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LETTER TO THE EDITOR

Ascorbic acid and healthy lymphocytes: a way to explain anticancer activity?

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Dear Sir,

We refer to the article by Ullah et al. [1] published in your issue 67 in January 2011.

The authors herein propose a putative molecular mechanism involving copper that accounts for the preferential cytotoxicity of ascorbic acid against cancer cells. They further argue that the results obtained by their work would "explain the findings of Levine and coworkers [2] toward the sensitivity of cancer cells and relative resistance of normal cells against the cytotoxic action of ascorbic acid."

To our opinion, the article contains two important aspects, which have not been communicated and interpreted correctly by the authors and thus could lead to misinterpretation of the results.

The first and main problem we see is the cell line used as a model system. For their study, the authors used freshly isolated lymphocytes from one single, healthy, non-smoking donor which were treated with different dosages of vitamin C up to 100 μM. The detection of vitamin C DNA breaking activity using the comet assay showed a clear dose-related increase in strand breaks with increasing vitamin C concentrations. The crucial misinterpretation in this context is the authors' conclusion that this would explain the findings of Levine and coworkers [2–4] concerning the selective cytotoxicity of vitamin C against tumor cells and the concurrent relative resistance of healthy cells against this treatment. In fact, because all experiments of Ullah and coworkers were conducted with healthy and not with tumor cells, the results definitely do not support the results of Levine and his group. In contrast, the result that vitamin C kills healthy lymphocytes is rather contradictory to the relative resistance of healthy cells against vitamin C proposed by Levine and coworkers. Unfortunately, the authors seem not to be aware of this discrepancy.

The second aspect that has not been discussed sufficiently is the relatively low concentration of vitamin C (25 μM) needed to induce strand breaks in the lymphocytes used. At first glance, this is really an interesting and unexpected result. Conferred on the whole organism, this would mean that every person with normal vitamin C plasma levels (40–100 μM) should have damaged and therefore inoperative lymphocytes. Actually, this cannot be the case. Also, there are a couple of other publications showing a DNA protective effect of vitamin C in lymphocytes [5–7]. Unfortunately, the authors did not even mention this controversy.

A possible explanation for those apparently illogical results can be found looking at some findings of Wilms and coworkers published in 2007 [8]. Examining the potential cytoprotective effect of vitamin C on hydrogen peroxide–treated lymphocytes from 12 healthy volunteers, they found contradictory results—in some individuals ascorbic acid seemed to be protective, whereas in other subjects it actually exacerbated the cytotoxic effects of hydrogen peroxide. Execution of a genotype analysis for those 12 volunteers revealed a variance in a particular protein of the glutathione-S-transferase-superfamily, namely GSST1, being the probable reason for the diverging susceptibility of lymphocytes against ascorbic acid treatment. In lymphocytes of subjects with wild-type GSST1, ascorbic acid incubation decreased oxidative DNA damage determined by Comet assay, while in lymphocytes carrying the variant GSST1 protein, the incubation led to a statistical significant

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increase of DNA strand breaks. Regarding the worldwide occurrence of this polymorphism at a percentage between 10 and 60% (European and Chinese population, respectively) [9], there seems to be a high probability for the lymphocyte donor of the study of Ullah and coworkers to be a bearer of the variant GSST1 protein. In order to exclude this polymorphism being the cause for the low vitamin C concentrations needed for DNA damaging of the examined lymphocytes, the authors should perform an appropriate genotype analysis of the donor. Further, to achieve reliable results concerning vitamin C DNA damaging activity, lymphocytes from more than one single donor should be examined.

Conflict of interest None.

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