in cancers of breast (Narvaez et al., 2014) and prostate (Wang and Tenniswood, 2014). Furthermore, the pleiotropy of vitamin D suggests additional mechanisms for its anti-cancer effects, such as the modulation of intracellular metabolism. However, in case when supra-physiological concentrations of 1,25(OH)<sub>2</sub>D<sub>3</sub> would be required, in order to obtain a therapeutic effect, the application of synthetic vitamin D analogs is suggested (Leyssens et al., 2014).

Taken together, the 15 chapters of this Research Topic present the wide physiological impact of vitamin D and link it to its molecular basis, which is the genome-wide action of the transcription factor VDR in most human tissues and cell types.

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