Chemosensitising Non-Hodgkin Lymphoma Cells using Protein Synthesis Inhibitors?

Professor Anne Willis, School of Pharmacy, University of Nottingham

The Background

Non-Hodgkin lymphomas (NHL) comprise at least thirty distinct subtypes of B and T cell malignancies although over 90% of NHL are of B cell origin (Fischer 2003). At present NHL account for 2.6% of all cancer deaths in England and Wales and the incidence is increasing by approximately 5% per year, although reasons for this increase are unknown.

The Experiments

To gain a better understanding of the biology underlying NHL, polysomal mRNA profiling was performed on 6 cell lines (Ros 50, Val, DoHH-2, SuDHL-6, OCI-LY19 and DB) derived from patients with either follicular lymphoma or DLCBL (diffuse large cell B cell lymphoma) that have the t(14:18)(q32:q11) translocation and as a consequence many have increased expression of BCL2 (figure 1). Two controls were used, either B cells purified from adult tonsils or cell lines (EBV transformed, GM0892 and GM1953) derived from disease-free individuals. Only changes in polysomal association that were present between both control cell types and all 6 NHL cell lines were scored as positive. The mRNAs that showed an altered distribution on the polysomes were sorted into functional groups to identify those that could be relevant to the biology of the disease. In particular, those whose protein products are associated with the processes of apoptosis, cell signalling and protein synthesis, and cell adhesion (see Figures 2, 3 and 4) were identified.

The Experimental Data

Overall the data suggest that in NHL cells there are changes that would lead to an up-regulation of global rates of protein synthesis alongside up-regulation of anti-apoptotic proteins (e.g. DAXX) and down regulation of pro-apoptotic signals (e.g. TNF) and up-regulation of proteins involved in cell adhesion (e.g. LAMB2).

The Study Group Questions

Chemicals that inhibit translational initiation include inhibitors of p38Mapkinase pathways (e.g. SB203580), ERK pathway (e.g. PD98059) and FRAP/mTOR pathway (e.g. Rapamycin and Wortmanin) (Figure 2). We wish to determine whether it is possible to alter the recruitment of the anti-/pro-apoptotic mRNAs to the polysomes by treating the 6 NHL cell lines with these inhibitors. We wish also to establish whether this pre-treatment would sensitise cells to the effects of chemotherapeutic agents (including rutuximab, etoposide, vincristine or belomycin).

The Study Group is asked to develop mathematical models of the signalling pathways associated with NHL and to use these models to predict whether it is possible to use translational inhibitors to chemosensitise NHL cells.