6

CONTROL OF ONCOGENE EXPRESSION BY SENSE AND ANTISENSE OLIGONUCLEOTIDES. NON-SENSE OR REALITY ?

Claude HELENE, Laboratoire de Biophysique, INSERM U.201, CNRS URA 481, M.N.H.N., 43 rue Cuvier, 75005 Paris (France).

Activation of proto-oncogenes and inactivation of tumor-suppressor genes play a major role in tumor development. Several strategies based on synthetic oligonucleotides have been recently proposed to selectively inhibit oncogene expression in tumor cells. In the "antisense" strategy an oligonucleotide is targeted to a selected mRNA and inhibits its translation. In the "antigene" strategy the oligonucleotide is targeted to the gene itself and inhibits transcription. In the "sense" strategy a single-stranded or double-stranded oligonucleotide is used to trap a transcription- or translation-activating factor. In the "ribozyme" strategy an oligoribonucleotide complementary to a mRNA induces cleavage and inactivation of the target sequence. The oligonucleotide can be engineered in such a way as to become resistant to nucleases and can be administered to animals by intravenous, intraperitoneal or subcutaneous routes. Several examples of selective inhibition of tumor growth have been described. Alternatively a gene therapy technology can be developed whereby a gene vector is used to deliver an antisense, a ribozyme, an antigene or a sense RNA *in situ*. Some recent experiments on rats using a cell therapy approach provide hope that the antisense technology can be used to cure selected tumors in humans.

7

RETINOIDS AS A MODEL OF DIFFERENTIATING DRUGS IN MALIGNANCIES.

L. DEGOS, Hopital St Louis, Paris 75010 FRANCE

In vitro differentiating effect of retinoic acid on fresh cells from acute promyelocytic patients as well as in vivo differentiation of malignant cells until complete remission achievement is now well established. The major advantages are the absence of bone marrow aplasia and the rapid correction of the bleeding diathesis due to a primary fibrinolysis induced by the release of lysozomial enzymes (elastase, cathepsine, protease 3). However patients under treatment experienced an hyperleucocytosis and a clinical syndrome of leucocyte activation. All trans retinoic acid (ATRA), the natural and efficient derivative, induces its own catabolism which could explain the progressive resistance and the early relapses. We proposed to add an early consolidation by chemotherapy after complete remission (CR) obtained by ATRA. A pilot study (December 1989 - April 1991) including 26 patients showed a high CR rate (95%) and a reduce number of relapses. A multicentric randomized trial (April 1991 - December 1992) including 101 patients, comparing conventional chemotherapy to ATRA before chemotherapy, demonstrates a statistically significant difference in the event free survival (50% versus 76% at 12 months). When ATRA is administered CR rate is increased (91% versus 81%) and relapses are less frequent.

In this disease a specific gene rearrangement PML-RAR due to the translocation t(15;17) provokes the expression of an abnormal hybrid product. Using transfection experiments we have shown that the hybrid product impairs the normal transactivating effect of RAR alpha (retinoic acid receptor) and blocks the retinoic acid induced differentiation of HL60 which could explain the arrest of maturation of leukemic cells. The intracellular localization of PML-RAR is abnormal (cytoplasmic and microgranulation in the nucleus) compared to normal PML (macrogranules exclusively in the nucleus).

The addition of ATRA inhibits the intracellular enzyme release (elastase, cathepsine and protease 3) provokes the cellular differentiation and probably induces the cell death program (decrease of bcl-2 expression). PML proteins are rapidly relocalized in the nucleus with a normal shape.

Other malignancies could be treated with ATRA (as neuroblastoma), and other differentiating agents could be used in malignancies. Differentiating agents coupled with cytostatic drugs open a new era in the strategy against malignancies.

8

GROWTH FACTORS IN CANCER THERAPY: THE CONTROL OF HEMATOPOIESIS AS A MODEL SYSTEM

Sachs, L., Dept. of Molecular Genetics & Virology, Weizmann Institute of Science, Rehovot, Israel.

The establishment of a cell culture system for the clonal development of hematopoietic cells has made it possible to discover the proteins that regulate cell viability, growth and differentiation of different hematopoietic cell lineages. These regulators include cytokines now called colony stimulating factors and interleukins. Different cytokines can induce cell viability, growth and differentiation, and hematopoiesis is controlled by a network of cytokine interactions. Viability is induced by inhibiting programmed cell death (apoptosis). Normal hematopoietic cytokines, and some other compounds, can suppress malignancy in certain leukemias by inducing differentiation. Hematopoietic cytokines are now being used clinically to correct defects in hematopoiesis in cancer patients. The results provide new approaches to cancer therapy. The existence of a network and the ability of cytokines to regulate programmed cell death has to be taken into account in the clinical use of cytokines for therapy.

Sachs, L. The molecular control of blood cell development. *Science, 238*: 1374-1379, 1987. Sachs, L. The control of growth and differentiation in normal and leukemic blood cells. *Cancer, 65*:2196-2206, 1990. Sachs, L. The molecular control of hematopoiesis: From clonal development in culture to therapy in the clinic. *Int. J. Cell Cloning, 10*:196-204, 1992.