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Time course and epigenetic control of glucocorticoid-induced cell death in malignant lymphoid cells

Certain malignant lymphoid cells, e.g. acute lymphoblastic leukemias (ALL) and myelomas are killed through glucocorticoid (GC)-induced apoptosis. This requires a relatively long exposure to GCs and involves complex regulation of interactive gene networks before the cells are irrevocably locked in an apoptotic pathway. By use of a model ALL system of GC-sensitive and -resistant CEM cell clones, we followed the GC-dependent regulation of genes up to the point of initiation of apoptosis. The results show that increasing numbers of genes are regulated over time, suggesting a "domino effect" of progressive gene control. We and others have identified several major signaling pathways that appear in this process. These include the MAP kinases, c-myc, calcium-dependent pathways, regulation of GR function, and others. Comparison of gene expression patterns in GC-sensitive and -resistant cells suggested that epigenetic controls might account, in part, for resistance. We therefore exposed three lines of resistant cells to 5 aza-2' deoxycytidine (AZA) to promote DNA demethylation. Resistant CEM, MOLT-4 (ALL) and RPMI 8226 (myeloma) cells were treated with AZA for 24-48 h and then challenged with the GC dexamethasone. All three lines had become GC-sensitive. Detailed examination of selected stable revertants revealed both shared and unique mechanisms that all involved the functionality of the GC receptor. The results encourage additional experiments on the AZA effect. Since such compounds are already in use in the treatment of certain myeloid malignancies, pending further experiments, the results offer hope that AZA-type compounds could be "repurposed" for use in GC-resistant malignancies.

Biography

E Brad Thompson (BA Rice University, MD Harvard Medical School, Biochemistry Studies University. of Cambridge) was founding Editor-in-Chief of *Molecular Endocrinology* and Editor-in-Chief of *Endocrine Reviews*. He was a Section Chief in the Laboratory. of Biochemistry, National Cancer Institute. 1973-1984, Chairman of Human Biological Chemistry and Genetics, University Texas Medicine Branch 1984-2003, and presently is Professor Emeritus UTMB, Seinior Research Professor, Center for Nuclear Receptors and Cell Signaling at University of Houston, and Visiting Professor, Johns Hopkins University. He has published over 300 papers on the mechanisms of steroid hormone action and applications to clinical situations.

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