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This paper provides a comprehensive review of the molecular and cellular characteristics of inducer-mediated differentiation of murine erythroleukemia cells. [The *SCI*® indicates that this paper has been cited in more than 555 publications.]

Induced Differentiation of Transformed Cells

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As a postdoctoral fellow in the laboratory of Jacques Monod at the Pasteur Institute in 1961, I began studies on globin synthesis in reticulocytes, demonstrating that globin mRNA was long-lived compared to that of *E. coli*, and globin synthesis proceeded on polyribosomes.[1] Returning to Columbia University's College of Physicians and Surgeons, I entered a collaboration with R.A. Rifkind to study control of globin synthesis during erythropoiesis, first using the maturing reticulocytes and, later, erythropoiesis in fetal mouse yolk sac and liver. Rifkind, with training in quantitative electron microscopy, focused on the changes in intracellular structural elements involved in globin synthesis, as I worked on understanding the events involved in the synthesis and accumulation of the different globin mRNAs and proteins during erythroid differentiation.[2]

These studies with normal erythropoietic cells were limited by several factors, including the difficulty of establishing normal erythroid precursor cells in long-term culture, the limited availability of developmental genetic variants, and inability to synchronize cells with respect to the cell division cycle.

The report of C. Friend and colleagues in 1971, that dimethylsulfoxide (Me_2SO) induces Friend virus-transformed murine erythroleukemia cell (MELC) to erythroid differentiation, prompted us to turn to this system as a model for our studies.[3] MELC could be maintained indefinitely in vitro, were readily synchronized with respect to the cell cycle, and could be induced to express characteristics of mouse erythroid cells. Among our initial observations was the demonstration that the polar group was the active chemical structural element in Me_2SO needed for inducing differentiation.

With Ronald Breslow of Columbia University's Department of Chemistry, we determined that diacetylated diamines, in particular hexamethylene bisacetamide (HMBA), was 50-fold more potent as inducer than Me_2SO, on a molar basis.[4] We went on to identify a critical period during late G_1/early S of the cell cycle during which inducer-mediated changes led to subsequent commitment to cessation of cell division, marked increase in globin gene transcription, and expression of other characteristics of terminal erythroid differentiation. This review paper was, probably, the first comprehensive review of erythroleukemic differentiation and stimulated use of this model for the study of terminal cell differentiation and for analysis of the block to differentiation characteristic of transformed cells.

Recently, we have identified new, more potent differentiation inducers, characterized aspects of the molecular action of these chemicals during differentiation-induction, and we have initiated preclinical and clinical studies with HMBA as a potential new approach to the therapy of cancers, namely, differentiation induction.[5,6]

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