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The Development of new Generation Inducers that Promote Differentiation of Leukemia and other Malignant Cells

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Although remarkable progress have been achieved in cancer treatment by conventional antineoplastic agents and radiotherapy in several cases, the overall success is limited. These difficulties in treating tumours can be attributed to cellular heterogeneity, multidrug resistance (MDR) and inadequate accumulation of drugs in cancer cells. Furthermore, conventional chemotherapy produces severe side effects by killing normal cells as well (especially those in rapid turnover under physiological conditions, such as bone marrow cells and epithelia) because it lack selectivity towards tumour cells. The early observations that some neoplastic cells can be differentiated in vitro and /or in vivo into cells that resembling their normal counterparts via treatment with a large variety of agents including growth factors and chemical inducers led to a new effective approach to treat cancer, the so called "Differentiation Therapy of Cancer". This approach has been already efficiently applied in the treatment of acute promyelocytic leukemia (APL) with all-trans retinoic acid (ATRA).

The large variety of chemical agents that have been developed to promote maturation in a number of leukemias and other tumours act at relatively high concentrations, which limit them for clinical use. We developed a new class of potent inducers of differentiation, the ureido derivatives of pyridine (UDPs), that promoted the maturation of leukemic cells as well as induced the morphological differentiation of human medulloblastoma TE-671 cells at relatively low concentrations (0.1-0.075 mM). The maturation is accompanied by decrease in the rate of cell proliferation, DNA replication and in cellular clonogenic potential, an increase in differentiation markers (e.g. hemoglobin biosynthesis in MEL cells), suppression of c-myc, p53, c-fos proto-oncogenes in both MEL and TE-671 cells, increase in RNA methylation etc. In order to delineate the mechanism of action of differentiation inducers at cellular and molecular level, we used radiolabelled UDP as ligand and performed binding studies. We found that UDPs bind specifically to MEL cells. Furthermore, we fractionated soluble intracellular proteins prepared from MEL cells incubated with radiolabelled UDP by gel filtration, UDP-agarose affinity chromatography and SDS-PAGE electrophoresis. These studies have shown that MEL cells contain a 40 kDa protein that forms stable complexes with UDP. We are currently constructing cDNA libraries in an attempt to clone, isolate and characterize the corresponding gene. This will be very helpful in order to understand the mechanism of action of differentiation inducers and design more effective agents.