Letters to the Editor

Natural Killer Cells Activity and Neuroimmunological Treatment of Cancer

To the Editor: We read with great interest the article by Krause et al. (1). They report on the role played by activated natural killer cells in the treatment of colon and lung cancer patients. With respect to the above, we would like to inform readers of our experience with this issue.

In 1987, we found that neuropharmacological therapy was able to improve different types of cancer patients (2). In addition, we showed that the clinical improvement was paralleled by an increase in the cytotoxicity activity of natural killer cells against the K-562 target cells (3). This first report was confirmed by further research published in 1989 (4) and 1990 (5). All our patients were submitted to neuroautonomic and immunological investigations. Neuroautonomic research included the assessment of circulating neurotransmitters: noradrenaline, adrenaline, dopamine, platelet serotonin, and plasma serotonin. We showed that clinical severity correlated negatively with the noradrenaline/adrenaline ratio, which in our experience is associated with “uncoping stress” situation (6, 7). Conversely, clinical improvement correlated positively with the noradrenaline/adrenaline ratio. According to the above, the neuropharmacological manipulations we prescribed were addressed to enhance central noradrenergic activity (8–10). The above findings were also the subject of lectures in many cancer hospitals and departments (M. D. Anderson, Ohio State University, University of South Florida, Rosewell Hospital, Hospital de Buenos Aires, and others).

Up to the present, we have treated more than 2,000 advanced cancer patients, which include many types. Prostate, gastric, mammary cancer, and non-Hodgkin’s lymphoma patients were shown to obtain maximal improvement by our neuropharmacological therapy. Our long experience dealing with this issue has been summarized in our recently published book (11).

Fuad Lechin
Bertha van der Dijs
Department of Physiological Sciences
Sections of Neurochemistry, Neurophysiology, Neuroimmunology, and Neuropharmacology
Instituto de Medicina Experimental
Universidad Central de Venezuela
Apartado 80,983
Caracas 1080-A, Venezuela
Phone: 58-212-961-1048
Fax: 58-212-961-0172
E-mail: flechin@telcel.net.ve

Alex E. Lechin
Department of Clinical Science
University of Houston
Houston, Texas

References

In Response: We want to thank Dr. Fuad Lechin for his comments about the impact of natural killer (NK) cells in different tumor types including prostate, gastric, mammary and non-Hodgkin lymphoma. His finding that clinical improvement correlated with an increased cytotoxicity against K562 cells, a classical NK target cell line, is of major interest and further confirmed our hypothesis that Hsp70 plasma membrane expression serves as a tumor-specific, stress-inducible recognition site for NK cells. Screening of more than 800 different tumor samples and corresponding normal tissues including lung, colorectal, stomach, pancreas, mammary, head and neck cancers, and leukemic blasts revealed that Hsp70 membrane localization was frequently detected on human tumors (50–80% of the cases) but never on normal tissues (refs. 1 and 2; Gabriele Multhoff, Lydia Rossbacher, Mathias Gelermann unpublished observation). Also K562 cells present Hsp70 on their plasma membrane (3). This Hsp70 membrane expression could be further enhanced by exogenous stress induced by chemotherapy (4, 5). High Hsp70 levels have been found to exert dual functions: i.e., on the one hand, they mediate protection against chemotherapy-induced effects (6); on the other hand, they serve as a danger signal for NK cells (7). Incubation of NK cells with the Hsp70-derived peptide “TKD” (TKDNNLLGRFELSG, amino acid 450–463), mimicking the danger signal, was able to enhance the cytolytic and migratory capacity of NK cells toward Hsp70 membrane-positive tumor cells (8). Granzyme B could be identified as the effector protease inducing programmed cell death in Hsp70 membrane-positive tumor cells (9). After rein-
fusion of \textit{ex vivo} Hsp70-activated autologous NK cells in tumor patients, granzyme B serum levels were found to be elevated (10). Furthermore, Hsp70 but neither Hsp60 nor Hsp65 antibody levels in the serum also seemed to be affected. The prognostic value of these serum parameters and the clinical efficacy of “TKD”-activated NK cells will be addressed in a multicenter clinical phase II trial in the near future.

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Gabriele Multhoff  
Karin Pfister  
\textit{University Hospital Regensburg}  
Franz-Josef Strauss Allee 11, 93053  
Regensburg, Germany  
E-mail: gabriele.multhoff@klinik.uni-regensburg.de.

Ilona Hromadnikova  
Denisa Zlacka  
\textit{Cell Biology Lab}  
\textit{Paediatric Clinic}  
\textit{2nd Medical Faculty}  
\textit{Charles University}  
\textit{University Hospital Motol}  
Prague, Czech Republic

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