

ALLERGY, GENETICS

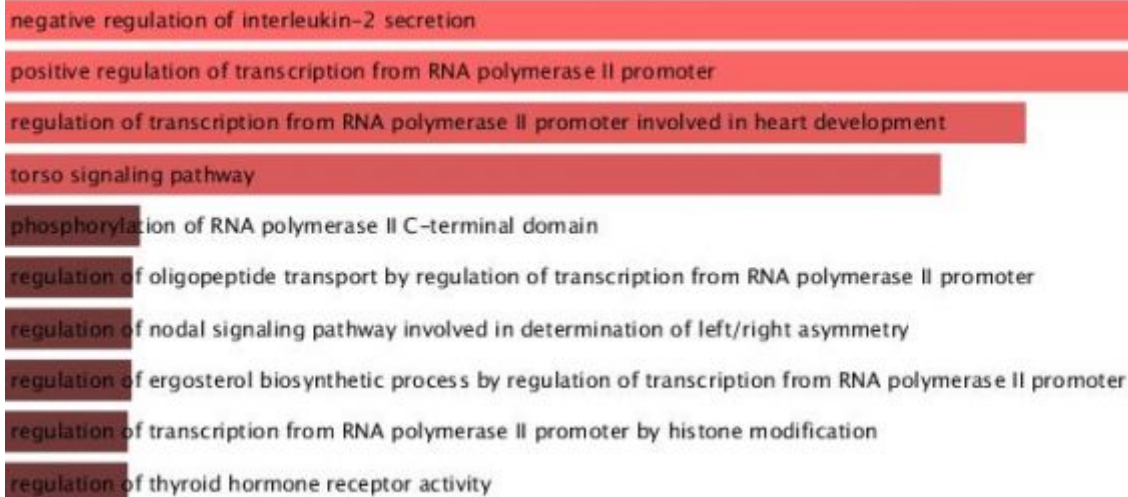
AN UPDATE OF IL2 FUNCTION

8.11.2017

More than 7 years ago, I wrote a blog post that there is [nothing new under the sun](#) predicting the next asthma genetics study for 2020 to include 100K asthmatics.

Ok, I am wrong the [paper](#) appeared already a week ago with 360K asthmatics while basically doubling the number to 136 independent risk variants. It's not an asthma only study as the authors had a rather loose definition of asthma or rhinitis or eczema – is is more about the allergy/atopy complex.

It will be a long time reading and replicating the data while my first interest was to examine the affected gene list as shown in table ST15. Using the online [Enrichr database](#) I get the following result from the GO ontology



GO Ontology Term
negative regulation of interleukin-2 secretion
positive regulation of transcription from RNA polymerase II promoter
regulation of transcription from RNA polymerase II promoter involved in heart development
torso signaling pathway
phosphorylation of RNA polymerase II C-terminal domain
regulation of oligopeptide transport by regulation of transcription from RNA polymerase II promoter
regulation of nodal signaling pathway involved in determination of left/right asymmetry
regulation of ergosterol biosynthetic process by regulation of transcription from RNA polymerase II promoter
regulation of transcription from RNA polymerase II promoter by histone modification
regulation of thyroid hormone receptor activity

This is basically the same result as the authors see in their table ST20.

The highest combined score is with a negative regulation of IL-2. What does that mean? A genetically disturbed pathway predicted by a gene ontology network?

IL2 was discovered in [1976 by Robert Gallo](#) by growing T-cells in culture for more than nine months by stimulating lymphocytes with phytohemagglutinin. ((IL1 was described back in [1972 by Charles Dinarello](#)). Gallo identified T-cell growth factor (TCFG), now known

as interleukin-2 (IL-2) as being absolutely important for a protective immune responses ([Science 1976](#)).

The next important paper was also published in [Science 1984](#) showing the following figure

1,25-Dihydroxyvitamin D₃: A Novel Immunoregulatory Hormone

Abstract. *The hormonal form of vitamin D₃, 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], at picomolar concentrations, inhibited the growth-promoting lymphokine interleukin-2, which is produced by human T lymphocytes activated in vitro by the mitogen phytohemagglutinin. Other metabolites of vitamin D₃ were less effective than 1,25(OH)₂D₃ in suppressing interleukin-2; their order of potency corresponded to their respective affinity for the 1,25(OH)₂D₃ receptor, suggesting that the effect on interleukin-2 was mediated by this specific receptor. The proliferation of mitogen-activated lymphocytes was also inhibited by 1,25(OH)₂D₃. This effect of the hormone became more pronounced at later stages of the culture. These findings demonstrate that 1,25(OH)₂D₃ is an immunoregulatory hormone.*

The importance of 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] in mineral and skeletal metabolism is well established (1). However, the widespread distribution of receptors for 1,25(OH)₂D₃ in tissues not regarded to participate in mineral metabolism has made it apparent that 1,25(OH)₂D₃ plays a wider biologic role

than was previously thought (2). We and others have found that 1,25(OH)₂D₃ receptors are present in normal human monocytes and malignant lymphocytes but are absent from resting T and B lymphocytes (3). Nevertheless, T and B lymphocytes obtained from normal human subjects express the 1,25(OH)₂D₃ receptor when the cells are activated in vitro by mitogenic lectins and Epstein-Barr virus, respectively (3). The mitogenic lectin phytohemagglutinin (PHA) stimulates T lymphocyte proliferation (4) and induces the production of various lymphokines, including interleukin-2 (IL-2), which is important for the growth of T cells (5). In the present investigation we report that 1,25(OH)₂D₃ suppresses IL-2 and inhibits the proliferation of PHA-stimulated lymphocytes.

Peripheral mononuclear leukocytes were isolated by Ficoll-Hypaque gradients from blood samples obtained from normal adults. The cells were cultured for 2 days in medium containing PHA (1 percent) alone or in the presence of increasing concentrations of 1,25(OH)₂D₃ (10⁻¹³M to 10⁻⁸M). The IL-2 content of the media was determined by means of a bioassay that involves titration of the media on the proliferation of the murine cell line CTLL-2; proliferation of the CTLL-2 cells depends strictly on the presence of IL-2 (5). Using this assay method, we found that the media from

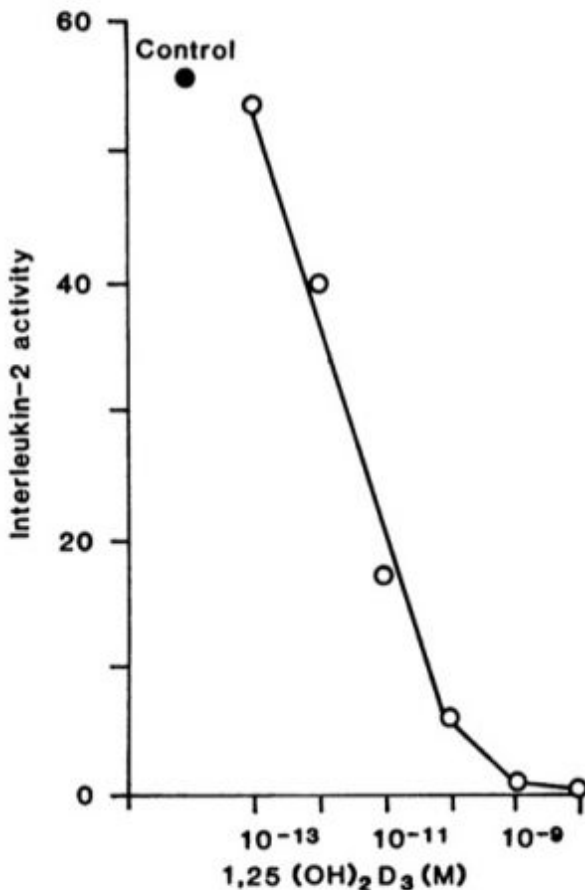


Fig. 1. Effect of 1,25(OH)₂D₃ on IL-2. Human peripheral blood mononuclear cells (1 × 10⁶).

So we have in allergy 2 hits on IL2: by genetics (as show in the new study) and by early vitamin D supplementation (as I reviewed earlier). Maybe we need more clinical studies like the [Zhang 2016](#) study:

In a general population-derived birth cohort, we found that in infants who developed food allergy, cord blood displayed a higher monocyte to CD4(+) T cell ratio and a lower proportion of natural regulatory T cell (nT(reg)) in relation to duration of labor. CD14(+) monocytes of food-allergic infants secreted higher amounts of inflammatory cytokines (IL-1 β , IL-6, and tumor necrosis factor- α) in response to lipopolysaccharide. In the presence of the mucosal cytokine transforming growth factor- β , these inflammatory cytokines suppressed IL-2 expression by CD4(+) T cells. In the absence of IL-2, inflammatory cytokines decreased the number of activated nT(reg) and diverted the differentiation of both nT(reg) and naïve CD4(+) T cells toward an IL-4-expressing nonclassical TH2 phenotype.

Suppressed IL2 is a key for allergy development shown also in experiments by [Bonnet 2016](#):

We previously demonstrated that Tregs can be selectively expanded and activated by low doses of IL-2 (ld-IL-2) inducing immunoregulation without immunosuppression and established its protective effect in autoimmune diseases. In this study, we evaluated the ability of ld-IL-2 to control allergy in an experimental model of food allergy. Ld-IL-2 induced Treg expansion and activation that elicited protection against clinical manifestations of food allergy in two mouse models with OVA and peanut. This clinical effect was lost in Treg-depleted mice, demonstrating the major contribution of Tregs in ld-IL-2 efficacy. Mechanistic studies further indicated that protection from allergy could be explained by a Treg-dependent local modification of the Th1/Th2 balance and an inhibition of mast cell recruitment and activation. Preventive and therapeutic effects of ld-IL-2 were observed over a 7-mo-period, highlighting its long-term efficacy. This study demonstrated that ld-IL-2 is efficient to prevent and to treat allergic immune responses, and thus represents a promising therapeutic strategy for managing allergic diseases.

What we do need now for allergy prevention is a [trials of newborns with low dose IL2](#) and

also more trials refining the IL2 antagonist application of vitamin D.

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