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**“Nutrigenomics of vitamin D action in the proximal and
distal intestine”**

by

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Molecular Biology, Genetics, & Cancer Track

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Monday, August 31st, 2020

1:30 P.M.

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ABSTRACT

Although $1,25(\text{OH})_2\text{D}_3$ is critical in the function of the intestine, the mechanisms by which $1,25(\text{OH})_2\text{D}_3$ regulates intestinal biology are unresolved. While most studies have focused on calcium absorption in the proximal intestine, published data from our lab demonstrated that transgenic expression of the vitamin D receptor (VDR) only in the distal intestine (KO/TG mice) reversed VDR dependent rickets. To understand the role of vitamin D in the distal as well as the proximal intestine, this thesis examined VDR target gene expression in the KO/TG mice and compared the findings to vitamin D targets in the intestine of $1,25(\text{OH})_2\text{D}_3$ treated vitamin D deficient mice. The $1,25(\text{OH})_2\text{D}_3$ activated genes in the proximal intestine associated with active calcium transport (*Trpv6*, *S100g*, *Atp2b1*) were also induced in the distal intestine of the KO/TG mice. In addition, one of the genes most induced by $1,25(\text{OH})_2\text{D}_3$ in the proximal and distal intestine was *Slc30a10*, a manganese (Mn) efflux transporter that is critical for protection against neurotoxicity and liver damage occurring in the presence of high Mn levels. Both villus and crypt were found to express high levels of VDR and result in $1,25(\text{OH})_2\text{D}_3$ mediated target gene induction. RNA-seq analysis of human enteroids showed that the effects of $1,25(\text{OH})_2\text{D}_3$ on intestinal target genes (*TRPV6*, *SLC30A10*, *CYP24A1*, *ATP2B1* and *S100G*) are conserved in humans, indicating for the first time direct transcriptomic responses to $1,25(\text{OH})_2\text{D}_3$ in human enteroids in both crypt and villus like compartments. Studies in *Slc30a10*^{-/-} mice showed a loss of cortical bone and a marked decrease in *S100g* and *Trpv6* in the intestine of these mice. Since *Slc30a10* has been reported to use a calcium gradient for active counter ion exchange, these findings suggest that TRPV6, S100g and *Slc30a10* work together in Mn efflux and that $1,25(\text{OH})_2\text{D}_3$ may have a role not only to maintain calcium homeostasis but also in the cellular homeostasis of other divalent ions. These findings also indicate the importance of both crypts and villi, the distal and proximal intestine, and studies in human enteroids to understand $1,25(\text{OH})_2\text{D}_3$ action in intestinal biology.