Re: Depression as a Risk Factor for Cancer: Renewing a Debate on the Psychobiology of Disease

Robert T. Croyle, in his excellent editorial regarding the very fine study by Penninx et al. (2), suggested that three areas of follow-up research would be indicated to further delineate the association between depression and cancer. One of those recommendations was to extend the study of a younger population, because it may be that the mechanisms responsible for the relationship between depression and cancer are related to the aging process.

I don’t anticipate that a negative study in younger patients would justify the conclusion that aging is the cause of the association between depression and cancer death that was found in the study by Penninx et al. (2). Cancers in general have a long latency. As pointed out by Croyle, stress and depression have been associated with the causation and acceleration of cardiovascular disease. Cardiovascular disease tends to cause death at a younger age than does cancer. Therefore, one would have a common risk factor (for cardiovascular disease and cancer) and a competing cause of death (from cardiovascular disease and cancer), which would confound any epidemiologic study where death from cancer is in part or in whole an end point.

I think the main value of studies in younger patients would be to determine whether stress and depression can have an effect on the recurrence or progression of cancer. The fact that such an association is being found more frequently (3) would lend further credence to the study by Penninx et al.

David S. David

REFERENCES

NOTE
Correspondence to: David S. David, M.D., F.A.C.P., Clinical Professor of Medicine, U.C.L.A. School of Medicine, 2222 Santa Monica Blvd., Suite 302, Santa Monica, CA 90404.

CORRESPONDENCE

Editor’s Note
Robert T. Croyle declined to respond to David S. David’s correspondence.

Brenda W. J. H. Penninx
Jack M. Guralnik

Affiliations of authors: B. W. J. H. Penninx, Institute for Research in Extramural Medicine, Vrije Universiteit, Amsterdam, The Netherlands; J. M. Guralnik, Epidemiology, Demography and Biometry Program, National Institute on Aging, Bethesda, MD.

Correspondence to: Brenda W. J. H. Penninx, Ph.D., Institute for Research in Extramural Medicine, Vrije Universiteit, v.d. Boechorststraat 7, 1081 BT Amsterdam, The Netherlands.
tumor effects of Linomide. In an editorial accompanying the article by Joseph and Isaacs, Wahl and Kleinman (2) suggested, on the other hand, that tumor therapy protocols that combine Linomide with the antiangiogenic cytokine interleukin 12 (IL-12)—which induces interferon-gamma release and activates rather than inhibits TAMs—would be worth pursuing.

The results of our present studies demonstrate the pertinence of this suggestion. In a murine melanoma model, in which the antitumor activity of Linomide has already been demonstrated (3), we show that administration of IL-12 in combination with Linomide results in potentiated antitumor effects over single-agent therapy (two-sided P < 0.05; Mann–Whitney U test) (Fig. 1).

To confirm that IL-12 and Linomide, used alone or in combination, exert the antiangiogenic effects that were expected on the basis of previous reports, we used a tumor-induced angiogenesis model. This model was proven effective in a previous study of IL-12 and tumor necrosis factor (5). Short-term (3 consecutive days) intraperitoneal administration of either 0.1 μg IL-12 or 400 μg Linomide resulted in significant inhibition of blood vessel formation at the site of B16F10 murine melanoma cell inoculation (16.4 blood vessels per microscope field [95% confidence interval {CI} = 14.7–18.1 vessels] and 16.0 blood vessels per field [95% CI = 15.2–16.8 vessels] in IL-12 and Linomide-treated mice, respectively) as compared with diluent-injected controls (18.7 vessels per field [95% CI = 17.8–19.5 blood vessels]; two-sided P = 0.007 for IL-12 versus control group; two-sided P = 0.0003 for Linomide versus control group; Mann–Whitney U test). Combined treatment with IL-12 and Linomide was statistically significantly more effective in inhibiting the formation of new blood vessels than was the treatment with either agent alone (13.7 blood vessels per field [95% CI = 12.3–15.1 vessels]; two-sided P = 0.012 for IL-12 versus combined treatment group; two-sided P = 0.0028 for Linomide versus combined treatment group).

Our results demonstrate potentiation of antitumor and antiangiogenic effects for combination therapy with IL-12 and Linomide in a murine melanoma model. These observations would appear to be clinically interesting because antitumor efficacy of both these agents is currently being evaluated in clinical trials (6,7).

Anna Dabrowska
Jakub Golab
Adam Giernasz
Maria Marczak
Marek Jakobi{siak}

Fig. 1. Effects of treatment with interleukin 12 (IL-12) and/or Linomide® on B16F10 melanoma growth (IL-12 was a gift from the Genetics Institute Inc., Boston, MA, and Linomide was a gift from Pharmacia and Upjohn, Lund, Sweden). B6D2F1 mice were inoculated with 1 × 10⁶ melanoma cells in the footpad of the right hind limb and treated intratumorally with 0.1 μg IL-12 for 7 consecutive days and/or intraperitoneally with 400 mg/kg of Linomide for 21 days starting on day 7 after inoculation of tumor cells. As a control, the following diluents were used: 0.1% bovine serum albumin–phosphate-buffered saline (PBS) administered intratumorally for 7 consecutive days and 0.01% Tween in PBS administered intraperitoneally for 21 consecutive days. Groups consisted of seven to eight mice. Doses of IL-12 and Linomide were established in previous experiments (data not shown). Tumor growth was monitored as described previously (4). Tumor volumes are expressed as means with 95% confidence intervals. * = two-sided P < 0.05 as compared with all other groups (Mann–Whitney U test). ● = control; ○ = IL-12; □ = Linomide; and ▽ = IL-12 + Linomide.

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Affiliations of authors: A. Dabrowska, Department of Immunology, Institute of Biostructure, Medical University of Warsaw, and Department of Lymphoproliferative Diseases, Maria Sklodowska-Curie Memorial Cancer Center, Institute of Oncology, Warsaw, Poland; J. Golab, A. Giernasz, M. Jakobi{siak} (Department of Immunology, Institute of Biostructure), M. Marczak (Department of Dermatology), Medical University of Warsaw.

Correspondence to: Marek Jakobi{siak}, M.D., Ph.D., Department of Immunology, Institute of Biostructure, Medical University of Warsaw, ul. Chalubinskiego 5, 02–004 Warsaw, Poland (e-mail: mjakobi@ib.amwaw.edu.pl).