A Chemical Dynamics Approach to Understand Role of Vitamin D in Human Immunity

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Abstract. Vitamin D is believed to play important role in human immunity. 1-alpha-hydoxylase enzyme plays a dual role in vitamin D activity in human body, by converting vitamin D from inactive to active form, and also governing the T cell activation, which depends on vitamin D-VDR complexation. Activated T cells and macrophages kill pathogens inside our body, which in turn is dependent on vitamin D concentration. Here we propose a quantitative model which takes into several different competing factors and which is based on a rate equation description. We solve the resulting kinetic equations under steady state approximation. We find an interesting interplay between the activated T cell concentrations and the macrophage concentration, due to the role of macrophage in destroying pathogens. Under steady state approximations, active T cell concentration is proportional to the macrophage concentration in the body. The concentration of activated T cells is non linearly dependent on vitamin D concentrations in the body. A time dependent solution can be obtained to show the dependence of time taken to cure a disease (kill pathogen inside body) on activated vitamin D concentration in our body.

Keywords: Vitamin D, VDR, 1,25(OH)2D3 , T-Cell

1. Introduction

A vitamin is an organic compound required as a nutrient in tiny amounts by an organism. Often it cannot be synthesized in sufficient quantities by an organism, and must be obtained from the diet. Thus, the term is conditional both on the circumstances and on the particular organism. The reason for recommended intake of such high dose of vitamin D is the inability of our body to process more than 20% vitamin D acquired from dietary intake. Most people meet at least some of their vitamin D needs through exposure to sunlight [1, 2]. Ultraviolet (UV) B radiation with a wavelength of 290–320 nm penetrates uncovered skin and converts cutaneous 7-dehydrocholesterol to previtamin D_3.Body heat then catalyzes the rapid isomerisation
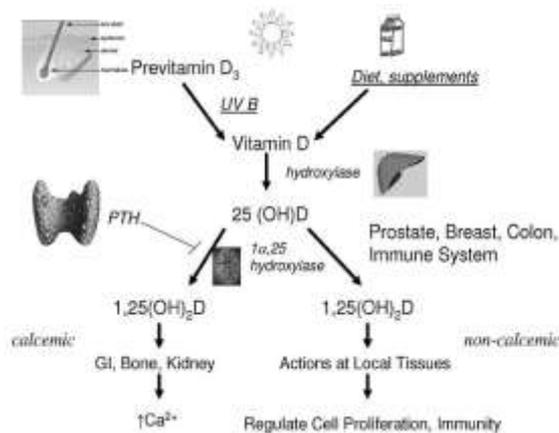
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of previtamin D_3 to vitamin D3 (cholecalciferol), this binds to the vitamin-D-binding protein (VDBP) in the extracellular space. Vitamin D_3 is transported to the liver, which uses 25-hydroxylase to produce 25-hydroxyvitamin D_3 , or $25(OH)D_3$. [1,3]. Season, time of day, length of day, cloud cover, smog, skin melanin content, and sunscreen are among the factors that affect UV radiation exposure and vitamin D synthesis [1].

2. Chemistry of vitamin activity

Most of the biological actions of vitamin D are regulated by transcriptional regulations of target genes through vitamin D receptor (VDR), a member of steroid hormone/thyroid hormone super family. . It is believed that role of active vitamin D in cancer prevention takes place through DNA binding domain of vitamin D-VDR-Vitamin D binding protein complex, where the action of vitamin D in immunity takes place through its interaction with T-cell, and T-cell antigen receptors.
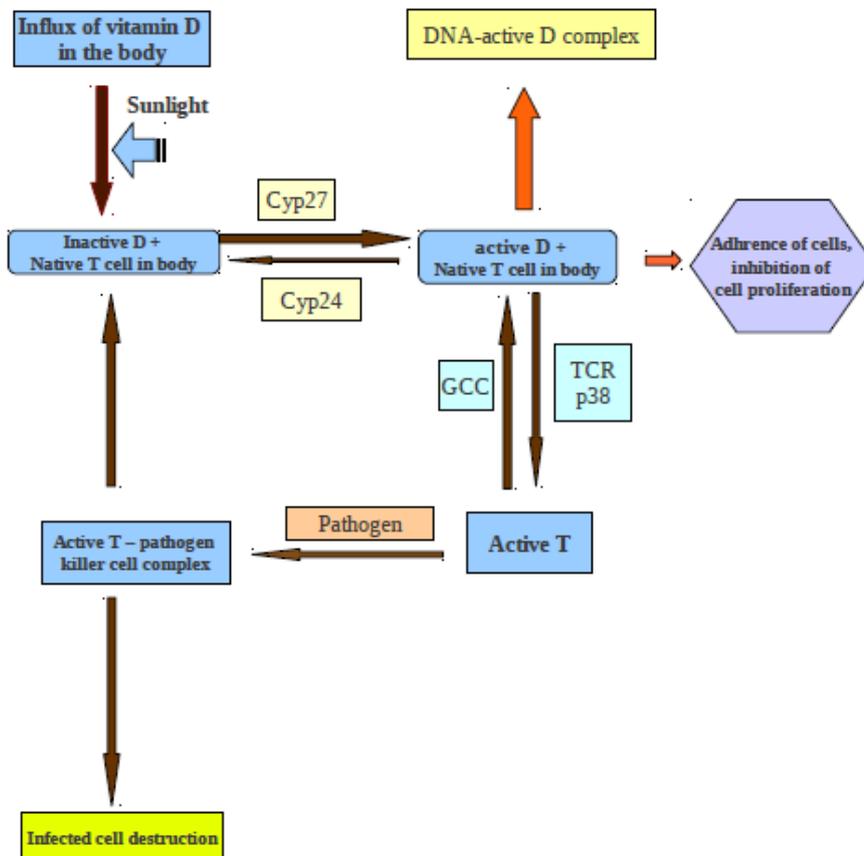

Fig. 2: Flow chart model of vitamin D activity in bio-systems

2.1. Vitamin D and the Immune System

$1,25(OH)_2D_3$ appears to modulate immunity principally via regulating T-cell function. VDR has been found to be expressed on virtually every type of cell involved in immunity [4,5]. Vitamin D regulates T cells both directly and indirectly via T cell antigen receptor. When concentration of activated vitamin D is diminished in the body, expressions through VDR is weakened, Th1 cell actions are intensified, whereas regulatory T cells and Th2 cells are diminished, thus favouring an autoimmune Th1 response [6,7]. $1,25(OH)_2 D_3$ increases action of T cells and Th2 cells (anti-inflammatory cytokines) while suppressing Th1 cell activities[8]. VDRs are required to maintain a physiologic balance of Th1 and Th2 cell responses, and furthermore in the absence of the VDR, Th2 cell functions are diminished [9] . In the absence of vitamin D and signals delivered through the VDR, auto reactive T cells develop, whereas in the presence of active 1 ,25

(OH) 2 D3 and a functional VDR, the balance in the T-cell responses is restored and autoimmunity is avoided [10]

2.2. Vitamin D and its role in anticancer activity

Anticancer properties of vitamin D and its analogy induces a multipronged attack that involves growth arrest at the G1 phase of the cell cycle, apoptosis, tumour-cell differentiation, disruption of growth-factor-mediated cell survival signals, and inhibition of angiogenesis and cell adhesion. It is known that activated vitamin D-VDR complex is the main element in subsequent activity of vitamin D in various biological systems. Most of the biologic activities of $1,25(OH)_2D_3$ (active D) are mediated by a high-affinity receptor that acts as a ligand-activated transcription factor. The major steps involved in the control of gene transcription by the VDR include ligand binding, heterodimerization with retinoid X receptor (RXR), binding of the heterodimer to VDREs, and recruitment of other nuclear proteins into the transcriptional pre-initiation complex. Thus, genetic alterations of the VDR gene could lead to important defects on gene activation, affecting calcium metabolism, cell proliferation, and immune function.

The increase in the concentration of activated vitamin D – VDR complex is responsible for the T-cell activation and its action against pathogens. The biologic effect that glucocorticoids exert on peripheral T cells is immunosuppression, which is due to inhibition of expression of a wide variety of activation induced gene products. Thus kinetically, glucocorticoids and 24-hydroxylase enzymes have similar negative effects on the activation of T-cells.

2.3. T cell macrophage interactions

T cells are designed to recognise the molecular signatures of particular proteins, such as those from bacteria, in order to activate an immune response. Macrophages eat other cells and are able to pull apart their proteins in order to present them to T cells. Macrophages interact with T cells in order to bring about T cell activation in target organs, and are themselves activated by inflammatory messenger molecules (cytokines) produced by the T cells. Macrophages produce toxic chemicals, such as nitric oxide, that can kill surrounding cells. Macrophages take part in phagocytosis, and after digesting a pathogen, a macrophage will present the antigen (a molecule, most often a protein found on the surface of the pathogen, used by the immune system for identification) of the pathogen to the corresponding helper T cell. Thus the decay of the pathogen in the body will depend kinetically on the concentration of both activated T cell and macrophage, as well as the production rate of pathogen.

3. Towards a chemical dynamic theory formulation

We propose a theoretical model involving vitamin D-VDR complex and its interaction with T cell and activated T cell, through the following set of equations. First step is the formation of activated T-cell by the D-VDR complex, as indicated below

$$D - VDR + T_{cell}(T) \xrightarrow{\quad 1\alpha H \quad} T_{cell}^*(T^*)$$
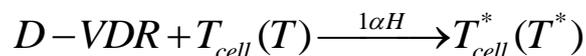
where D mentioned in all the equations denotes activated vitamin D $(1,25\text{-}(OH)_2D_3)$, and VDR denotes vitamin D receptor. D-VDR indicates the complex formed by activated vitamin D with vitamin D receptors, with the help of co-activators. This complex is mainly responsible for various biological activity of vitamin D, as described above.

1-alpha hydroxylase enzyme plays a dual role in controlling the activation of T cells in the body. As mentioned earlier, 1-alpha-hydroxylase enzyme catalyses the conversion of vitamin D from its inactive for to active form, after the generation of inactive vitamin D in the body via sunlight.

The dual role of 1-alpha hydroxylase enzyme thus is related to one another, as it increases the concentration of active vitamin D to make sure the subsequent T cell activation takes place in proper way.

$$[1\alpha H] \infty [D]$$

T cells are produced in the body from the precursor cells and the productions of T cells are opposed by the expression of CYP24A1 gene, which represents 24-hydroxylase enzyme. This enzyme acts on native T

cell to inhibit the up regulation of genes responsible for T cell antigen receptor expression, which in turn finally inhibits T cell activation.

The above conditions lead to the following equation of motion for the concentration of the T-cells, [T(t)]

$$\frac{d[T(t)]}{dt} = \sigma_T(t) - k_0[24H][T] \tag{1}$$

We shall adopt a steady state approach to simplify the treatment here. Since [1αH] is directly proportional to the concentration of activated vitamin D concentration, we get the following equation after substitution.

$$\frac{d[T^*]}{dt} = k_1[D(t)]^2[VDR(t)][T(t)] - k_2[T^*(t)][P(t)] \tag{2}$$

Substituting the concentration of 1-alpha-hydroxylase with rate constant and concentration of activated vitamin D, (which is independent of concentration of vitamin D in D-VDR complex) we arrive at the above equation.

$$\frac{d[P(t)]}{dt} = \sigma_P(t) - k_2[T^*(t)][P(t)] - k_M[M(t)][P(t)] \tag{3}$$

4. Steady state solution

We now obtain a steady state solution of the above system of equations. Towards this we introduce the following notation

[T_S] = Steady state concentration of the T-cells
[T^*_S] = Steady state concentration of active T-cells.
[P_S] = concentration of pathogen in body

At the steady state,

$$\frac{d[T]}{dt} = 0$$

which leads to the following expression for the steady state concentration of T-cells

$$[T_S] = \frac{\sigma_T}{k_0[24H]}.$$

Similarly at steady state,

$$\frac{d[T^*]}{dt} = 0$$

From equation 2, we get

$$k_1[D]^2[VDR]\frac{\sigma_T}{k_0[24H]} = k_2[T_S^*][P_S]$$

We now define,

$$\alpha = k_1[D]^2[VDR]\frac{\sigma_T}{k_0[24H]}$$

Therefore,

$$\alpha = k_2[T_S^*][P_S]$$

From equation 3, we obtain,

$$\frac{d[P]}{dt} = 0$$

This leads to,

$$P_S = \frac{\sigma_P}{k_2 T_S^* + k_M[M]}$$

Combining the above equations, we obtain the following final expressions for $[T_s^*]$ and $[P_s]$,

$$[T_S^*] = \frac{\alpha k_M[M]}{k_2(\sigma_P - \alpha)} \quad (4)$$

$$[P_S] = \frac{(\sigma_P - \alpha)}{k_M[M]} \quad (5)$$

The steady state solution for $[T_s^*]$ solution shows that the concentration of activated T cells in our body is directly proportional to macrophage concentration [M] and α. The term $\alpha = k_0[D]^2[VDR]\dfrac{\sigma_T}{k_1 [24H]}$, which shows that the production activated T cell is directly proportional $[D]^2$ to, showing a non-linear dependency on activated vitamin D concentration in the body.

This can be attributed to two-fold action of vitamin D in T cell activation process;
    i)   Activation of vitamin D by 1-alpha-hydroxylase enzyme
    ii)   Formation of activated vitamin D – VDR complex and its participation in up-regulation of T cell antigen receptor genetic expression.

These two fold participation is directly related to activated T cell concentration in the body, which acts as killer cells against the pathogens, after the action of Macrophages.

The production rate of T cells from the precursor cells are also obviously directly proportional to

$$[P_s^*]$$

$[T_s^*]$, and the concentration of 24-hydroxylase enzyme is inversely proportional to activated steady state T cell concentration, as it is known that the genetic expression of 24-hydoxylase enzyme inhibits the up-regulation of T cell antigen receptor, and subsequently inhibits T cell activation.

$(\sigma_P - \alpha)$ term denotes the amount of pathogen left in the body after the action of T cell and D-VDR complex on the pathogen. This term denotes the residual pathogen present.

The inverse proportional dependence of $[T_s^*]$, with the $(\sigma_P - \alpha)$ term also supports the fact that more the production rate of pathogen , lesser will be the concentration of the activated T cell in the body, and vice-versa, as more activated T cells will kill more residual pathogens.

Similarly $[P_s^*]$ directly depends on this $(\sigma_P - \alpha)$ term, as mentioned above, it denotes the residual pathogen in the body after action of biological elements that can kill pathogens. It is evident that the concentration of pathogen in the body will be inversely proportional to macrophage concentrations, as macrophages are the principal destroyer of pathogens after its entry to body.

5. Time dependent solution

For time dependent solution, we first try to get an approximate solution for [P], as the full solution is nontrivial. We make the following approximations. First, we assume that the production rate of pathogen σ_P is proportional to pathogen concentration [P], σ_P (t) = γ [P] (t).

Second, we assume that the concentration of active T-cells, $[T^*]$, in the body is much larger than the pathogen concentration so that we can replace the time dependent active T cell concentration by its steady state concentration, hence $[T^*] = [T^*_s]$. We also assume that [M] is time independent.

Under these approximations, equation (3) shows that pathogen concentration decays exponentially

$$[P] = [P]_{t=0} e^{k_p t} \quad (1)$$

With a rate constant given by

$$k_p = \gamma - k_2[T^*] - k_M[M] \quad (2)$$

This embodies a rather straight-forward result where the rate of decay of pathogen concentration is the result of production versus consumption. However, it has a few interesting consequences.

Equation (7) shows that when the following condition is satisfied,

$$\gamma = k_2[T_S^*] + k_M[M] \tag{8}$$

we get $k_p = 0$. That is, concentrations cancel each other. This is the case of marginal immunity for the system.

On the other hand, [P] increases when $\gamma > (k_2[T^*] + k_M[M])$. When we put $[T_S^*] = \dfrac{\alpha k_M[M]}{k_2(\sigma_P - \alpha)}$ in equation (8), we can get a simpler expression

$$\gamma = \alpha + k_M[M]$$

Now we know that there is a time lag between the production rate and action of pathogen and action of activated T cell and macrophages on pathogen. Thus it is possible to find a critical time value (t_{cure}), when the production rate of the pathogen will be taken over by the combined action of activated T cells and macrophages (Figure 3).

The production of a pathogen can grow rapidly in the initial phase. In this initial stage of infection, the deterrence to this growth (or resistance from body immunity) comes primarily from the macrophages. Activation of T-cells takes some time and depends critically on the concentration of vitamin D. Once activated and formed in sufficient numbers, activated T-cells destroy the pathogens. Therefore, after a certain period of time, when all pathogens get exhausted, the 2nd and 3rd term of the rate constant (combined effect of macrophage and activated T cell, will consume the pathogens. The production rate and pathogen concentration will decay subsequently.
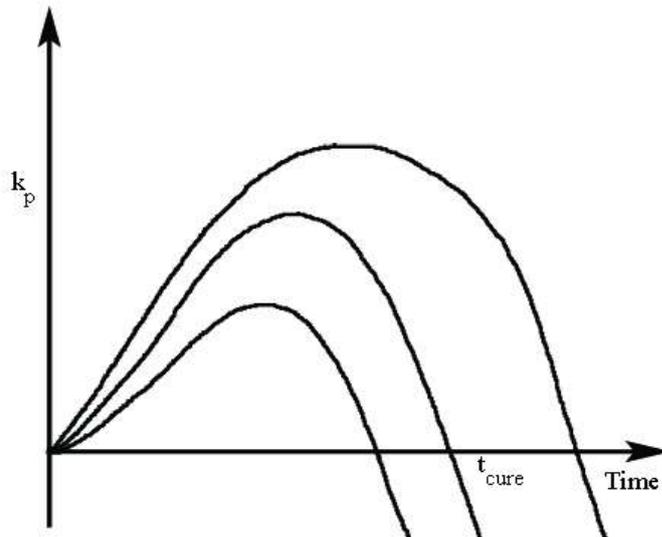

Fig. 3: Rate of pathogen production vs time (with action of macrophage and pathogen).

6. Conclusion

Main object of this work is to understand various processes involved affecting human immune system. The role of vitamin D in human immunity has been discussed in the above work, and a time dependence of its concentration on the production rates of pathogen has been described. But as we know vitamin D is not the only player governing human immunity.

Glucocorticoids (G) are a class of steroid hormones that bind to the glucocorticoid receptor (GR), which is present in almost every vertebrate animal cell. Glucocortioids are known for their role as immunosuppressant, are therefore used in medicine to treat diseases that are caused by an overactive immune system, such as allergies, asthma, autoimmune diseases and sepsis. They have structural and functional similarity to vitamin D, with a less flexible fused ring system than the former.

Glucocorticoids are direct competitors of vitamin D in binding mechanisms as substrates, and often compete out and reduce active vitamin D concentration in the body. The Glucocorticoid receptor family has similarity to the Vitamin D receptor family (VDR and RXR). When the GR binds to glucorticoids, its primary mechanism of action is the regulation of gene transcription. [11]

It would be worthwhile to establish a relation between the glucocorticoids level in the body and rate of pathogen production, based on the later's dependence on vitamin D concentration, and our knowledge of cortisol-receptor binding.

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