IMMUNE REGULATION

Vitamin D shuts down T cell-mediated inflammation

> complement stimulates T cells to both activate and respond to vitamin D

The importance of maintaining a balance between inflammatory responses necessary for pathogen clearance and their timely resolution to prevent tissue damage is clearly exemplified by patients with severe COVID-19, who develop life-threatening hyper-inflammation characterized by high levels of complement activation. Complement itself has been shown to drive both the differentiation of interferon-γ (IFNγ)-producing T helper 1 (T_H1) cells as well as the eventual shutdown of their pro-inflammatory features through IL-10 expression. This study by Chauss et al. links the complement-mediated retraction of T_H1 cell responses to vitamin D receptor (VDR) signalling, which provides a possible mechanistic explanation for the epidemiological associations between vitamin D deficiency and adverse outcomes in COVID-19 and potentially other infectious diseases.

Single-cell RNA sequencing of $CD4^+$ T cells from the blood and bronchoalveolar lavage fluid (BALF) of eight patients with COVID-19 showed that they have a prominent pro-inflammatory T_H1 cell signature, enriched for IFNγ and complement pathway genes, but with lower levels of expression of *IL10* than $CD4^+$ T cells from healthy controls. To better understand the pro-inflammatory nature of these COVID-19-associated T_H1 cells, the authors looked in more detail at the previously described effects of complement on contraction of T_H1 cell responses. Transcriptomic analysis of $CD4^+$ T cells activated with anti-CD3 and anti-CD46 (the receptor for complement component C3b) showed upregulation of both *VDR* and *CYP27B1*, which encodes the enzyme catalysing the final activation step of vitamin D. This suggests that complement stimulates T cells to both activate and respond to vitamin D. T cells from CD46-deficient individuals or T cells treated with an inhibitor that blocks intracellular generation of C3b did not upregulate *VDR* or *CYP27B1*. In response to inactive vitamin D, T cells stimulated with anti-CD3 and anti-CD46 repressed IFNγ expression and upregulated IL-10 expression, suggesting that complement-induced VDR signalling promotes shutdown of T_H1 cell responses.

Further transcriptomic and proteomic analysis showed that vitamin D promotes the production of IL-10 by inducing expression of IL-6, IL-6 receptor (IL-6R) and the transcription factor STAT3, leading to STAT3 phosphorylation and activation downstream of IL-6R. Vitamin D also induced genome-wide changes in histone acetylation and recruitment of transcription factors, including at *STAT3*, *IL10* and *BACH2* loci. A significant proportion of vitamin D-driven transcription was shown to be BACH2 dependent, including *IL6R* transcription. Indeed, vitamin D-treated $CD4^+$ T cells from a *BACH2* haploinsufficient individual did not upregulate the expected vitamin D-dependent gene set, and the IL-6–STAT3–IL-10 signalling axis was disrupted.

Given the observed association of COVID-19 severity with vitamin D deficiency, the authors looked at the expression of vitamin D-regulated genes in the BALF $CD4^+$ T cells of patients with COVID-19. On a per-cell basis, they observed a reciprocal relationship between the expression of T_H1 cell-associated genes and vitamin D-modulated genes. The results suggest that in patients with severe COVID-19, who have a strongly pro-inflammatory T_H1 cell phenotype, the transcriptional response to vitamin D is impaired, leading to a failure to switch to IL-10 production and inflammatory resolution. This could be a result of vitamin D insufficiency or some other dysregulation of complement-induced autoregulatory VDR signalling; in either case, clinical trials may help shed light on whether there is clinical benefit to using vitamin D as an adjunct therapy for COVID-19. Furthermore, IL-6 is generally thought to be a pro-inflammatory cytokine involved in cytokine storm responses, but the results also suggest that vitamin D as adjunct therapy for COVID-19 might divert IL-6 to pro-resolution functions and thus provide an alternative to blocking IL-6R signalling. The researchers did not test vitamin D as an adjunct treatment for COVID-19 and caution the results should not be taken as a clinical recommendation.

Kirsty Minton

Credit: Yulia Reznikov/Getty

ORIGINAL ARTICLE Chauss, D. et al. Autocrine vitamin D signaling switches off pro-inflammatory programs of T_H1 cells. *Nat. Immunol.* https://doi.org/10.1038/s41590-021-01080-3 (2021)