EFECTOS DE CADMIUM Y GC-MACROPHAGE ACTIVATING FACTOR (GMCAF) ON INTRACELLULAR HIV TARGETS IN NORMAL HUMAN BREAST CELLS

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BOX 1

CASE REPORT 1. 61-year-old woman diagnosed as an AIDS patient with HIV-1 infection and increased CD10 levels. She was treated with antiretroviral therapy and observed a decline in general health conditions with improved fatigue. In 2009-2010 the patient developed resistance to conventional antiretroviral therapy and received a new therapy that included GC-MAC (GMCAF) and observed an improvement in health conditions. These observations might prove encouraging in testing the effectiveness of GC-MAC.

CASE REPORT 2. 45-year-old woman with breast cancer treated with GC-MAC (GMCAF) and observed an improvement in health conditions. The patient reported a decrease in cancer-related symptoms and an improvement in quality of life. These observations might be used to test different sensitivities of cultured cells to GC-MAC (see Fig. 3).

REVERSAL OF HUMAN BREAST CANCER MALIGNANT PHENOTYPE

Fig. 2, shows Panpseudocladous staining of MCF-7 cells (magnification X40) before (A) and after (B) 72 h exposure to GC-MAC. In panel A, large nuclei and several mitoses are clearly visible. Untreated MCF-7 cells appeared morphologically normal and large and small cells were present. Cells grew over the bottom of the dishes and colonies were observed. Cells grew in monolayer and no colonies could be observed. Cells grew in smaller, regular polygonal and uniform in morphology and size. Cells appeared well adherent to each other and to the well surface. This phenotype can be interpreted as GCMCAF-induced reversal of epithelial-mesenchymal transition, a hallmark of breast cancer malignant progression.

EFFECTS OF GMCAF ON NORMAL BREAST CELLS AND MONOCYTES/MACROPHAGES

GMCAF did not modify normal human breast cells (MCT-10) proliferation whereas it inhibited proliferation of the human monocytic/macrophage cell line Mono Mac 6 (MM6). Inhibition of MM6 cell proliferation is consistent with the known effects of GMCAF on macrophage activation. In fact, it was demonstrated that monocytic/macrophages activated by GC-MAC displayed blocked DNA synthesis and rapidly differentiated (J Med Virol 2009; 81:16-28). Fig. 3, shows dose-dependent inhibition of MM6 proliferation (Columns 2, 4, GMCAF 0.4, 40 ng/ml). * indicates p < 0.05 vs control, i.e. column 1; ** indicates p < 0.01 vs control, i.e. column 1). The effects of GMCAF on MCF-7 cells were pronounced than those observed in MCF-7 cells as different cells lines showed different sensitivities to GMCAF. It is worth noting that MM6 VDR haplotype is BRF (see BOX 1).

Fig. 1

Fig. 3

MONO MAC 6 CELLS AS A TOOL TO TEST GMCAF-LIKE ACTIVITY

We recently proposed chick embryo chorionicarionatonic membrane (CAM) assay as a simple method to determine the relative potencies of different GMCAF preparations and their stability (Cancer Immunol Immunother 2010 doi:10.1007/s00262-010-0953-7).

We demonstrated that the cell line is an excellent system to test GMCAF activity in vivo. Thus, we tested a reproducible treatment obtained in our laboratory, putatively containing GMCAF, on MM6 cell proliferation. This preparation was treated with colcemid and stained with MM6 in order to reduce the number of cells and a normal phenotype was observed, with blasts and mitoses and MM6 cell for 72 h in the experiments reported in Figs 1 and 2. Increasing concentration of MM6 supernatant (expressed as total protein content, i.e. 4.8 – 8.30 g/ml) significantly inhibited MM6 proliferation in a manner similar to that observed with GMCAF.

GCMCAF AND CADMIUM IN MCF-7-INDUCED AGING

We had previously demonstrated that exposure of MCF-7 cells to subtoxic levels of Cd inhibited their angiogenic potential, suggesting the possibility that Cd might exert a paradoxical effect in breast cancer: on the one hand, it could promote angiogenesis, and on the other, it could delay the onset of tumours by inhibiting breast cancer cell-induced angiogenesis (Environ Pathol Toxicol Oncol 2009: 28:85-88). Since Cd and GCMCAF exerted similar effects on MCF-7 and on MCF-7-induced angiogenesis, we hypothesized that both Cd and GPABP are involved also in the GMCAF signaling pathway.

CONCLUSIONS

Our data demonstrate that GMCAF exerts multiple effects on normal and transformed cells; these effects are consistent with, and could be responsible for, its well-documented anti-cancer effects. Our observations (BOX 1) also suggest that GMCAF might prove useful in AIDS patients. In addition, the data presented in J Med Virol 2009: 81:16-28 indicate that the evidence indicates that GC-MAC is a promising new therapeutic strategy for breast cancer and AIDS.

Acknowledgements. This research project has been subsidized by the Italian Ministry of Health (Progetto Strategico “La Medicina di cure e come obiettivo strategico per la società pubblica: L’approfondita della cura per il tumore del seno della donna”), The authors wish to thank Prof. M. Ruggiero for constructive, helpful discussions.