Vitamin D, -nuclear receptor-independent actions, in primary sclerosing cholangitis: Potential role of protein disulfide isomerase family A member 3 (PDIA3) as a therapeutic target

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The project has been completed by the end of 2020, and the results have been published in BBA – Molecular Basis of Disease : https://doi.org/10.1016/j.bbadis.2020.166067

Lay summary

Vitamin D deficiency is common in chronic liver diseases, notably cholestatic liver diseases, where it is associated with increased inflammation and fibrosis. Two vitamin D receptors have been identified. A nuclear receptor, the vitamin D receptor (VDR), is the best characterized. A membrane-associated receptor, protein disulfide-isomerase A3 (PDIA3), has also been described. To evaluate the protective functions of VDR in PSC, we invalidated *Vdr* expression in *Abcb4* knockout mice, a widely used model of PSC. We also evaluated the potential of vitamin D and calcipotriol, a vitamin D analog to exert protective effects in this model and in cholangiocyte cell models.

We found that the lack of VDR aggravated PSC features (*i.e*, cholestasis, ductular reaction, inflammation and fibrosis) in the *Abcb4* knockout mice. The proinflammatory phenotype of cholangiocytes was also exacerbated as a result of *VDR* silencing in these cells. Unexpectedly, the treatment with calcipotriol, or vitamin D supplementation, alleviated PSC features in the *Abcb4;Vdr* double knockout mice but not in the *Abcb4*

simple knockout mice. Likewise, calcipotriol ameliorated the proinflammatory phenotype of cholangiocytes lacking VDR, and this beneficial effect was abolished by *PDIA3* silencing.

In conclusion, ours results demonstrate anti-inflammatory functions of VDR signaling in cholangiocytes and in a PSC mouse model. They indicate that PDIA3 mediates VDR-independent anti-inflammatory effects of vitamin D and calcipotriol in these settings. Therefore, while a treatment aimed to maintain normal levels of vitamin D may be sufficient in a large number of patients with PSC, a subset of patients would benefit from supra-physiological doses of vitamin D acting *via* PDIA3, *e.g.*, patients with *VDR* gene variants that lead to low VDR expression in the liver. Our results also provide rationale to therapeutically target PDIA3, which may be of clinical interest regardless of VDR expression status.