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Editorial

Therapeutic Applications of Vitamin D

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Vitamin D is a secosteroid hormone produced physiologically or obtained from food. The conventional pathway of vitamin D synthesis includes three steps. First, vitamin D is synthesized in the skin from 7-dehydrocholesterol. Then, the skin-derived vitamin D is converted to 25-hydroxyvitamin D (25(OH)D) by 25-hydroxylase in the liver. Finally, 25(OH)D is further converted to active vitamin D, *i.e.*, $1,25(OH)_2D$, in the kidney by 25-hydroxyvitamin D 1α-hydroxylase (1α-hydroxylase). $1,25(OH)_2D$ executes its biological functions by binding to the nuclear vitamin D receptor (nVDR) and is eventually metabolized into biologically inactive calcitroic acid by 24-hydroxylase. The study of this conventional metabolic pathway led to the discovery of the classic functions of $1,25(OH)_2D$, *i.e.*, regulation of calcium and phosphate metabolisms. These classic functions are achieved via the action of $1,25(OH)_2D$ in the kidneys, intestines, and bones.

Despite the early detection of extra-renal 1α-hydroxylase [1], $1,25(OH)_2D$ produced in extra-renal tissues has only been intensively investigated in the past two decades. It has been found that the nVDR is widely expressed, and $1,25(OH)_2D$ has many non-classical functions. For example, $1,25(OH)_2D$ can regulate immune responses by stimulating $CD4^+$ regulatory T cells (Tregs) by directly upregulating the expression of regulatory molecules (*e.g.*, forkhead box P3 and interleukin 10) in $CD4^+$ T cells [2] and indirectly tolerizing dendritic cells [3]. In addition, the VDR is essential for the normal function of intestinal stem cells [4]. Moreover, $1,25(OH)_2D$ enhances the differentiation of intestinal stem cells without compromising their stemness [5,6]. Because there are currently no effective medications for repairing damaged tissues caused by autoimmune diseases, these findings suggest that the regenerative function of $1,25(OH)_2D$ can be harnessed as a novel therapy for these diseases.

Promising preclinical data have led to numerous large clinical trials of vitamin D supplementation for treating autoimmune diseases (*e.g.*, multiple sclerosis, type 1 diabetes, and inflammatory bowel disease). However, these clinical trials did not produce the expected outcomes. Consequently, current strategies to harness the non-classical functions of $1,25(OH)_2D$ in humans are not fully optimized [7,8].

Several clinical trials testing vitamin D supplementation failed due to safety concerns, which precluded dose escalations. Many newly discovered functions of $1,25(OH)_2D$ require concentrations that are significantly higher than physiological blood levels and lead to hypercalcemia if present systemically [5]. Hypercalcemia refers to a condition where blood calcium levels are significantly elevated, which can lead to severe consequences. Accordingly, two primary strategies have been proposed to address hypercalcemia: using low-calcemic $1,25(OH)_2D$ analogs and promoting tissue-specific *de novo* synthesis of locally high $1,25(OH)_2D$ concentrations.

Low-calcemic $1,25(OH)_2D$ analogs have been extensively investigated for treating human diseases such as secondary hyperparathyroidism and cancer [9]. The detailed mechanisms by which these $1,25(OH)_2D$ analogs execute other biological functions while reducing the risk of hypercalcemia are not fully understood. Recent data suggest that these analogs can still cause hypercalcemia if present in high concentrations in the bloodstream [10]. In addition, these analogs may have other biological functions that differ from $1,25(OH)_2D$. Hence, low-calcemic analogs may not be effective at the same concentrations required for optimally executing the full range of non-classical $1,25(OH)_2D$ functions. Accordingly, preclinical data are lacking that support the use of these analogs for autoimmune disease treatment.

We propose that overexpressing 1α-hydroxylase in immune cells that have tissue-specific targeting capability, *e.g.*, dendritic cells (DCs), which can specifically home to lymphoid tissues, allows for local, *de novo* tissue-specific synthesis of high concentrations in a defined tissue without causing hypercalcemia. Upon *in vivo* injection, the engineered immune cells migrate specifically to the targeted tissue where overexpressed 1α-hydroxylase *de novo* synthesizes locally high $1,25(OH)_2D$ concentrations. Due to the short half-life of $1,25(OH)_2D$, the *de novo* synthesized locally high $1,25(OH)_2D$ concentrations work via a paracrine mode and do not induce hypercalcemia. To this end, we have shown that 1α-hydroxylase-overexpressing DCs deliver locally high $1,25(OH)_2D$ concentrations in peripheral lymphoid tissues to stimulate $CD4^+$ Tregs, conferring myelin-specific suppression of experimental autoim-

mune encephalomyelitis (animal model of human multiple sclerosis) without inducing hypercalcemia [11,12]. Using inflammation- and gut-homing macrophages overexpressing the 1α-hydroxylase enzyme, we demonstrated that the locally high 1,25$(OH)_2$D concentrations are delivered to inflamed intestines without causing hypercalcemia, enhancing the differentiation of intestinal stem cells without compromising their stemness [5,6].

Because low-calcemic analogs can still cause hypercalcemia at high concentrations and may have functions that 1,25$(OH)_2$D does not, the *de novo* synthesis of locally high 1,25$(OH)_2$D concentrations has the unique advantage of not causing hypercalcemia in all disease models that we evaluated. Hence, our data strongly support that *de novo* synthesis of locally high 1,25$(OH)_2$D concentrations is a valid therapeutic strategy for tissue-specific autoimmune diseases and other diseases linked to vitamin D deficiencies [13,14]. Challenges to clinical translation may include the need for autologous immune cells as well as potential off-target effects, which our laboratory is addressing.

In conclusion, significant progress has been made in harnessing the novel 1,25$(OH)_2$D therapeutic functions while minimizing the risk of hypercalcemia. However, several outstanding questions remain. The mechanisms that separate 1,25$(OH)_2$D's calcium effect from other biological functions are not fully understood, which is necessary for improving the design of 1,25$(OH)_2$D analogs. Although some studies using cell-specific ablation of the 1α-hydroxylase indicate that local endogenous 1α-hydroxylase activation plays a vital role in regulating tissue functions, the physiological roles of 1α-hydroxylase in most tissues remain unknown. In addition, it has been shown that 1,25$(OH)_2$D can also function via membrane VDRs (mVDRs) [15]. However, the rapid response (usually minutes) of mVDRs suggest that they do not trigger new gene expression and may not have long-term biological consequences, which require more studies. Moreover, investigations are also needed to understand how the two strategies reshape 1,25$(OH)_2$D metabolism in tissues. Finally, how these novel delivery strategies work with existing therapies warrants further investigation.

Author Contributions

XT conceptualized, directed, and supervised all the studies and is accountable for all aspects of the work. XT wrote, edited, and approved the final version of this manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Given his role as the Guest Editor and Editorial Board member, Xiaolei Tang had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Graham Pawelec.

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