Vitamin D and Control of Infectious Diseases

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Declaration: Nothing to Declare

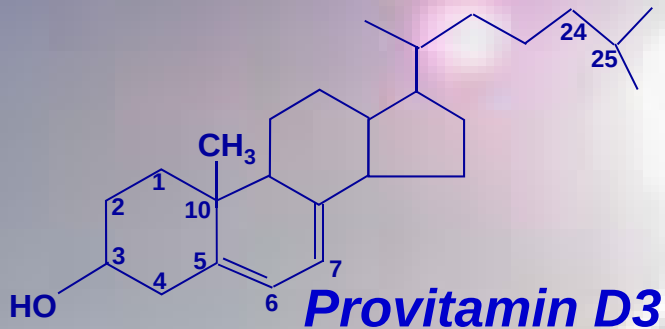
Disclosure

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

Objectives

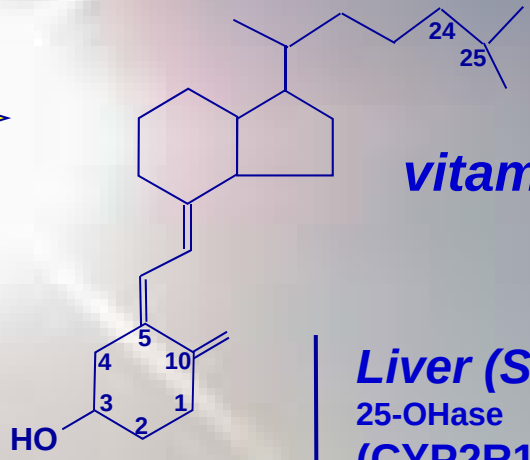
- Quick overview of the molecular mechanisms of action of vitamin D.
- Evidence for association between vitamin D deficiency and rates of TB infection.
- How vitamin D functions to combat bacterial infections – role of innate immunity.
- Vitamin D and viral infections.

1,25-dihydroxyvitamin D3 Biosynthesis



Provitamin D3

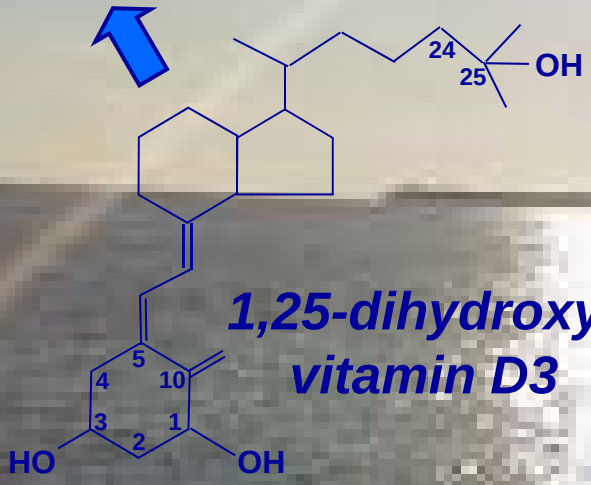
Skin



vitamin D3

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

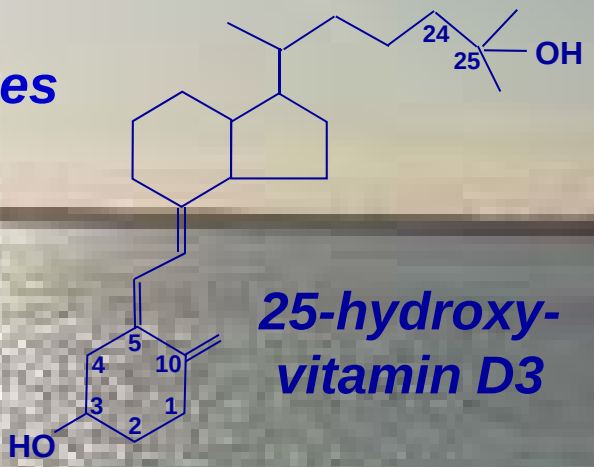
VDR



1,25-dihydroxy-vitamin D3

Peripheral Tissues (incl. Skin)

1α-OHase (CYP27B1)



25-hydroxy-vitamin D3

-ormonal vitamin . functions through the nuclear vitamin . receptor (. \) 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*.

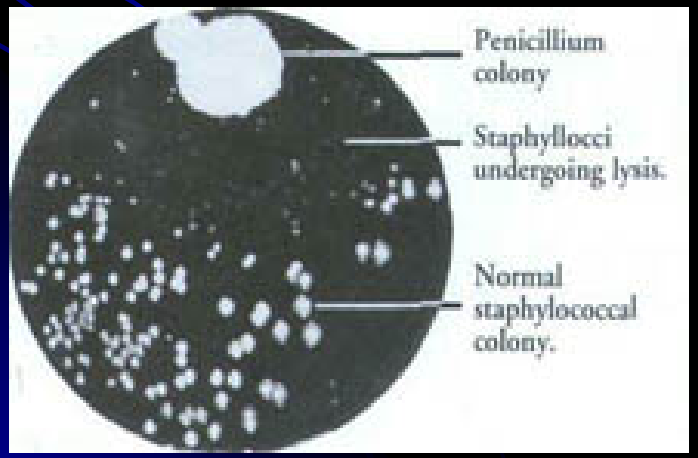
Vitamin D and TB:

Mechanisms of action (1)

- **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.**

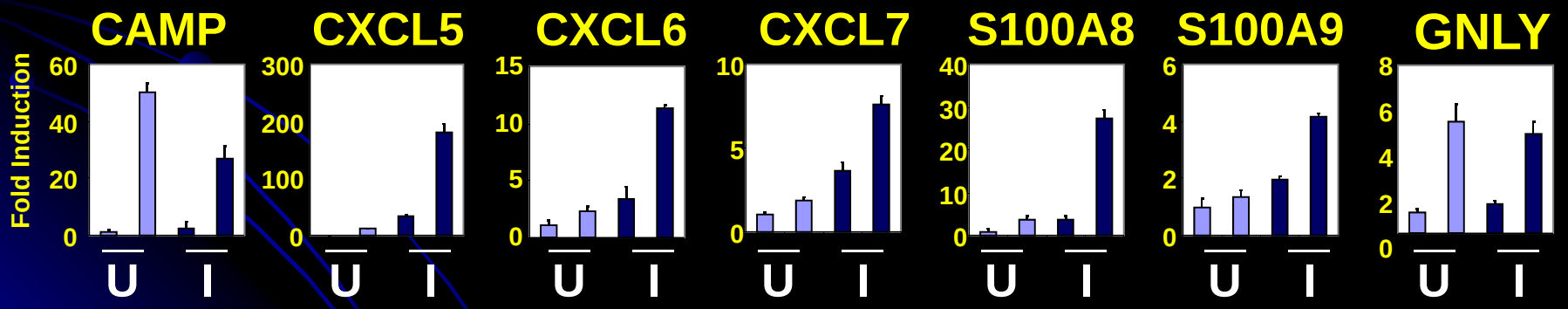


Fleming, A. Brit. J. Exper. Pathol. (1929) X: p.226.

Vitamin D and TB:

Mechanisms of action (1)

- 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial innate immunity.
- **1,25D3 through the vitamin D receptor directly stimulates the transcription of genes encoding the body's natural antibiotics – antimicrobial peptides.**



U - uninfected macrophages
I - TB-infected macrophages

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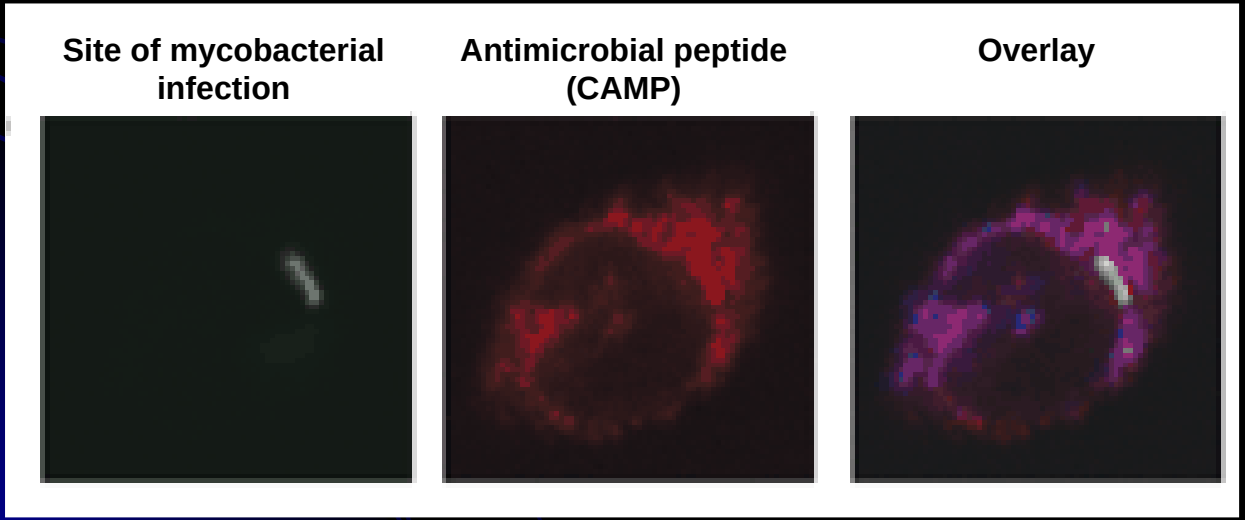

Mycobacterial infection in 1,25D3-treated macrophages

Vitamin D and TB:

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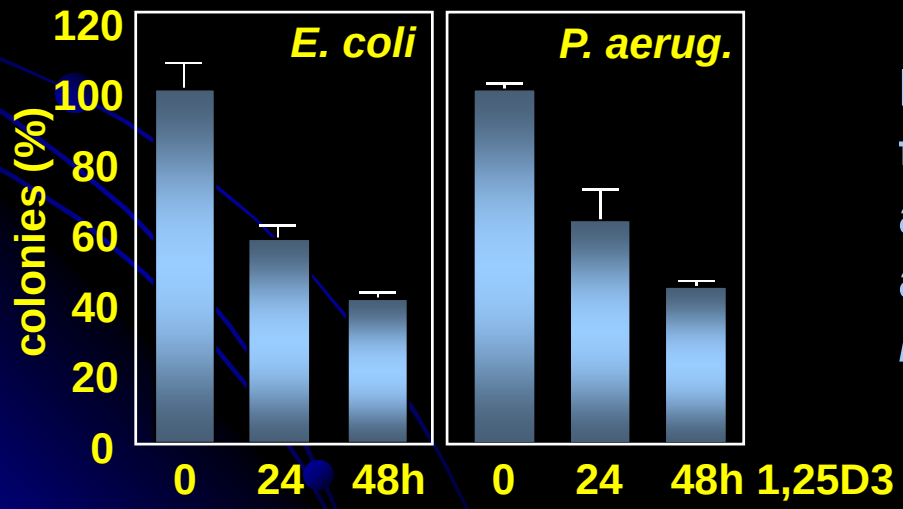
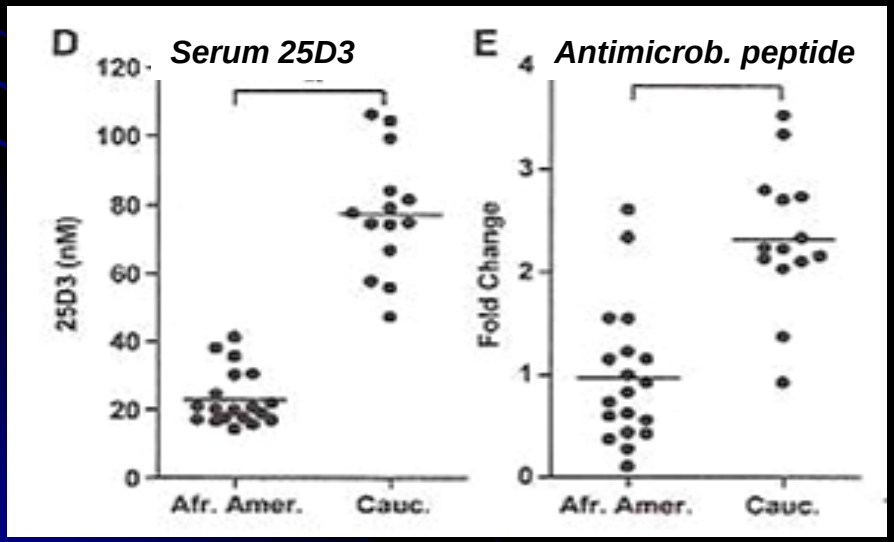


Lung epithelial cells treated with 1,25D3 release antimicrobial activity against *E. coli* and *Pseudomonas aeruginosa*.

Vitamin D and TB:

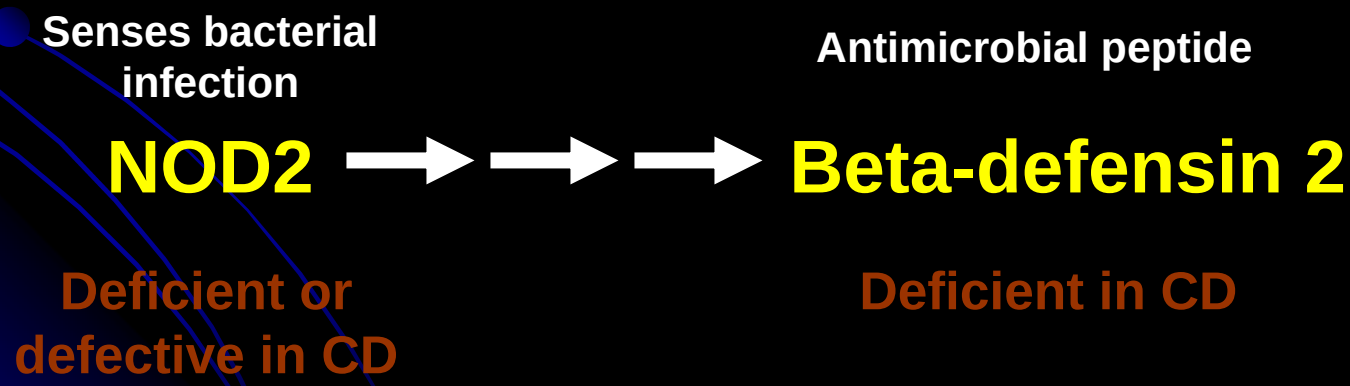
Mechanisms of action (2)

- 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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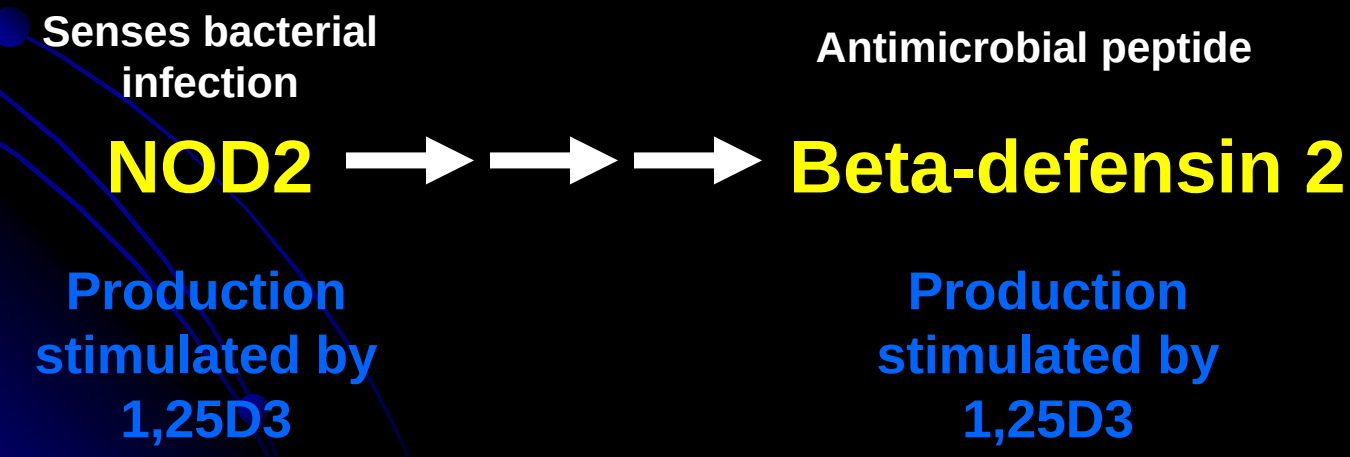

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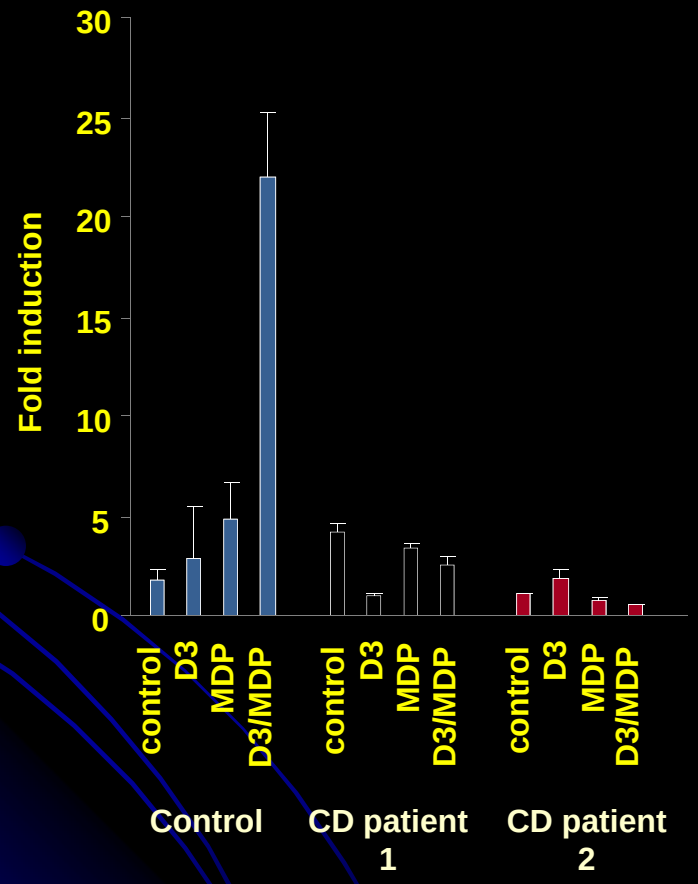

1,25D3 stimulates beta defensin 2 production in normal macrophages but not macrophages from CD patients with defective NOD2

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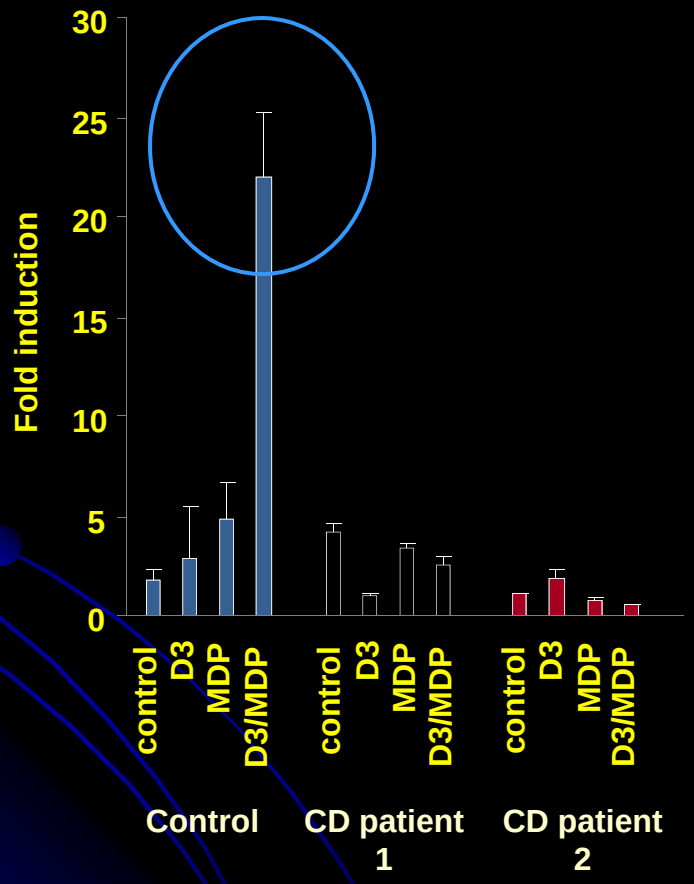
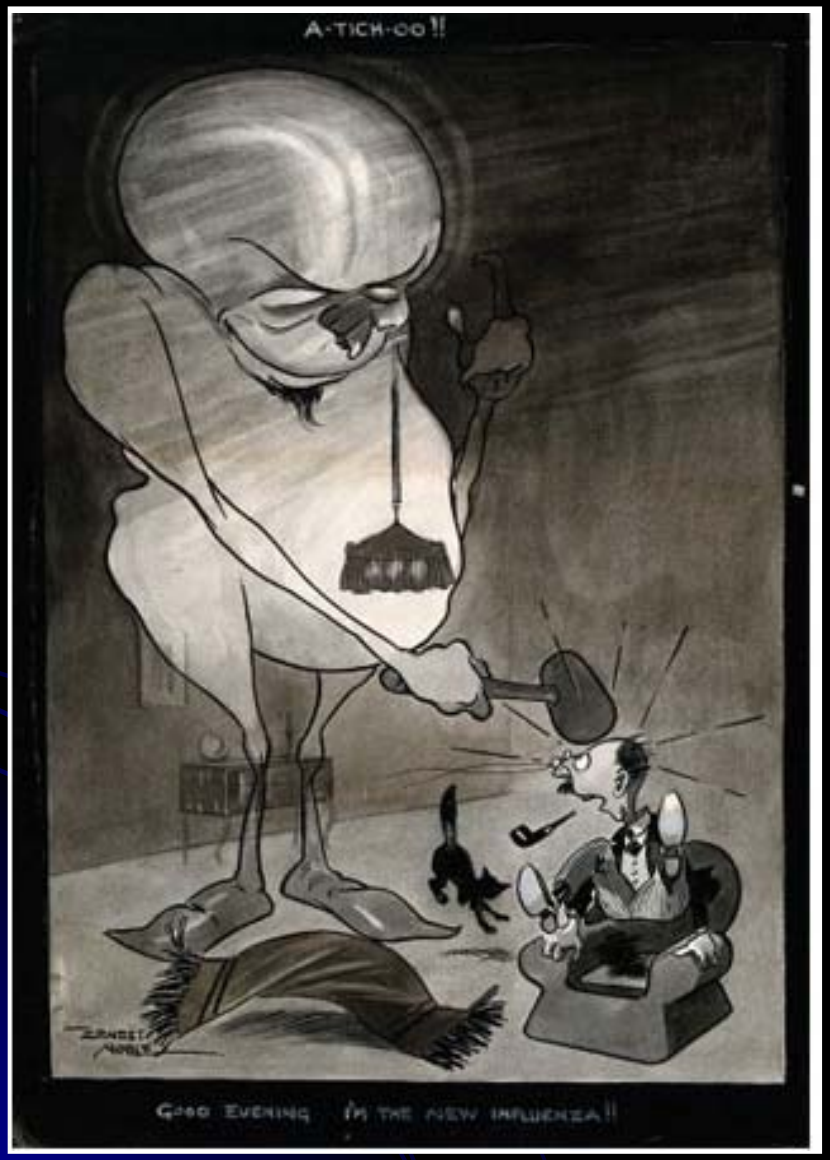


1,25D3 stimulates beta defensin 2 production in normal macrophages but not macrophages from CD patients with defective NOD2

- 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



Pen and ink drawing by Ernest Noble, c.1918.

-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

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Dr. Ernest Seidman

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Fonds de la recherche en santé Québec

McGill

Thank you