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Vitamins gone bad: Vitamin A and human T cell leukaemia

Acute T cell leukaemia (T-ALL) is an aggressive tumour arising from immature T cells (a type of lymphocyte or white blood cell that plays a central role in cell-mediated immunity). T-ALL frequently presents with clinical features, such as high cell counts and invasion of the central nervous system.

Survival rates for T-ALL have improved, but only through the use of intensified therapies with consequent side effects. The overall outcome still remains inferior compared to the more common acute B cell leukaemia (B-ALL).

We need to better understand the mechanisms that mediate T cell transformation to leukaemia. A better understanding of the molecular pathogenesis of T-ALL offers the prospect of developing improved treatment strategies.

Methods and results

To gain insight into the importance of expression levels of various genes in T-ALL, we examined 100 primary T-ALL tumour specimens compared to 55 with B-ALL by microarray profiling (GeneChips). Notably, genes encoding aldehyde dehydrogenase 1A (ALDH1A) enzymes, whose main physiological function is synthesis of retinoic acid from vitamin A, showed aberrantly elevated levels at a high frequency in T-ALL (Figure 1, Table 1).

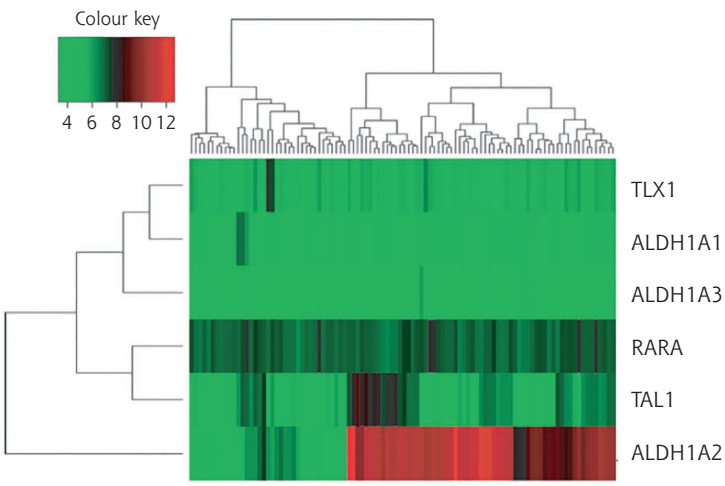

FIGURE 1 Aberrant ALDH1A gene expression is a common feature of acute T cell leukaemia. Red, high gene expression; black medium; green low

TABLE 1 Percent of acute T cell leukaemia specimens expressing retinoic acid pathway genes

Gene	% specimens
ALDH1A1	13
ALDH1A2	63
ALDH1A3	3
Any ALDH1A gene*	**72**
RARA	100
RARB	100
RARG	100
RXRA	100
RXRB	100
RXRG	7

In contrast, B-ALL tumours showed no significant increase in ALDH1A expression. Thus, aberrant expression of genes encoding ALDH1A enzymes (particularly ALDH1A2) is almost exclusively associated with T cell tumours, which are competent for retinoic acid signalling via expression of retinoid receptor genes (Figure 1, Table 1).

This result suggests that the retinoic acid pathway may be specifically relevant to T-ALL tumour growth. We therefore assessed the functional importance of ALDH1A enzymes to the growth of T-ALL cells compared with B-ALL cells. Tumour cell growth was determined by a cell proliferation assay after exposure to a

ALDH1A inhibitor (citral). All four T-ALL cell lines tested showed higher sensitivity to citral compared to the B-ALL cell lines (Figure 2A). Conversely, the T-ALL cell lines all responded positively to the addition of the retinoid receptor agonist TTNPB, whereas the B-ALL tumours did not benefit at all (Figure 2B). Together, these data indicate that T-ALL cells positively respond to signalling via retinoid receptors and that retinoic acid-synthesising ALDH1A enzyme activity specifically contributes to cell growth in T-ALL.

Consistent with this, genes associated with cell proliferation, survival and differentiation correlated with ALDH1A expression in T-ALL tumours (Figure 3).

Conclusions and recommendations

In this study, we have demonstrated that ALDH1A genes are aberrantly switched on in a large majority (close to three quarters) of T-ALL tumours. This study therefore implicates abnormal synthesis of retinoic acid from vitamin A in the development of T-ALL. These results are consistent with previous studies in humans and mice that have shown that retinoic acid is stimulatory to T cell growth but inhibitory to the growth of B cells, providing a plausible explanation for why aberrant ALDH1A expression is almost completely restricted to T cell leukaemia.

Trial attempts at treating T-ALL with retinoic acid itself have, not surprisingly, been unsuccessful. Indeed, multiple cases of secondary T cell leukaemia following therapy with retinoic acid for acute promyelocytic leukaemia have been reported. If substantiated, this work may lead to more specific therapies for acute T cell leukaemia based on small molecule inhibitors of retinoic acid signalling. ■

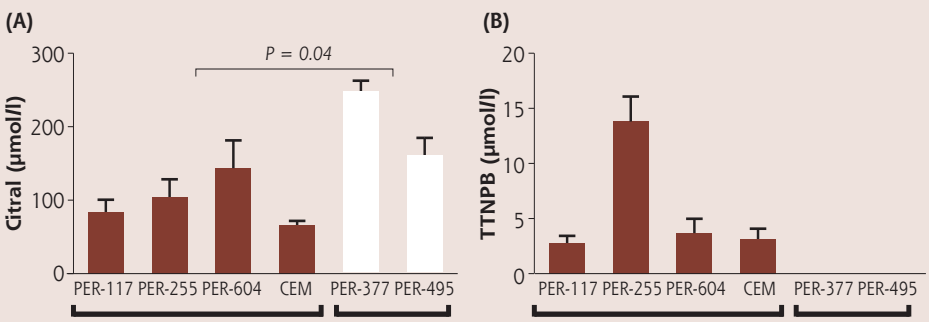

FIGURE 2 T cell leukaemia growth is sensitive to modulation of the retinoic acid pathway. A) Inhibition of ALDH1A enzymes with citral. B) Stimulation with TTNPB. Brown bars, T-ALL; white bars, B-ALL

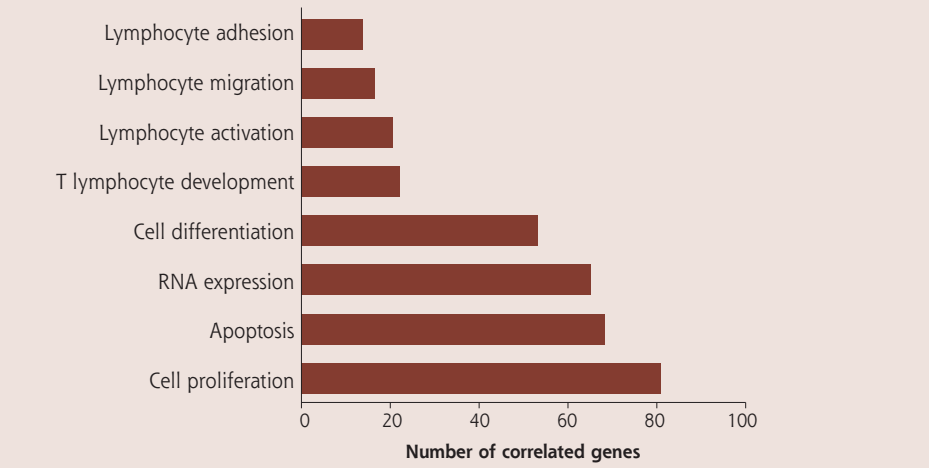

FIGURE 3 Function of the top 200 genes correlating with ALDH1A expression in T-ALL

More information

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References

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