Multiple Sclerosis Journal 2021; 27: (2S) 805–834
P333. (IF = 6.312; 5 yr impact 6.403)

Differentially regulated pathways by endogenous vitamin D in multiple sclerosis identified by transcriptomics of immune cell subsets

W. Yeh[1], M. Gresle[1], R. Lea[2], V. Jokubaitis[1], A. van der Walt[1], M. Jordan[3], A. Baxter[4,5], L. Smith[4], H. Butzkueven[1]

[1]Monash University, Neuroscience, Melbourne, Australia, [2]Queensland University of Technology, Genomics Research Centre, Brisbane, Australia, [3]James Cook University, Immunogenomics, Townsville, Australia, [4]James Cook University, Townsville, Australia, [5]Monash University, Clayton, Australia

Introduction: Vitamin D deficiency is a risk factor for MS. Apart from its role in skeletal health, vitamin D is also recognised to have immunomodulatory effects, which have predominantly been determined by in vitro studies. It remains unclear how vitamin D regulates immune cells in an in vivo setting.

Objectives: We used transcriptomic datasets from immune cell subsets and aimed to identify pathways regulated by vitamin D in vivo, and whether there are differences in pathway regulation between people with MS and healthy controls.

Methods: 73 MS cases and 102 healthy controls had microarray transcriptomic datasets available for at least one immune subset (monocyte, B, CD4, CD8, NK cell), and an independent cohort of 35 MS cases and 33 healthy controls had RNAseq datasets available. Latent variables were identified by RUV-4 or RUVg. Gene expression was corelated with serum 25(OH)D level (LIAISON 25 OH Vitamin D TOTAL assay) using Limma or edgeR. Gene set enrichment analysis (GSEA) was performed using ClusterProfiler and MSigDB. To identify differences in vitamin D-regulated pathways between MS cases and controls, genes whose expressions were correlated differently with 25(OH)D level by case/control status were determined and then used in GSEA.

Results: Vitamin D-related pathways seen across multiple cell types were involved in RNA processing and splicing, mitochondrial function and oxidative phosphorylation, and immune signalling (FDR<0.05). In monocytes, the Gene Ontology term “vitamin D metabolic process” was enriched by genes

downregulated with increasing 25(OH)D level in MS cases compared to controls. The Hallmark gene set “TNF-alpha signalling via NFKB” was enriched by genes downregulated in controls relative to cases. In CD4 cells, interleukin and TNF-alpha signalling gene sets were enriched by genes whose expressions were overall downregulated with increasing 25(OH)D level in cases relative to controls.

Conclusions: Our pathway analyses identified signals for vitamin D regulation of immune function in vivo. These inferred differences in pathway regulation by vitamin D in MS cases and controls suggest differences in response to endogenous vitamin D.

Disclosure

Wei Yeh: nothing to disclose

Melissa Gresle: nothing to disclose

Rodney Lea: nothing to disclose

Vilija Jokubaitis: nothing to disclose

Anneke van der Walt: nothing to disclose

Margaret Jordan: nothing to disclose

Alan Baxter: nothing to disclose

Letitia Smith: nothing to disclose

Helmut Butzkueven: nothing to disclose