Vitamin D and Control of Infectious Diseases

John H. White,
Physiology and Medicine, McGill University

Declaration: Nothing to Declare
Disclosure

I have no actual or potential conflict of interest in relation to this program.
Objectives

- Quick overview of the molecular mechanisms of action of vitamin D.
- Evidence for association between vitamin D deficiency and rates of TB infection.
- How vitamin D functions to combat bacterial infections – role of innate immunity.
- Vitamin D and viral infections.
1,25-dihydroxyvitamin D3 Biosynthesis

Provitamin D3

Skin

Liver (Skin)
25-OHase
(CYP2R1, CYP27A1 and others?)

Peripheral Tissues (incl. Skin)
1α-OHase
(CYP27B1)

1,25-dihydroxyvitamin D3

25-hydroxyvitamin D3

VDR

1
2
3
4
5
10
-ormonal vitamin D functions through the nuclear vitamin D receptor (VDR) as a gene “switch”

-s “... makes \... makes protein”,

Vitamin D and TB:
What are the associations?

- **19th Century**: Recognition that solar irradiation was beneficial for patients suffering from tuberculosis.
- **1903**: Niels Finsen awarded Nobel Prize for Medicine for showing UV fights cutaneous TB.
- **1980s**: Associations established between vitamin D deficiency and rates of tuberculosis.
- **1980s**: First studies showing that hormonal vitamin D inhibits replication of *M. tuberculosis* in infected macrophages *in vitro*. 
1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial innate immunity.
Innate Immunity

- The innate immune system comprises the cells and mechanisms that defend the host from infection by other organisms in a non-specific manner.

- The innate system recognizes and responds to pathogens in a generic way, but unlike the adaptive immune system, does not confer long-lasting or protective immunity to the host.

- Innate immune systems provide immediate defense against infection, and are found in all classes of plant and animal life.

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Vitamin D and TB:

Mechanisms of action (1)

Site of mycobacterial infection | Antimicrobial peptide (CAMP) | Overlay

Mycobacterial infection in 1,25D3-treated macrophages
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1,25D3 through the vitamin D receptor directly stimulates the transcription of genes encoding the body’s natural antibiotics – antimicrobial peptides.

Lung epithelial cells treated with 1,25D3 release antimicrobial activity against *E. coli* and *Pseudomonas aeruginosa*. 
Detection of an infection by cells of the immune system stimulates their capacity to respond to circulating levels of 25-hydroxyvitamin D3 and elicit an antimicrobial response.

“Primed” macrophages convert 25D3 to 1,25D3.

The magnitude of the downstream antimicrobial response is strongly dependent on the circulating 25D concentration.
Crohn’s disease (CD):
a defect in innate immunity, a link with vitamin D

- CD arises from a defect in intestinal innate immunity that leads to an inflammatory bowel condition (that leads to an autoimmune response).
- Vitamin D deficiency associated with CD, and rates of CD exhibit a north-south gradient typical of other diseases where vitamin D deficiency is implicated.
- The NOD2 – beta defensin 2 innate immune pathway is compromised or inactive in some patients with CD.
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Senses bacterial infection

NOD2 \[\rightarrow\] \[\rightarrow\] \[\rightarrow\] Beta-defensin 2

Antimicrobial peptide

Production stimulated by 1,25D3

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1,25D3 stimulates beta defensin 2 production in normal macrophages but not macrophages from CD patients with defective NOD2
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The sensitivity of the NOD2-beta defensin 2 innate immune pathway to 1,25D3 argues that vitamin D deficiency plays a causative role in development of CD.
Vitamin D and other infections

- Several studies have provided links between vitamin D deficiency and increased rates of both upper and lower respiratory tract infections, which can arise from a variety of etiological agents, some of which are viral.

- Seasonal variations in influenza outbreaks suggest that vitamin insufficiency may contribute to risk.

- Clinical data suggesting that vitamin D supplementation reduces rates of viral infections and leads to loss of ‘seasonality’ of infections.

White, J.H. Infection & Immunity, 76,3837,2008
Possible antiviral mechanisms of vitamin D

- Antimicrobial peptides (particularly defensins) are active against enveloped viruses.
- Cathelicidin antimicrobial peptide (CAMP/LL37) inhibits replication of HIV isolates.
- NOD2 detects genomes of ssRNA viruses [paramyxoviruses (e.g. RSV), rhabdoviruses (rabies, VSV), and orthomyxoviruses (influenza viruses)], which induces an innate immune response. Mice deficient in NOD2 have impaired antiviral responses. (Nature Immunol, 10, 1073, 2009).
Summary

- Cells of the immune system respond to infection by becoming sensitive to circulating levels 25D3 and converting it to 1,25D3.
- 1,25D3 stimulates antimicrobial innate immunity.
- 1,25D3 is a direct inducer of production of several antimicrobial peptides as well as pathogen sensor NOD2.
- Enhanced production of antimicrobial peptides and NOD2 provide a molecular basis for both antibacterial and antiviral activities of vitamin D.
Collaborators

**White laboratory:**
Tian-Tian Wang,
Luz Tavera-Mendoza,
Fred Nestel,
Basel Dabbas,
Ari Bitton,
Mark Verway

**Mader laboratory:**
David Laperriere,
Veronique Bourdeau

**Behr Laboratory:**
Hafid Souleymane

**Dr. Alain Bitton**
**Dr. Ernest Seidman**
Thank you