I. Cyclic glycerophosphates – Novel signaling molecules

II. Pressure induced tumor vaccines

III. Pathophysiology of mental disorders

These simple (though overlooked) molecules were found to be formed as intermediates in the enzymic cleavage of phosphatidyl glycerol [Shinitzky et al. J. Biol. Chem. 268: 14109 (1993)]. The structural analogy between 1,3 cGP and cyclic AMP prompted us to investigate the signaling potential of 1,3 cGP, 1,2 cGP and their deoxy analogues. The linear forms of 1,3 cGP and 1,2 cGP, i.e. α-glycerophosphate and β-glycerophosphate served as control compounds.

The results of 6 years of intensive investigation can be summarized as follows:
1. 1,3 and 1,2 cGP and their deoxy analogues, at the micromolar range, can induce intracellular tyrosine phosphorylation of a series of signaling proteins.
2. Breast cancer cells can be differentiated to an estrogen receptor positive state by these compounds.
3. Similarly, these compounds can induce neuronal differentiation of PC12 cells (see picture).
4. In collaboration with the group of Dr. Gal Yadid in the Bar-Ilan University, studies on Parkinsonian rats indicated a significant therapeutic potential for Parkinson’s disease of these compounds.

II. When tumor cells are subjected to hydrostatic pressure (P) in the presence of a specially designed membrane crosslinker (CL) they become highly immunogenic due to a substantial increase in the surface presentation of MHC components and antigen presenting stress proteins. We have lately shown [Goldman et al. Cancer Res. in press] that subsequent reduction of surface protein disulfides with N-acetyl-L-cysteine (NAC) further augments the immunogenic potential of PCL-modified tumor cells both in vitro and in vivo. Immunotherapy with PCL+NAC modified 3LL-D122 Lewis lung carcinoma cells plus intravenous delivery of NAC in mice bearing established lung metastases provoked the most effective anti-tumor response capable of eradicating the metastatic nodules as demonstrated by restoration of normal lung weight and histology. In addition, immunization with PCL+NAC modified tumor cells gave rise to a strong delayed type hypersensitivity (DTH) recall response against parental D122 cells. We propose that this novel two-prong
strategy, based on local immunization with autologous PCL+NAC modified tumor cells and systemic boosting with NAC, could provide a practical, effective immunotherapeutic regimen for the treatment of human cancer. Clinical studies with this novel and innocuous regimen are about to commence.

III. Schizophrenic patients bear a unique autoimmune reaction against their own platelets. The platelet antigen and its epitope responsible for this reaction have been identified. They provide a basis for a blood test for schizophrenia, which is currently at a final stage of development. In a recent study [Tafet et al. Psychobiology, in press] we observed that elevated cortisol which prevails both in stress and depression promotes the synthesis of the serotonin transporter. This finding offers a novel mechanism which can explain the common state of depression which follows external stress (delineated in Fig. 2).

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