

## To the editor:

### Role of vitamin A deficiency in the pathogenesis of myeloproliferative disorders

Kuwata et al's recent article<sup>1</sup> reports that vitamin A deficiency in mice causes a systemic expansion of myeloid cells. Based on their findings, the authors conclude that retinoids critically control the homeostasis of myeloid cell population in vivo and suggest that retinoid status may have an important role in the pathogenesis of various myeloproliferative disorders (MPDs). How valid is this suggestion?

Kuwata et al's study unequivocally demonstrates that vitamin A deficiency causes expansion of myeloid cells, but it provides no information as to the nature of these expansions, that is, whether they are monoclonal or polyclonal. Myeloproliferative diseases are, by definition, clonal disorders of hemopoietic precursor cells. If, for instance, the vitamin A deficiency-induced myeloid proliferations were polyclonal (and reversible), as occurs in response to a variety of stimuli such as infections, and inflammation, the relevance of this finding to the pathogenesis of MPDs would be questionable indeed. For this reason, clonality studies, either by cytogenetic analysis or molecular biologic methods to confirm monoclonal nature of the myeloid expansions, would be imperative and should be part of any animal experiments attempting to study the role of vitamin A in the pathogenesis of myeloproliferative diseases.

Although their experiments were carried out in mice, Kuwata et al state that "results obtained with this animal model are relevant to many studies performed with human myeloid cells in culture, showing that retinoids affect myeloid cell growth, differentiation, and apoptosis."<sup>1(p3355)</sup> Is there any clinical evidence to substantiate the notion that vitamin A deficiency may contribute to various myeloproliferative disorders in humans? Supporting evidence, if there is any, may be obtained from 2 sources: (1) epidemiological information that there is a high incidence of MPDs in areas where severe vitamin A deficiency is prevalent, and (2) biochemical evidence that serum vitamin A levels are significantly reduced in patients with MPDs.

Severe vitamin A deficiency with clinical manifestations such as xerophthalmia and keratomalacia is highly prevalent on the Indian subcontinent and in parts of Africa. Yet there is no obvious increase in the incidence of MPDs in these countries, compared to the West, where vitamin A deficiency is rare.<sup>2</sup> Indeed, unlike in certain solid tumors such as carcinoma of the breast and colon, where an association between vitamin A deficiency and occurrence of these

tumors has been reported, no such association has been identified between MPDs and vitamin A-deficiency states.<sup>2,3</sup>

A preliminary study was carried out to ascertain whether serum vitamin A levels are reduced in patients with MPDs. Estimation of serum vitamin A levels of 34 patients with various types of MPD [polycythemia rubra vera (17), essential thrombocythemia (10), and chronic myeloid leukemia (7)] was carried out by high-performance liquid chromatography (HPLC) analysis. The normal range of serum vitamin A level is 1.1 to 2.9  $\mu\text{M/L}$ . The vitamin A levels of our patient cohort ranged from 1.2 to 4.1  $\mu\text{M/L}$ , with a mean of 1.9  $\mu\text{M/L}$ . In other words none of the patients with MPD in this cohort has any biochemical evidence of vitamin A deficiency. Although the vitamin A status of these patients was not studied prior to the onset of their illness, the observation that their serum vitamin A levels are normal would suggest that continued myeloproliferation is not associated with deficiency of this vitamin.

It appears that there is no documented epidemiologic or demonstrable biochemical evidence currently available to support the notion that vitamin A deficiency plays an important role in the pathogenesis of MPDs as suggested by Kuwata et al. Although the role of retinoids in the pathogenesis of acute promyelocytic leukemia (APML), which is associated with a specific genetic defect involving retinoic acid receptors, is well established, it is unclear as to whether vitamin A deficiency is directly involved in the causation of these disorders in the general population in the absence of such gene defects.

**Muttuswamy Sivakumaran**

*Correspondence: Department of Haematology, Peterborough District Hospital, Peterborough, United Kingdom*

### References

1. Kuwata T, Wang I-M, Tamura T, et al. Vitamin A deficiency in mice causes a systemic expansion of myeloid cells. *Blood*. 2000;95:3349-3356.
2. Boyle P, Vecchia CL, Maisonneuve P, et al. Cancer epidemiology and prevention. In: Peckham P, Pinedo H, Veronesi U, eds. *Oxford Textbook of Oncology*. Vol 1. Oxford, England: Oxford University Press; 1995:199-273.
3. Hunter DJ, Willett W. Vitamin A and cancer: epidemiological evidence in humans. In: Blomhoff R, ed. *Vitamin A in Health and Disease*. New York, NY: Marcel Dekker; 1994:561-584.

## Response:

### Vitamin A deficiency and myeloid cell growth

First, we would like to stress that the major thrust of our paper<sup>1</sup> is that vitamin A deficiency causes abnormal expansion of granulocytes in mice under controlled conditions and that we have not claimed a direct cause-effect relationship with specific myeloproliferative disorders (MPDs), nor have we suggested that these observations should parallel epidemiologic data. What we suggested is that vitamin A deficiency may be a contributing factor for the pathogenesis of some MPDs.

Dr Sivakumaran argues that MPDs are monoclonal, but our study did not investigate whether granulocyte expansion in

vitamin A-deficient mice was polyclonal or monoclonal. Considering the almost 100% incidence of granulocyte expansion in deficient mice and the rapid recovery after retinoic acid repletion, we feel that the granulocyte expansion we observed may not be monoclonal in nature, a condition distinct from a genetic mutation resulting in selective monoclonal growth. Indeed, it seems unlikely that vitamin A deficiency itself causes a mutation in hematopoietic cells with high incidence, and none has been reported in this or in other systems. Therefore, whether this condition is polyclonal or monoclonal has not been a critical

issue, since we did not regard a genetic mutation to be a likely mechanism for the observed expansion.

With respect to the reference to MPDs, we had in mind chronic myelogenous leukemia (CML) and chronic neutrophilic leukemia (CNL), for which vitamin A deficiency may have a contributing role in the disease processes. We are not suggesting that systemic vitamin A deficiency has a significant role in the induction of MPDs, and we are not aware of any epidemiologic data to support this notion, just as there are no data suggesting that systemic vitamin A deficiency contributes to lung or breast or any other type of neoplastic disease in the absence of a mutational event. But intestinal<sup>2</sup> and liver<sup>3</sup> tumors or breast adenocarcinoma-derived cells,<sup>4</sup> as well as head and neck cancer and skin cancer cells<sup>5</sup> all show low retinyl ester levels and/or reduced ability to synthesize retinyl esters with respect to normal tissue. It is possible that some of these tumors either are derived from the expansion of vitamin A–depleted cells in the presence of a mutational event, as we have suggested,<sup>6</sup> or have acquired the vitamin A–deficient status as a result of a genetic mutation in one of the key retinoid signaling genes. Further, vitamin A deficiency may not occur systemically but may be generated locally because of chronic exposure to carcinogens, cytokines, and so forth. For instance, the lung tumor phenotype of squamous cell carcinoma may be due to mutation events operating on the lung epithelium rendered squamous metaplastic by chronic exposure to cigarette smoke and/or vitamin A deficiency.<sup>7</sup> This localized deficiency may not be reflected at the systemic level under normal conditions of vitamin A nutriture.

Finally, we would like to mention here that our intention was

not to link vitamin A deficiency with specific MPDs, but rather to suggest a potential role of vitamin A in the more general abnormalities in myeloid cell growth and survival, beyond the narrow hematologic definition of MPD.

**Luigi M. De Luca and Keiko Ozato**

*Correspondence: Keiko Ozato, Laboratory of Molecular Growth Regulation, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892-2753*

## References

1. Kuwata T, Wang I-M, Tamura T, et al. Vitamin A deficiency in mice causes a systemic expansion of myeloid cells. *Blood*. 2000;95:3349-3356.
2. Sundaresan PR, De Luca LM. Vitamin A contents of rat intestinal epithelium and jejunal mucinous adenocarcinoma. *J Natl Cancer Inst*. 1977;58:1643-1645.
3. De Luca LM, Brugh M, Silverman-Jones C. Retinyl palmitate, retinyl phosphate and dolichyl phosphate of postnuclear membrane fraction from hepatomas, host liver, and regenerating liver: marginal vitamin A status of hepatoma tissue. *Cancer Res*. 1984;44:224-232.
4. Andreola F, Giandomenico V, Spero R, De Luca LM. Expression of a smaller lecithin:retinol acyl transferase (LRAT) transcript and reduced retinol esterification in MCF-7 cells. *Biochem Biophys Res Commun*. 2000;279:920-924.
5. Guo X, Gudas LJ. Metabolism of all-*trans* retinol in normal human cell strains and squamous cell carcinoma (SCC) lines from the oral cavity and skin: reduced esterification of retinol in SCC lines. *Cancer Res*. 1998;58:166-176.
6. De Luca LM. The concept of nutritional exotrophism in carcinogenesis. *Clin Nutr*. 1989;8:187-191.
7. Lancillotti F, Darwiche N, Celli G, De Luca LM. Retinoid status and the control of keratin expression and adhesion during the histogenesis of squamous metaplasia of tracheal epithelium. *Cancer Res*. 1992;52:6144-6152.