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"Vitamin hypothesis": explanation for allergy increase?

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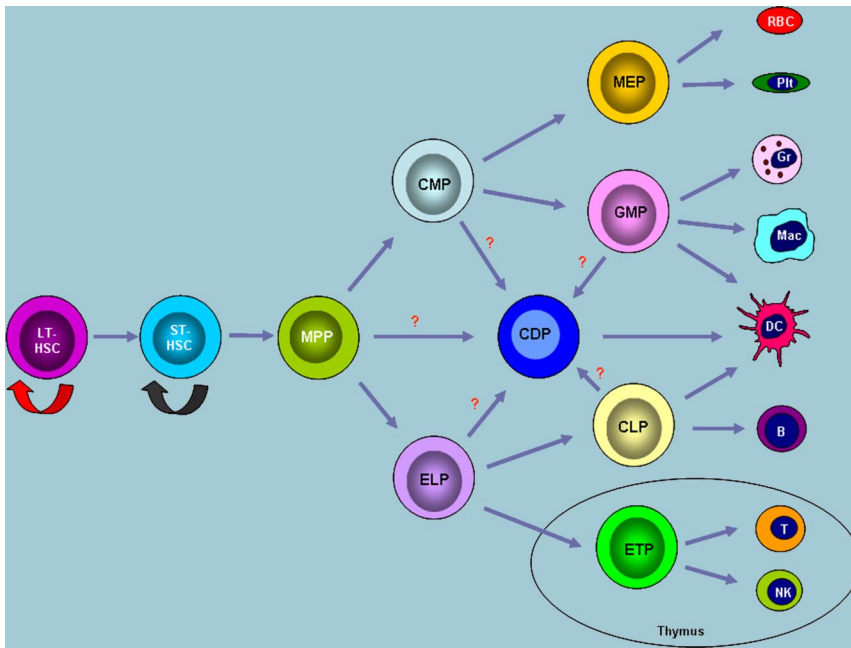
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The paradigm of hematopoiesis. During hematopoiesis, long-term hematopoietic stem cells (LT-HSCs) differentiate into short-term hematopoietic stem cells (ST-HSCs) and subsequently into multipotent progenitors (MPPs). LT-HSCs have unlimited abilities to self-renew, while ST-HSCs have limited self-renewal capacity. MPPs differentiate into CMPs and ELPs. Erythroid and myeloid lineage cells are differentiated from CMPs, whereas cells of the lymphoid lineage are derived from ELPs. Dendritic cells are developed from recently identified CDPs. Although this model represents the most widely accepted view, alternative theories exist regarding the commitment of lineage-restricted progenitors. Abbreviations: MEP, megakaryocyte erythrocyte progenitor; GMP, granulocyte monocyte progenitor; CLP, common lymphoid progenitor; ETP, early thymic progenitor; RBC, red blood cell; Plt, platelet; Gr, granulocyte; Mac, macrophage; DC, dendritic cell; B, B cell; T, T cell; NK, natural killer cell.

In the paradigm of hematopoiesis (see figure), the ontogeny of dendritic cells is probably the most debated issue, and there has been a constant interest in deciphering the lineage identity of the precursors/progenitors of these professional antigen-presenting cells. To date, several major categories of DCs in mice have been identified, which are broadly classified as conventional DCs (cDCs), plasmacytoid DCs (pDCs), and migratory DCs (mDCs).⁵ One of the long-standing questions of DC biology has been recently resolved, at least to a certain extent, by the identification of a distinct common DC precursor (CDP) that can differentiate into both cDCs and pDCs in vivo.⁶ Thus, according to the current model of “dendropoiesis,” most of the DC subtypes might differentiate either from CDPs or from macrophage DC precursors (MDPs).⁶ In this regard, the work described by Welner et al gains much importance as they have highlighted that during viral infection, DCs preferentially differentiate from CLPs instead of CDPs. Of note, the present study did not reveal an increase of CDPs during viral infections. In keeping with their findings, an earlier notion that a common pathway might exist between DCs and B cells has been supported.^{7,8}

However, it should be emphasized here that the observations of Welner et al might not reflect

lineage differentiation pathways during steady-state conditions and might be triggered only under specific inflammatory settings. Nevertheless, the present study raises many intriguing questions: Why would DCs differentiate from CLPs instead of CDPs during infections? Why would TLR ligation suppress B-cell differentiation but not NK-cell differentiation capacity of CLPs? What are the genetic factors favoring the “transdifferentiation” of CLPs into DCs? What are the functional properties of DCs that are differentiated from CLPs? How can external stimuli reprogram the genetic control of hematopoiesis? How economical would it be, for

the hematopoietic system, to reroute lineage differentiation pathways?

One more interesting highlight from the present study is the involvement of TLRs in hematopoiesis. The current study by Welner et al confirms and extends the previous findings of the same group that TLRs play a critical role in directing the hematopoietic cell fates under inflammatory conditions. It is very interesting to learn that the functions of TLRs extend beyond its well known role in regulating the innate immune responses during infections. It is also surprising to observe that TLRs violate normal paradigm of hematopoiesis and have the ability to reroute the normal differentiation pathways.

To date, the in vivo significance of “trans-differentiation” and relevance of such a phenomenon has not been appreciated, even though the concept has been known for some time. The present study by Welner et al warrants further consideration of this possibility and sheds light on the epigenetic control of hematopoiesis.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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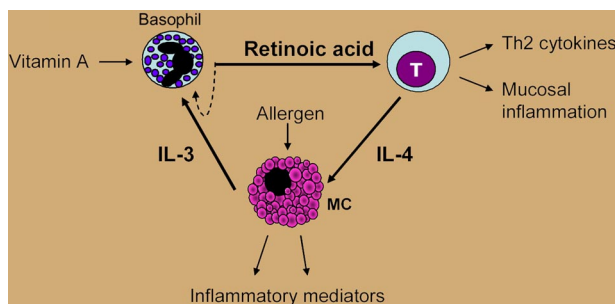
IMMUNOBIOLOGY

Comment on Spiegl et al, page 3762

“Vitamin hypothesis”: explanation for allergy increase?

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In this issue of *Blood*, Spiegl and colleagues show that basophils express retinaldehyde dehydrogenase-2 and thus are a new and unique cellular source of RA, known to be an important regulator of immune-cell functions.



The “vitamin hypothesis.” Local production of RA by basophils at sites of allergic inflammation could enhance Th2 gene-expression programs as well as the phenotype and functions of T cells, B cells, and mast cells, supporting the concept that RA acts as a mediator of mucosal allergy.

In humans, vitamin A (retinol and its esters) is either taken up directly from meat and fish, or, as β -carotenes (provitamin A), from plants. Retinol and its active metabolites, retinoic acid (RA) and retinal, have major biologic effects on cell growth and differentiation, reproduction, vision system development, and immune regulation. In particular, RA regulates immune defense against infections, inflammation, epithelial barrier functions, and lymphocyte function and trafficking to the gut.¹⁻⁴ The clinical relevance of these findings is strengthened by the observations that vitamin A deficiency severely compromises host defense, and that vitamin A supplementation can correct these abnormalities.⁵

The ability of retinol to control growth and development depends on tissue-specific metabolism of retinol to RA, which is then able to function as a ligand for retinoid receptor signaling through the nuclear receptors RAR and RXR. Genetic studies in mice revealed that cytosolic alcohol dehydrogenases (ADH1-4) were involved in the first step (oxidation of retinol to retinaldehyde), and cytosolic retinaldehyde dehydrogenases (RALDH1-3) in the second step (oxidation of retinaldehyde to RA). Metabolism of retinol to retinaldehyde is not tissue restricted; further metabolism of retinaldehyde to RA is the limiting step, and is tissue restricted insofar as the most effective enzymes identified are tissue specific.⁶

The origin of locally elevated RA levels in post-embryonic mammals is unknown. RALDH1 is abundantly expressed in adult tissues and likely responsible for low RA levels present in tissues throughout the body. RALDH2 and 3 are the more efficient and selective RA-synthesizing enzymes; however, their localization and regulation in adults is largely obscure. Here, Spiegl et al provide new and exciting data by showing that an often-neglected cell type, the basophil granulocyte, expresses

high levels of RALDH2 and thus is a major and unique source of immunomodulatory RA among human blood cells. Moreover, preliminary data on the regulation of RALDH2 in basophils are provided. Allergen-dependent basophil activation mimicked by Fc ϵ R1 crosslinking induced low levels of RALDH2, whereas IL-3 not only induced RA receptor activity but also strongly induced the expression of RALDH2 as well as the generation of RA.

However, at particular tissue sites, other cells besides basophils might contribute to RA formation. Recent studies indicate that dendritic cells from mouse mesenteric lymph nodes constitutively express RALDH2 mRNA and produce RA, which regulates the function and gut-homing properties of T and B cells and may be involved in intestinal tolerance induction.²⁻⁴ Moreover, intestinal mucosa and Peyer patch dendritic cells express the low-efficiency, RA-synthesizing enzyme RALDH1, suggesting that RA formation at this site may also depend on high local vitamin A concentrations from food. Similar suggestions have been made for vitamin D3, the active form of which is generated locally by dendritic cells and T cells, and induces CCR10 in naive T cells, thereby attracting them to the skin.⁷ Thus, vitamins might “sense” the local immune system as local concentrations of specific vitamins control the intensity and character of the local immune response. For instance, vitamin D metabolites attract specific populations of lymphocytes to the skin, and vitamin A metabolites direct lymphocytes to the gastrointestinal mucosa. So, locally produced food metabolites program T-cell homing, which offers a new mechanism to explain why hypersensitivity reactions occur at particular body sites.

At present, one can only speculate on the consequences of the findings by Spiegl and colleagues. The authors provide evidence that basophil-derived RA acts not only in an autocrine manner on basophils, but also on neighbor cells such as T cells. Basophil-derived RA polarized naive human T cells to produce Th2 cytokines, namely IL-4, and induced the expression of the adhesion receptors CD38 and $\alpha 4/\beta 7$ -integrin, which may guide them to mucosal sites of inflammation. IL-4 induced

by basophil-derived RA in T cells promotes mast-cell activation, which in turn enhances their production of IL-3, itself shown to be a major trigger for RA formation in basophils.⁸ Therefore, RA generation might be an important missing link in the communication between basophils, mast cells, and T cells, between innate and adaptive immunity that results in Th2 immune responses (see figure).

On the other hand, several important questions need to be addressed in future studies. For example, which other endogenous or exogenous factors, apart from IL-3, might regulate RALDH2 expression in basophils? Is RALDH2 expression enhanced in allergic patients? What are the local factors leading to RALDH2 expression in dendritic cells of mesenteric lymph nodes? Is mucosal RA synthesis dependent on vitamin A status, which needs to be measured by accurate means? Nevertheless, the findings from Spiegl and fellow members of Dahinden’s group suggest that basophils are exciting “agent cells” between the food environment and the immune system leading to a down-regulation of Th2 responses in case of vitamin A deficiency, and enhancing the risk of allergy in response to vitamin A excess. Additional epidemiologic and basic studies are needed to further support this attractive vitamin hypothesis, alongside the widely accepted “hygiene hypothesis,” as a new explanation for the rapid increase in allergy and autoimmune diseases in industrial countries.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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