Aggressive mucosa associated lymphoid tissue lymphomas are associated with mutations in Bcl10

Structurally, wild type Bcl10 protein consists of a caspase recruitment domain (CARD), which has significant homology with other known CARDs, and a novel distal amino acid sequence. Caspases are involved in the apoptotic pathway and it was hypothesised that Bcl10 could be functionally associated with this process, though CARD proteins can be either pro- or anti-apoptotic. In functional assays, wild type Bcl10 was shown to be weakly pro-apoptotic and it could also activate nuclear factor (NF)-κB. Activation of NF-κB, a DNA binding factor, is the ultimate goal of many intracellular signalling pathways, and the consequence is considered to be pro-inflammatory. It was shown that, like p53, which is probably the most widely investigated tumour suppressor gene implicated in many malignant processes, wild type Bcl10 had tumour suppressor activity as it could inhibit cellular transformation by oncogenes in vitro. In contrast, the truncated Bcl10 mutants used by the aggressive MALT lymphoma variant had notably different properties in some of these assays, though they retained the capability to activate NF-κB. Truncated Bcl10 was no longer pro-apoptotic, and not only did it fail to have tumour suppressor activity, evidence was presented that it has tumorigenic properties.

The precise role of truncated Bcl10 in the aggressive behaviour of this subset of MALT lymphomas is unclear. The characteristic behaviour may be due to the dissociation of activation of NF-κB and the pro-apoptotic activity as the truncated protein has lost the latter function only. Phorbol esters, chemicals which stimulate many cells in vitro, are known to activate NF-κB. Earlier studies have shown that aggressive variants of MALT lymphomas are refractory to the effects of phorbol esters and it is clear that the disruption of Bcl10 affects the intracellular signalling pathways in these tumours. In addition, the oncogenic activity of Bcl10 is likely to enhance tumour progression.

Mutations in Bcl10 were not restricted to aggressive variant MALT lymphomas; examples of B cell and T cell lymphomas of various histogenetic types with no t(1;14) translocation, but with mutated Bcl10 were observed. In some cases, the mutations would be expected to result in the production of truncated protein. Remarkably, mutations in Bcl10 were also observed in cell lines derived from other groups of tumours with known association with abnormalities in chromosome 1p22; three of three mesothelioma cell lines and three of three male germ cell tumours had significant mutations in Bcl10. By contrast, Bcl10 mutations were not observed in 15 breast, 11 pancreatic or 15 lung carcinoma cell lines. Although Willis et al’s study was restricted to cell lines, there is a good chance that mutation of Bcl10 is a significant event in the evolution of at least some cases of mesothelioma and male germ cell tumours.

In conclusion, we can expect to see a frenzy of activity in Bcl10 research in the future. Aggressive MALT lymphoma, by its behaviour as a “wolf in sheep’s clothing”, has brought to the forefront a gene of great importance in oncology and tumour cell biology.
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