expression of B-cell receptor signalling molecules, and high expression of interleukin-13 signalling molecules (including JAK2 and STAT1), tumour necrosis factor family members and several targets of the NF- κ B transcription factor (including TRAF1). Savage *et al.* went on to show that the NF- κ B pathway was activated in almost all cases of PMBL, and suggest that this might be the mechanism by which PMBL and HL cells resist apoptosis. Despite these similarities, the two lymphoma types were clearly distinguishable by the expression of other genes — such as several mature B-cell genes that were only detectable in the PMBL cells.

Molecular diagnosis of PMBL could help guide management of patients with DLBCL and lead to development of targeted treatments.

Ezzie Hutchinson

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WEB SITE

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http://gpp.nih.gov/researchers/viewbook/Staudt_Louis.html

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DRUG RESISTANCE

Clinging on

If you manage to cling on for dear life, as the saying goes, you survive, but in the case of acute myelogenous leukaemia (AML) cells, clinging on to the bone-marrow stromal cells seems to allow AML cells to resist cell death caused by chemotherapy, so decreasing the survival chances of the patient. Matsunaga *et al.* report in *Nature Medicine* that interaction between a β 1 integrin, VLA4, on AML cells and fibronectin on stromal cells is crucial in the development of minimal residual disease (MRD) and prognosis in patients with AML.

Studies of two AML cell lines, U937 and HL60, which express the β 1 integrins VLA4 and VLA5, showed that they were more resistant to loss-of-anchorage induced apoptosis (anoikis) after treatment with the anticancer drugs daunorubicin and AraC if attached to fibronectin-coated plates than those incubated on plates with no fibronectin coating. Antibodies to VLA4, but not to VLA5, reversed this resistance — as measured by the effect on cell viability and the increase of expression of the apoptosis pathway proteins annexin V, caspase 3, BCL2 and phosphatidylinositol 3-kinase.

Anti-VLA4 antibodies also abrogated MRD in severe combined immunodeficient (SCID) mice inoculated with the AML cell lines. If VLA4 antibodies were given with AraC to the mouse model of MRD, the mean survival of the mice was significantly higher than those receiving AraC alone.

So, what is the relevance of VLA4 expression to patients with MRD of AML? The authors showed that VLA4-positive leukaemic cells taken from 20 patients were more viable when cultured with fibronectin in the presence of daunorubicin or AraC than the cells taken from 10 patients whose leukaemic cells were VLA4 negative. When the VLA4-positive cells were incubated with VLA4 antibodies, they were more susceptible to drugs than those cultured without antibodies. When SCID mice transplanted with VLA4-positive leukaemic cells taken from patients were treated with VLA4 antibodies and AraC, no MRD was detected, unlike when VLA4-positive cells without antibody were used.

Furthermore, analysis of 25 AML patients showed that the complete response rate for

the 15 VLA4-positive patients was significantly lower (60%) than that of the 10 VLA4-negative patients (100%) and the relapse rate was higher in the VLA4-positive patients (55.6%) than in the VLA4-negative patients (0%). Of all the possible risk factors tested — including age, gender, performance status, white blood cell count and blast count — only VLA4 positivity was a significant unfavourable variable for response, relapse and survival.

VLA4 might, therefore, be a useful clinical marker and antibodies to VLA4 might be of value for treating MRD. Further work needs to be done with larger patient numbers to confirm these results.

Ezzie Hutchinson

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